Neurological Sciences (2022) 43 (Suppl 1):S1–S530
https://doi.org/10.1007/s10072-022-06531-9

ABSTRACTS

Abstracts of the 52nd Annual Conference of the Italian Society of Neurology

CASE REPORTS

SUCCESSFUL TREATMENT OF CHRONIC MIGRAINE COMORDIDS WITH MYASTHENIA GRAVIS AND ARTHRITIS WITH MONOCLONAL ANTIBODY AGAINST CGRP: A CASE REPORT

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Introduction: Monoclonal antibodies against CGRP and its receptor are the first target therapy for migraine prevention. CGRP is a 37-aminoacid peptide produced in central and peripheral sensory neurons throughout the CNS. This peptide is also localized in nonneuronal tissues throughout the body. For this reason, some researchers emphasized that circulating antibodies could affect all peripherally accessible sites where CGRP acts. CGRP-immunoreactive fibers were identified in the thymus, where it inhibits IL-2 production and proliferation of thymocytes in vitro. Transcription of the acetylcholine receptor alpha subunit, the main autoantigen in myasthenia gravis (MG), is induced by CGRP and VIP in human thymus and thymomas from MG patients. Autoimmune dysfunction of CGRP and its receptors is postulated to give rise to fatigue-related conditions such as chronic fatigue syndrome. Nonetheless, CGRP plays a role in the painful component of other chronic pain conditions, such as arthritis.

Case report: A 49-year-old woman presented to our clinic in 2016 with a history of chronic migraine. She had twenty days of headache per months. She has had 2 episodes of visual aura. Her neurologic examination was negative. She tried 3 oral preventive therapies: with amitriptyline she had no efficacy, with calcium channel blocker and topiramate she had no durable improvement. In 2019 she presented chronic fatigue and blurred vision, performed EMG repetitive stimulation, and Myastenia gravis was diagnosed without specific antibodies, for this reason she began pyridostigmine bromide therapy. In 2021, for her chronic joint pain, she was diagnosed with psoriatic arthritis and fibromyalgia, for this reason she started therapy with methotrexate and folate once a week. Meanwhile her headache became daily and disabling, so she started therapy with fremanezumab 225 mg once a month with important improvement of her migraine: after 3 months she had only 2 migraine attacks per months with less intensity and duration.

Discussion and conclusions: As mentioned above, a CGRP-related mechanism has been hypothesised for myasthenia, chronic fatigue, and arthritis, all pathologies comorbid with chronic migraine in our patient. In this case report, anti-CGRP molecule fremanezumab did not interfere negatively with the other comorbid conditions.

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CV2 POSITIVE DISIMMUNE PARANEOPLASTIC ENCEPHALITIS IN SMALL CELL PULMONARY CARCINOMA AND HHV6 NEURO-REACTIVATION

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A 70-year-old woman came to our attention because of acute language impairment, mental confusion and marked agitation. Brain MRI did not show acute focal lesions, but chronic and multi-infarct vascular encephalopathy. The patient had cronic coronary artery disease, cronic peripheral artery disease and multiple cardiovascular risk factors (smoking, arterial hypertension, dyslipidemia and hyperuricemia). Given the acute onset of symptoms, she underwent diagnostic lumbar puncture. The cerebrospinal fluid showed a slight increase in proteins without significant cellularity and HHV6-DNA positivity on meningitis/encephalitis panel. Therefore, treatment with foscarnet was initiated, without substantial benefit and subsequent iatrogenic acute renal failure, which resolved after hemodialysis. On total body CT and gastrointestinal endoscopy, the patient did not have heteroproliferative lesions, but para-tracheal lymphadenopathy and pulmonary microembolism. CYFRA 21.1 and NSE were weakly positive on serum. The electroencephalogram showed a diffuse slowing of the background rhythm, especially in the left temporal area, without irritative elements. Fluoro-dexoxy-glucose positron emission tomography (PET-FDG) showed a faint hypermetabolism in the left medial cerebral temporal region and a slight hypercaptation at the left lung apex that was subjected to bronchoscopic biopsy. Histological examination showed the presence of small cell neuroendocrine lung cancer (lung microcytoma) and antibodies anti- CV2 were significantly positive on serum. Anti-amphiphysin antibodies were weakly positive too. Given the compromised general conditions, the patient underwent a course of chemotherapy with cisplatin and etoposide with subsequent moderate clinical improvement. The patient underwent another 6 cycles of chemotherapy with good clinical response on behavioral and cognitive aspects, but subsequently the treatment lost its effectiveness. She died after about 10 months because of respiratory complications.

Conclusion: Isolated HHV6 encephalitis in an apparently immunocompetent patient should lead to suspicion of other pathologies determining virus reactivation. Paraneoplastic encephalitis, in this case mediated by antibodies versus intracellular onconeural antigens, as well as pulmonary microembolism likely secondary to paraneoplastic thrombophilia, preceded the diagnosis of lung microcytoma, which was evidenced only thanks to PET-FDG. Brain MRI never showed significant elements of encephalitis, event after infusion of contrast medium. The response of neurological disorders to chemotherapy treatment for the underlying malignancy was good only initially and lost efficacy thereafter, this probably because, as demonstrated by the temporal hypermetabolism to PET-FDG, the neuronal damage had not yet completely began.

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ATYPICAL PRESENTATION OF ANTI NEUROFASCIN-155 AUTOIMMUNE NODOPATHY

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Introduction: Autoimmune nodopathies are newly defined nosological entities distinct from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) due to their different pathogenetic characteristics. The node-paranodopathy most frequently described is the anti-neurofascin 155 (anti-NF 155), which has a typical clinical presentation pattern characterized by ataxia, distal weakness, prevalence of young men. We describe an atypical clinical presentation of a patient suffering from anti-NF 155 paranodopathy.

Case report: A 77-year-old woman came to our attention with a sub-acute flaccid tetraplegia from 8 weeks, generalized hypoesthesia, hypopallesthesia and areflexia. The patient was previously in good health, not suffering from significant comorbidities. The clinical conditions were rapidly complicated with involvement of cranial nerves resulting in a drooping head, dysphagia and facial diparesis, as well as a respiratory failure due to an impairment of the respiratory muscles, requiring a mechanical ventilation. She performed neurophysiological study showing a motor conduction velocity in the range of demyelination, a significant increase of the distal latencies and the duration of compound muscle action potential (CMAP), absence of F waves, generally reduced amplitudes of the CMAP, absence of temporal dispersion of the signal, absence of potential sensory action, denervation activity evident only in the lower limbs at electromyographic examination. The search for nodal and paranodal antibodies documented high levels of anti-NF 155 IgG. Empirical treatment was ordered with intravenous immunoglobulin and steroid bolus, considering the critical clinical conditions. After two days the patient presented spontaneous motility in the upper limbs, an increase in her vital capacity and oxygen therapy was not necessary. After 14 days the patient showed a regression of the cranial symptoms and a significant improvement of strength in the upper limbs (MRC 4/5). Distal leg muscle plegia persisted with denervation as evident on neurophysiological study. Neurographic re-evaluation performed after 10 days showed improvement in motor conduction velocities and increase in CMAP amplitudes in the upper limbs of 100-400%.

Discussion: Anti-NF 155 paranodopathy generally presents with severe ataxia, distal weakness, tremor in young patients. Our case presents an aggressive sub-acute onset of disease in an elderly patient with rapid flaccid tetraplegia, cranial nerve involvement and respiratory failure. This case broadens knowledge about the possible clinical presentations of the disease.

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DESCRIPTIVE STUDY ON THE CORRELATION BETWEEN VISUAL AND AUDITORY EVOKED POTENTIALS ASSOCIATED WITH VISUAL AND AUDITORY P300S USING WAVELET ANALYSIS OF INDIVIDUAL TRACES IN NORMAL, MCI AND SDAT SUBJECTS

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Introduction: The discovery of electroencephalography, made in animals by Caton and in humans by Berger, a century ago, has profoundly changed the vision of the structures and functions of the central nervous system. This work will present the results of the visual and auditory evoked potentials, associated with event related potentials (ERPs) followed by wavelet analysis of each individual trace. The analyses were done in a small sample of subjects: normal, MCI (minimal cognitive impairment) and DAT (dementia Alzheimer type).

Materials and methods: the subjects were randomly selected from the authors' database using the keywords: normal subjects, MCI, SDAT, have been selected: 28 SDAT; 21 MCI; 25 normal, of both sexes and aged between 50 yrs and 75 yrs. SDAT MOCA = 19/30; SMID MOCA= 20/30 NORMAL 28/30.

Results: The data show an altered functioning of the visual and auditory systems highlighted by the wavelet analysis, with the following organized gradient: NORMAL better than MCI better than SDAT. Visual and Auditory P300 also have higher amplitude values in NORMAL > MCI > SDAT, latency SDAT >> MCI >> NORMAL.

Conclusion: The results of this study show a good correlation between perceptual abnormalities at latency, amplitude of VEPs and AEPs and visual and auditory P300, supported by wavelet analysis that highlights an altered frequency composition that justifies the worsening of cognitive functions in the three classes of subjects. This data can help us in the development of new types of treatments with: COGNITIVE NEUROMODULATION and TRANSCRANIC MAGNETIC STIMULATION (TMS).

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HEMISPHERIC EEG ASYMMETRY IN DEPRESSIVE DISORDERS AND CONTROL SUBJECTS USING LORETA DATA ANALYSIS

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Introduction: The correlation between right frontal hyperactivation and depression has been known in literature since a long time. This is evident in two different conditions: 1.a left frontal hyperactivation (maniacality); 1.b right frontal hyperactivation (depression); 2.a left frontal deficit (depression); 2.b right frontal deficit (maniacality). Hyperactivation is identifiable in focal epileptic activity. Frontal deficits can be secondary to a tumor or a vascular event.

Aim of the study: The goal of this study is to verify the distribution of the different frequencies recorded with EEG technique and bringing them on the MRI maps reconstructed with Talairach method in depressed and normal subjects in order to confirm the hypothesis that depressed subjects present a right frontal hyperactivity.

Material and method:17 controls have been enrolled, whose mean age is 38,4 years and then 16 people affected by depression have been also enrolled, whose mean age is 40,72 years. The diagnosis of depression followed the DSMIV criteria. All the subjects underwent EEG recording with EEG headcap with derivations placed in the cephalic points according to the 10-20 criteria. The recording parameters were as follows: recording AVERAGE reference; Notch 50 Hz, Low-pass filter 70 Hz, High Pass filter 1,2 Hz. The phases with open and closed eyes lasted 10 minutes and from each of these recording phases, a 10-second interval was selected for analysis, with at least one ocular artifact.

Conclusion: This study confirms the abnormal activation of the right frontal and other cerebral regions at different frequencies, all reaching the level of statistical significance. What can we say then? I consider the neurophysiological evaluation useful in the treatment processes of the patient with a mood disorder. These subjects should be evaluated not only by the multiple scales for identifying the different aspects of the emotional, motor and behaviour abnormalities, but also we must consider associating to them electrophysiological studies with EEG with frequency and amplitude mapping, together with the analysis of the paths with Loreta method in order to be able to reach a multidimensional treatment: pharmacology, Cognitive rehabilitation and psychophysiological rehabilitation with methods such as BIOFEEDBACK and COGNITIVE NEUROMODULATION.

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CO-OCCURRENCE OF DERMATOMYOSITIS AND MYASTHENIA GRAVIS AFTER COVID-19 VACCINE: A CASE REPORT

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The association of myasthenia gravis and dermatomyositis is very rare but immune dysregulation plays a key role in both conditions. A 68-year-old man, with no prior history of any neurological or autoimmune disease, presented with a 1-month history of skin rash, myalgia and symmetrical proximal limb weakness. He developed these symptoms about three weeks after the second dose of Vaxzevria. On examination, he showed a diffuse facial, scalp, arm and trunk rash with periorbital edema. No Gottron papules were detected. Creatine kinase levels were markedly increased. Electromyography was normal, whereas muscle biopsy revealed a perivascular mixed cell infiltrate. Based on clinical features, elevated muscle enzymes and muscle biopsy, a diagnosis of dermatomyositis was established. A full-body CT scan and an esophagogastroduodenoscopy, performed in order to exclude a connection with malignancies, appeared unremarkable. The patient showed a gradual improvement of symptoms after treatment with intravenous methylprednisolone 80 mg for three days. After a month the patient was re-hospitalized because of symptoms worsening and sudden onset of dysphagia and diplopia. Anti-acetylcholine receptor (AChR) antibodies were found to be positive, and the patient was treated with intravenous immunoglobulins and pyridostigmine with clinical benefit. To the best of our knowledge, this is the first case of new-onset dermatomyositis associated with myasthenia gravis occurring after COVID-19 vaccination. Dermatomyositis occurring after vaccination is a well-known phenomenon and has been recognized as a manifestation of COVID-19-induced muscle disease (1,2). On the contrary, only few cases of dermatomyositis or myasthenia gravis occurring after COVID-19 vaccination have been described (3). It has been hypothesized that vaccines containing SARS-CoV-2 antigens may enhance autoimmunity by similar mechanisms such as polyclonal or bystander activation, epitope spreading or molecular mimicry. Alternatively, the inflammatory stimulus of vaccination may enhance autoimmunity in predisposed patients.

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TONIC-CLONIC SEIZURES IN A PATIENT WITH PSEUDOHYPOPARATHYROIDISM: A CASE REPORT

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Introduction: Hypochlacemia is an electrolyte disorder that can cause various neurological manifestations, including both generalised tonic-clonic or focal motor seizures, due to an increased neuronal excitability. Pseudohypoparathyroidism is a rare disorder where patients are resistant to parathyroid hormone; parathyroid hormone resistance leads to hypocalcemia and hyperphosphatemia.

Case Report: A 46-year-old man presented to emergency department with generalized tonic-clonic seizures that resolved spontaneously, followed by post-ictal confusion. He was diagnosed with epilepsy in course of hypocalcemia at the age of 11 and treated with Carbamazepine, Calcium and Vitamin D until the age of 16; he was seizures free since then. On examination, vital signs were within normal limits. He had short stature, a rounded face and central adiposity, with height and weight measuring 165.8 cm and 83 kg, respectively. A systemic physical exam was unremarkable, including a neurological and a musculoskeletal examination. On biochemical investigations, his serum ionized-calcium measured 4.24 mg/dl (5-5,3 mg/dl) combined with a high serum phosphorus level of 5,34 mg/dl mg/dl (2,5-4,5 mg/dl), total 25-OH vitamin D measured 7.6 ng/mL (30-100 ng/ml). His serum parathyroid hormone was 569 pg/mL (14-85 pg/L). A computed tomography (CT) brain scan showed calcification of the basal ganglia and cerebellum. All of these findings are indicative of psudohypoparatiroidism. Investigations for tissue resistance to other hormones that share the similar signaling pathway through Gs-coupled receptors (including TSH, LH, FSH, and growth hormone releasing hormone) came back normal. RX exam showed characteristic findings of short 4th and 5th metacarpals. This patient was treated with Calcium Sandoz cp 2/die, Rocaltrol 0,5 mg cp 2/die and Keppra 500 mg cp 2/die. The patient was discharged from hospital with full seizure control.

Discussion: Regarding the management of seizures in hypo or pseudohypoparatiroidism, we added an AED in prevention of epileptic seizures that can occur in the event of low adherence periods to the calcium correction therapy. In this choice we also consider that brain calcifications have an epileptogenic potential.
Conclusion: This case highlights the occurrence of brain calcinosis in hypoparathyroidism and the importance, in the correct clinical setting, of considering alternative, and sometimes treatable, causes of seizures other than epilepsy.

CHILDHOOD CASE OF GLYCOGENOSIS TYPE 2 WITH ABNORMAL CAPILLARIES AND AUTOPHAGY BLOCK

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Objective: Childhood Pompe disease, OMIM # 232300, has been considered a muscle disorder (cardiac and/or skeletal). This study focuses on small vessel changes in the muscle, that may contribute to the concept of the multisystem nature of Pompe disease.

Case Report: A 3-and-a-half-year-old girl with a childhood-onset of late-onset Pompe disease (LOPD), was hospitalized at the University Hospital of Ljubljana (Slovenia) and had a diagnostic biopsy of vastus lateralis muscle that was studied in Padova. The electron microscopy study was done in Slovenia. at the time of biopsy, at 3 years and 8 months, the child was in mechanical ventilation, and therefore this could be considered a natural history study because she died at 4 years and 4 months, before ERT was available. but may contribute to the concept of the multisystem nature of Pompe disease.

Methods: The biopsy was studied by immunohistochemistry, electron microscopy, and molecular forms of alpha-glucosidase were investigated on western blot, by immunohistochemistry as described by Nascimbeni et al [1]. Autophagy markers in biopsy were investigated as previously described [2,3].

Results: Muscle biopsy: by hematoxylin and eosin, there were many vacuolated fibers (70%), there was high variability in muscle fiber vacuolar degeneration, and many muscle fibers were positive with acid phosphatase stain, when stained with autophagic markers a high p62 quantity was detected in several vacuolated fibers due to a novel stop-codon GAA mutation (2227C to T in exon 16) and a missense mutation in exon 2 (14650 C to T) with mutant protein-protein interaction and autophagosome formation. Peculiar was the high level of precursor (95-110 kDa) of GAA protein in muscle as well as little mature forms (70-76 kDa) of GAA protein probably reaching lysosomes in less affected fibers. The level of acid-glucosidase was 29% of control. She had a novel missense mutation and a stop-codon mutation, what was peculiar is the high level of precursor (95-110K Da) in muscle and some 60-70KDa protein in muscle and high p62, similar to severe infantile cases, demonstrating the altered process of GAA inside the muscle and blocked autophagy.

Discussion: These recent findings suggest that GAA deficiency causes lysosomal dysfunction, autophagy impairment, and an alteration in several signaling pathways that might contribute to muscle dysfunction and resistance The concept of diffuse vascular involvement, including small vessels, in LOPD, may contribute to the multisystem nature of Pompe disease and may influence the efficacy of possible therapeutic interventions in Childhood-onset LOPD.
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LONG-TERM MISDIAGNOSIS OF MS IN A PATIENT WITH MOGAD: CLINICAL AND THERAPEUTIC IMPLICATIONS OF A CORRECT DIAGNOSIS

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Aims: The overlap of clinical and imaging features between multiple sclerosis (MS) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is still an open issue, making crucial targeted investigations and timely treatment strategies. We describe here a case of MOGAD misdiagnosed with MS twenty years ago, when antibody testing was not available, and her clinical course under MS treatments.

Materials and methods: A 31-years old female with a family history positive for MS, presented in 2001 with one month history of visual blurring in the right eye without pain. The first presentation was followed by many events characterized by sensory, motor and urinary symptoms, all treated with high dose intravenous steroids with complete recovery. Routine workup including complete blood count, basic metabolic panel, and serum infectious and autoimmune tests were all within normal range. Cerebrospinal fluid (CSF) showed normal white cell count, glucose, and protein, with unmatched oligoclonal bands (OCB). Brain and spinal cord magnetic resonance imaging (MRI) revealed multiple T2-hyperintense periventricular and deep white matter lesions and patchy lesions in the cervical cord. Based on her clinical course, OCB positivity, radiological findings, she was diagnosed with MS and started on disease modifying therapies (DMTs), initially with azathioprine (AZA) for six years, with low compliance to therapy, then with Teriflunomide. While on both treatments, she experienced new relapses and lesions on follow-up MRIs, especially during therapy with Teriflunomide, when the patient develops bilateral optic neuritis. During this last relapse, she was then further investigated and tested for serum MOG-Antibody (positive on CBA) and aquaporin4- Antibody (negative). The patient was diagnosed with MOGAD and started on Rituximab in 2018, with a good control of the disease and neither new relapses nor lesion after four years of treatment.
Conclusion: Our case highlights that a prompt identification of MOGAD patients with MS-like phenotypes is crucial and has relevant therapeutic implications. In particular, this case shows how first-line DMTs in MOGAD results in a low disease control, in opposition to rituximab.

ABNORMAL BRAIN STRESS-RESPONSE: A LESSON LEARNED FROM A FEBRILE INFECTION

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Objective: We report a case of early-onset parkinsonism with cerebellar-pyramidal signs, associated with drug resistant epilepsy and a supportive

familiar history. Differential diagnosis of potentially heredo-degenerative leukoencephalopathies will be considered.

Materials: A 28-years-old woman referred to our outpatient Clinic for a slowly progressive onset of gait disturbances with falls, urinary incontinence and cognitive decline since the age of 21 years. As disease progressed, a drug resistant epilepsy also occurred. At the age of 26, during a febrile infection, she presented a convulsive status epilepticus together with rapid deterioration of her preexisting neurological features. Familiar history was positive for epilepsy and gait disturbances in her grandfather and brother, respectively. Neurological examination showed hypomimia with mild bradykinesia of upper and lower limbs, ataxic-spastic gait, postural instability, truncal ataxia, upper limbs dysmetria, slow saccades and saccadic smooth pursuit, auditory-induced myoclonus of the upper limb.

Methods: Brain MRI showed extensive signal abnormalities and cystic degeneration within the white matter sparing the U-fibers and temporal lobes; atrophy of the cerebellum and brainstem were also reported. Genetic testing for the more frequent leukodystrophies revealed a c.338G>A (NM_003907.2) homozygous mutation within the EIF2B5 gene supporting the diagnosis of Vanishing White Matter (VWM) disease. Gynecological assessment revealed uterine myoma. No optic disc atrophy was reported on ophthalmological examination.

Results: VWM is one of the most frequent inherited leukodystrophy. It is characterized by chronic and progressive cognitive and motor impairment and epilepsy with subacute worsening following stressful events, such as fever or trauma. Optic atrophy with vision loss and ovarian failure are also reported [1].

Discussion: The loss of inhibition of protein synthesis, which is part of a protective mechanism of cells in the so called "cellular-stress response system", is probably responsible for the rapid deterioration after a febrile infection [2]. This case highlights the supportive role of brain MRI in driving genetic tests in the context of inherited leukodistrophy, in order to reach an early diagnosis.

Conclusions: In the presence of progressive cognitive and motor deterioration, a detailed clinical history may help to guide the diagnostic work-up. Diffuse brain white matter abnormalities support the diagnosis of VWM when a stressful event was reported.

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AN ULTRA-RARE MEDIASTINAL VASCULAR SARCOMA IN A PATIENT WITH CHRONIC OPHTHALMOPLEGIA (CPEO) AND MITOCHONDRIAL MYOPATHY DUE TO DEOXYGUANOSINE KINASE (DGUOK) DEFICIENCY: A CASE REPORT

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Objectives: The association between mitochondrial disorders and cancer is widely debated. There is evidence that some cancers recognize a mitochondrial dysfunction and few studies have evaluated a possible recurrence of neoplasm in patients with mitochondrial disorders. The objective of this report is to describe the clinical, genetic, and molecular features of a rare cancer presentation in a patient with mitochondrial myopathy due to deoxyguanosine kinase (DGUOK) deficiency.

Materials: Herein we report the case of a 75-year-old woman who presented with chronic progressive ophthalmoplegia (CPEO), exercise intolerance and mild proximal muscle weakness since the age of 40. 10 years later she was diagnosed with mitochondrial disorder.

Methods: Muscle biopsy showed several ragged red fibers and cox negative fibers, while LongPCR of mtDNA revealed the presence of mtDNA multiple deletions (MDELs). Several years later genetic analysis for nuclear genes associated with mtDNA MDELs showed the presence of two heterozygous variants in DGUOK gene (c.130G>A /c.704C>G; p. Glu44Lys / Thr235Arg). At age of 70 years, she developed a mediastinal neoplasm incidentally diagnosed after a thoracic CT scan.

Results: Complete resection was carried out and morphological study confirmed the diagnosis of mediastinal epithelioid hemangioendothelioma (EHE). Particularly, the immunohistochemical and molecular analysis showed a positivity for CD31, ERG, CAMTA and a negativity for TFE3. After five years of follow up she has a regular outcome.

Discussion: The case reported represents an example of an ultra-rare neoplasm in a patient suffering from a rare disease. There is evidence that some cancers recognize a mitochondrial dysfunction, although a clear relationship between mitochondrial disorders and neoplasm is not yet established, with literature data being often controversial.

Conclusion: Our case enhances how variable could be the clinical presentation and evolution of mitochondrial disorders. Further studies are needed to better understand the possible linkage between mitochondrial disorders and cancer.

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STROKE IN KLINEFELTER SYNDROME: CASE REPORT AND LITERATURE REVIEW

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Introduction: Klinefelter syndrome (KS) is a common abnormality of sex chromosomes (47, XXY or a mosaic karyotype) and is characterized by hypergonadotropic hypogonadism.

Case report: A 47-year-old man with KS on testosterone transcutaneus replacement therapy was referred to our Stroke Unit for acute onset of left facial weakness and dysarthria. Emergency clinical evaluation and neuroimaging at admission showed NIHSS 4, ASPECTS 10, parietal M2 branch occlusion with no carotid disease and penumbra in the right MCA territory. Actylise was administered (0.9 mg/kg). NIHSS scored 0 24 hours later, whereas the brain MRI showed a small right parietal and precentral acute ischaemia. The Transcranial Doppler Bubble test showed a severe right to left shunt with "curtain effect" after the Valsalva Maneuver. A mild dyslipidaemia and slight hypergonadotropic hypogonadism despite hormone replacement therapy were detected. No thrombophilic blood markers were found to be pathological. Echocardiogram was negative for cardiopathy and no atrial fibrillation

(AF) was recorded on 72 hours telemetry. Lower Limbs ultrasound showed a popliteal DVT, thus a direct oral anticoagulant (apixaban) was started (long-term therapy was later indicated in follow-up). NIHSS at discharge was 0. Discharge and three months follow-up modified Rankin scale was 0.

Discussion: A cerebral paradoxical embolism due to lower limbs DVT is likely to be the aetiology of stroke. The available literature about KS and the risk of stroke is limited. Data from large registry-based studies indicate that KS subjects are at increased risk of thromboembolic events and a higher risk of both recurrent venous and artery thromboembolism is present. [1] Although the direct and indirect physiological roles of testosterone and androgens on the coagulation system are well known, the role of hormonal replacement therapy is still unclear [2]. Several reports suggest that KS is associated with a higher cardiovascular risk profile or higher prevalence of cardio-metabolic risk factors mainly due to chromosomal abnormalities rather than low serum testosterone levels. [3] Furthermore, Klinefelter Syndrome is associated with a higher risk of AF development; diastolic dysfunction was actually correlated with the free testosterone level in patients with Klinefelter Syndrome and was established to be strongly associated with AF. [3]

Conclusion: Active cardiovascular and stroke prevention would be beneficial in patients with Klinefelter Syndrome.

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CEREBRAL FOREIGN BODY REACTION (CFBR) AFTER CAROTID ANEURYSM STENTING IN A PATIENT AFFECTED BY PSORIATIC ARTHRITIS - A CASE REPORT AND REVIEW OF LITERATURE

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Objectives: Cerebral foreign body reaction (CFBR) due to hydrophilic polymer embolization is a rarely diagnosed complication of cerebral angiography. Our main objective is to present a thorough clinical and radiological description of our case.

Material: We described a case of a 61-year-old woman, smoker, affected by arterial hypertension, mood disorder and psoriasis with arthritic involvement. She had an endovascular procedure to treat a double aneurysm located in the supraclinoid portion of left ICA. About one month later, she developed severe headache, generalized asthenia, progressive weakness of her right arm and dysarthria.

Methods: The patient underwent an angiographic treatment of a double aneurysm located in the supraclinoid of the left ICA tract using a flow-diverting stent. After the onset of neurological symptoms we performed serial MRI scans, both without and with and contrast, diagnostic angiography, cerebrospinal fluid examination and laboratory analysis. A clinical and MRIs follow-up was performed.

Results: Brain MRI showed hyperintense lesions in FLAIR sequences in subcortical white matter of left frontal, parietal, and temporal regions without diffusivity restriction on diffusion weighted imaging (DWI). After the administration of gadolinium, T1 images demonstrated multifocal areas of contrast enhancement. Cerebrospinal fluid examination and laboratory analysis showed no relevant abnormalities. She started corticosteroid therapy with progressive clinical improvement. Brain MRIs after treatment evidenced a significant improvement of the neuroradiological picture.

Discussion: Despite the considerable use of angiographic procedures in the literature, few cases of CFBR are described. Since it is a little known complication it could be underdiagnosed. The etiopathogenesis of this reaction is not well elucidated, some evidences suggested a possible role of predisposing conditions. Our patient suffers from psoriasis and this may have given her a greater immune reactivity towards polymer emboli that in most of people, undergoing angiography, are harmless.

Conclusions: The presence of focal neurological deficits with neuroradiological imaging characterized by enhancing brain lesions localized in the vascular territory of the catheterized arteries after an endovascular procedure of the cerebrovascular district should suggest a delayed granulomatous reaction to hydrophilic polymer emboli. CFBR should be considered in the differential diagnosis of post angiographic complications and adequately treated.

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SIMULTANEOUS PNS AND CNS INVOLVEMENT FOLLOWING COVID-19 VACCINATION: CLINICAL AND IMAGING FINDINGS OF A CASE

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Background and aims: Following 11.7 billion doses of COVID 19 administered vaccines, nervous system-damaging side effects have been rarely reported. We describe the case of post-vaccination sensitive-motor neurological symptoms.

Materials: Our patient underwent brain CT scan and angio-magnetic resonance imaging (angioMRI).

Methods: A 38-year-old female, with no history of recent infections, on beta-blocker therapy for extra systole, presented, 22 hours after injection of second dose of Pfizer-BioNTech vaccine in left deltoid, fronto-orbital headache, left hemi-face and upper limb hypoesthesia/numbness, right displacement of the lower dental arch.

Results: Neurological examination revealed left orbicularis oculi muscle hyposthenia with palpebral rhyme asymmetry (left< right), right displacement of the lower dental arch, sublevelling at Mingazzini's test within 10" and a counter-resistant hyposthenia of all segments (MRC 4/5) of the upper left limb, tactile-dolorific left facio-brachial hypoesthesia. Reflexes were normo-elicitable and no pathological findings were observed on the right hemi-soma. Brain CT scan showed no recent ischemic/haemorrhagic events; subsequent brain angioMRI showed a focal enhancement of left facial-acoustic package. Oral steroid therapy (prednisone 50mg/die for two weeks, then tapered) and amitriptyline were started. Two months later brain MRI was negative, with complete resolution of the enhancement of the left facial acoustic package; the peripheral involvement of VII cranial nerve was partially remitted, sensibility alterations occurred intermittently. At neurological examination, she still had left facio-brachial weakness. She also complained frequent migraine and tension-type headache, prevalent on the left side and only partially responsive to FANS.

Discussion: We described the case of a left sensory-motor hemi-syndrome, associated with a peripheral paralysis of the VII cranial nerve. Brain CT and angioMRI excluded tumours, vascular causes or demyelinating diseases: while the cranial nerve involvement was confirmed by imaging, no radiological findings could justify the hemy-syndrome. We hypothesized a post-vaccine inflammatory etiology since also the hemi-syndrome improved after anti-inflammatory therapy. The association with the vaccine is supported by the 22 hours-interval between vaccine administration and clinical onset. Furthermore, our patient also referred milder symptoms a few hours after receiving Pfizer-BioNTech first dose.

Conclusion: Although the vaccine is generally safe, rare neurological complications can be observed after its administration: we reported this case in order to highlight the uncommon but possible simultaneous involvement of cranial nerves and CNS by the vaccination-induced inflammatory process and to point out the possible acute onset of long lasting signs and symptoms in the absence of a radiological substrate.

CEREBROVASCULAR RISK MANAGEMENT, FROM GUIDELINES TO REAL-LIFE EXPERIENCE: A CASE REPORT

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Case presentation: A 68-year-old man came to Emergency Room for an accidental fall and subsequent concussive head injury. No previous therapy or medical history was reported. Laboratory assessments revealed 66% haematocrit and 21 g/dl haemoglobin. Brain-CT and CTA showed extensive acute ischaemia in the right lower cerebellar region, the right intracranial vertebral artery and basilar artery occlusion. No revascularisation treatment was indicated. Admitted to the Stroke Unit he appeared alert, oriented, dysarthric and dysphagic at the neurological examination. Rotatory nystagmus, dysmetria, marked retropulsion and strength deficit in the right upper limb were also observed. Brain-MRI confirmed the extensive ischaemia with a large haemorrhagic transformation contraindicating antiplatelet therapy. During hospitalization, atrial fibrillation with a high ventricular response at EKG and interventricular septum akinesia at echocardiography were demonstrated. The patient was cardioverted, but anticoagulant therapy could not be administered for the high haemorrhagic risk [1]. Coronarography was indicated but postponed to ischemic lesion improvement in case of indication for angioplasty and the risk of haemorrhagic complications due to dual anti-aggregation therapy (DAPT) [2]. During PICC placement, right brachial vein thrombosis was detected on ultrasound examination. Therapy with LMWH 8000 IU x 2/day was started. Bloodletting was carried out for poliglobulia. Seven days after demonstrating haemorrhagic infarction reduction at CT, the patient underwent coronary angiography with the deployment of four stents. To minimise the thrombotic risk and, at the same time, the haemorrhagic risk, therapy with DAPT was associated with a lower dose of LMWH (6000 IU x 2 die). Over the next 14 days, the brachial vein thrombus resolved, without affecting patient's neurological conditions.

Discussion: This patient had indication for anticoagulation because of septal akinesia and AF. There are no clear guidelines on the optimal time to restart anticoagulation after stroke; clinical and radiological aspects and the patient's specific risks should be evaluated. ESC 2016 and ESO 2019 guidelines advise against using LMWH in patients with AF as secondary prevention after stroke. Nevertheless, anticoagulant therapy is indicated for venous thrombosis; poliglobulia requires antiplatelet, and DAPT is needed after coronary stenting. A treatment aimed at safeguarding the prothrombotic-prohaemorrhagic balance is set up to cope with these indications.

Conclusion: This clinical case shows that Neurologists should adapt indications and guidelines, together with their expertise, to the specific patient, especially in cases of complex systemic vascular risk, looking at the patient as a whole.

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TREATMENT OF NEURO-PSYCHOLOGICAL COMPLICATIONS OF CRANIOPHARYNGIOMA WITH INTRANASAL OXYTOCIN: A CASE REPORT

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Craniopharyngiomas (CP) are rare brain tumors originated from remnants of the craniopharyngeal duct epithelium (Rathke's pouch), that can develop at any point along the pituitary–hypothalamic axis [1]. Hypothalamic dysfunction, such as hypothalamic obesity (HO), neuropsychological deficits, and disturbances of circadian rhythms occur in 35% of patients with CP at the time of diagnosis and up to 65% following surgical-radiological treatment. HO has a severe impact on the quality of life and prognosis after CP [2]. It has been postulated that oxytocin synthesis and release is disturbed in patients with CP, like the other hormones of the pituitary gland. Indeed, some evidence suggests that reduced levels of oxytocin correlate with BMI and neuro/psychological disturbances after CP [3]. Only case reports and anecdotical evidence from communities of HO patients have reported efficacy of intranasal oxytocin in reducing body weight and hyperphagia and improving psychological aspects in patients with HO [3]. We present the case of a 29 years-old woman followed in our center after a CP resection. She came to our attention in May 2013, when she was admitted to the ER for impaired consciousness. The clinical picture started a few months before with behavioral

disturbances and >20 kg weight gain, initially interpreted as a manifestation of a psychiatric disease, and treated accordingly. Brain MRI showed a round □ 5.5 cm suprasellar lesion with cystic-necrotic aspect and calcifications, showing contrast enhancement, with a severe compression of nearby regions. She underwent transcranial resection of the lesion, the histological diagnosis being adamantinomatous CP. Post-operative period was characterized by severe behavioral disorders, cognitive impairment (mainly attention and memory), severe psychiatric disturbances (including suicidal ideation), seizures, adipsic diabetes insipidus and hyperphagia, for which, the patient was admitted several times to the ER between 2013 and 2018. In 2018, the patient started intranasal oxytocin (1 puff bid) with a significant improvement of HO (85 kg to 56kg, following lifestyle modifications that were not possible before), behavioral and psychiatric manifestations (started attending school again and engaged in several social activities). Following the identification of a recurrence of CP, the patient stopped oxytocin in October 2020, gaining back the weight (73 kg) and with worsening of the behavioral aspects. The recurrence was treated with radiosurgery, she started oxytocin again in February 2022 with improvement of hyperphagia and behavioral disturbances. Further studies are needed to elucidate the mechanism of action of oxytocin and confirm its efficacy and safety.
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EARLY ONSET EPILEPSY AND DEVELOPMENTAL DISORDER: CASE REPORT OF A NOVEL SCN8A MUTATION

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Objectives: Developmental and epileptic encephalopathies (DEEs) are a group of syndromes characterized by developmental disorder and drug-resistant seizures, both responsible for significant encephalopathy, often related to single gene mutation. We report a case of a 24-year-old female with onset at the age of 6 with bilateral tonic-clonic and myoclonic seizures and subsequent developmental delay.

Case report: At the neurologic exam: wide-based gait, left eye ptosis, mild kinetic tremor in the arms, scoliosis. EEG reported a widespread sub-continuous theta rhythmic activity and paroxysmal activity over the central-frontal right areas (sharp and wave complexes). A recent head MRI has shown atrophy in the cerebellum. We administered the Wechsler Adult Intelligence Scale (WAIS) and the Rorschach Test, that showed a mild-moderate intellectual disability (IQ: 50), immature personality, poor affective integration, stereotyped thinking, and intellectual inhibition. The patient was studied to find a genetic etiology of the syndrome: SCL2A1 gene sequencing and FISH for the research of a ring chromosome 20 (both normal); array-CGH that found a partial duplication 8p23.1, inherited from healthy father; whole exome sequencing (WES). WES found a de-novo mutation of SCN8A (C.4473 A>C; p.Lys1493Asn), missense, unreported before. This finding, combined with clinical phenotype, EEG features and MRI report, fully fits the diagnosis of DEE13, the SCN8A mutation related syndrome (OMIM #614558).

Discussion: After the onset, the patient, with a story of drug-resistant epilepsy, has shown recurrence of tonic-clonic seizures upon carbamazepine reduction. At present, she has not had major seizures for 6 years, but only myoclonic seizures in perimenstrual cluster and is being treated with Perampanel, Carbamazepine and Clobazam. The addition of Perampanel to the therapy resulted in the disappearance of theta rhythmic activity on EEG and the reduction of myoclonic seizures frequency. Compared with other reported cases of SCN8A mutation, this finding represents a significant therapeutic novelty. We are investigating about possible appearance of side effects and drug resistance to perampanel.

Conclusions: We reported a case of DEE in an adult patient linked to a novel mutation of SCN8A gene. The patient has shown a good therapeutical response to perampanel, with reduced seizure frequency and improved brain electrical activity on EEG.
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A PECULIAR CASE OF CLIPPERS: A RARE AND UNDERDIAGNOSED INFIAMMATORY CENTRAL NERVOUS SYSTEM DISORDER

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Object: We report a patient with a probable Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS), although currently lacking the recognized diagnostic criteria. We underline the limitations of a strict classification in use.
Materials: A 35-year-old woman was referred to us with a 10-week history of dizziness and a progressively worsening in gait imbalance. A spontaneous abortion seven years earlier was reported. General examination was normal. Neurological examination showed moderate ataxia with right lateropulsion, gaze-evoked nystagmus, right facial nerve paresis, dysarthria and four limbs dysmetria.

Methods: Blood serum assay, autoantibodies and serological tests were unremarkable. An increased blood T-cell CD4:CD8 ratio was documented: 7.2 (normal range: 1.4-1.9). Cerebrospinal fluid analysis revealed mild pleiocytosis. Brain MRI showed hyperintense abnormalities in T2-weighted sequences and FLAIR, located in the transition between pons and medulla, in the middle cerebellar peduncle and in cerebellum. The same lesions showed a punctuated and curvilinear gadolinium enhancement pattern. Neither mass effect nor vasogenic oedema were described. Moreover, no lesions were found in the spinal cord. CT scan and 18-FDG total body PET scan showed no pathological findings.

Results: Based on clinical, laboratory features and typical MRI, a diagnosis of probable CLIPPERS was considered, even though spinal cord

lesions were absent. Our patient was then treated with a steroid pulse, followed by oral prednisone 25 mg per day. After a week from treatment start a marked improvement of both neurological deficits and MRI gadolinium enhancement was evident. As steroid sparing agent intramuscular methotrexate 10 mg per day was added. After a 2-month period of treatment our patient showed no relapse of central nervous system symptoms.

Discussion: Although diagnostic criteria are very useful to define correct diagnoses, a strict classification system may prevent the diagnosis of highly probable diseases. In our case, a prompt treatment may had avoided the development of spinal cord enhancing gadolinium lesions, required to diagnose CLIPPERS according to the current criteria.
Conclusions: CLIPPERS is a rare although treatable condition; it is often underdiagnosed, and it warrants further studies to make the diagnostic criteria more usable in clinical practice.
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A RARE CAUSE OF MYELOPATHY DUE TO VENTRAL CORD HERNIATION

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Aim: To describe an uncommon cause of thoracic myelopathy due to ventral cord herniation.

Methods: A 52-year-old woman was referred for a 3-year history of slowly progressive gait unbalance, weakness, and fatigue with need of double crutches to walk, and lower limb altered sensation and pain. She complained of a recent worsening of the symptoms with urinary urge incontinency. Her past medical history included bipolar disorder and diabetes mellitus, both in actual good control, L4-L5 anterolisthesis, and bariatric surgery performed at the age of 51.

Results: Neurological examination showed severe paraparesis, proximal lower limbs weakness, mild spasticity, reduced light tough and nociceptive sensation below D7 level and altered vibratory sensation, lower limb hyperreflexia, and bilateral Babinski sign. Nerve conduction study showed normal motor nerve conduction of peroneal and tibial nerve, reduced amplitude of sural sensory nerve action potentials (3μV; n.v. >6μV), and mild chronic neurogenic changes in lower limb muscles at needle electromyography (EMG). Transcranial magnetic motor evoked potential showed normal latencies whereas somatosensorial evoked potentials were absent. Magnetic resonance imaging (MRI) showed focal anterior displacement of the spinal cord at D5 level with T2 hyperintensity consistent with idiopathic ventral cord herniation. Computed tomography scan (CT) showed integrity of the vertebral posterior wall. The patient underwent surgical reduction of the herniated spinal cord with artificial dural patch closure. The procedure was performed without complications. In the following next days, she reported partial recovery of sensation and strength of the lower limbs, urinary control, and gait. She was then admitted to a rehabilitation centre. At 3 months follow-up, she still complained of lower limb weakness and rigidity with requirement of double crutches to walk. Neither tactile sensation nor sphincteric function had clearly improved. Neurological examination was comparable to the first clinical presentation.

Conclusions: Ventral cord herniation is a rare cause of myelopathy due to the focal displacement of the thoracic cord through a dural defect [1]. Treatment is surgical and outcome strictly depend on early intervention [2]. Delayed diagnosis can lead to long-term disability.
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MILLER FISHER SYNDROME SUBTYPE DUE TO BARTONELLA INFECTION: A RARE VARIANT FOR A RARE ASSOCIATION

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Introduction: Miller Fisher syndrome (MFS) is a variant of Guillain Barrè syndrome (GBS), featured by the clinical triad of ophthalmoplegia, ataxia and areflexia. The absence of specific clinical features designates the incomplete MFS forms, as the Acute Ataxic Neuropathy (AAN), characterized by ataxia and areflexia, in absence of ocular symptoms.[1] Acquired acute polyradiculoneuritis have typically an autoimmune pathophysiology and a previous infectious disease could be often recognized. We described a patient affected by AAN due to Bartonella henselae, without clinical manifestations of cat-scratch disease. This association has not been previously described.

Case Presentation: A 30-year-old man was admitted to our department for the onset of rapidly worsening postural instability. His past medical history was unremarkable. Seven days before the onset of symptoms, he experienced a cat scratch following to a one-day fever. Neurological examination showed ataxic gait, severe dysmetria in the four limbs, distal loss of touch and pinprick sensation and generalized hyporeflexia. He was bedridden on the second day of hospitalization because of his instability. Brain and spinal cord MRI before and after contrast administration were normal. NCS showed only the bilateral absence of H-waves. CSF examination revealed a severe albumin-cytological dissociation (cells 0 /uL; protein 213 mg/dL - n.v. 9–46). CSF HSV type 1-2-6-8, HZV, CMV, EBV and serum anti-ganglioside antibodies resulted negative. A seroconversion for Bartonella henselae (IgG titer 1/40; IgM titer 1/80), highlighted a recent infection. A diagnosis of AAN as MFS subtype was hypothesized.2 Patient underwent treatment with intravenous immunoglobulin 0.4 g/kg/per day for five days. Four days after starting medication, he was just able to walk by himself and his sensory symptoms regressed. Patient did not need any specific antibiotic therapy for cat-scratch disease, because of the absence of generalized clinical symptoms.

Discussion and Conclusions: Several infective agents have been demonstrated as trigger of polyradiculoneuritis. The association between GBS

and Bartonella henselae infection was reported in only one case. [3] Likewise, we could hypothesize that the Bartonella henselae has induced a cross reaction towards peripheral nerve antigens triggering the inflammatory process also in MFS subtype. The association between Bartonella infection and AAN was not previously reported. Therefore, when a patient presents with acute onset of ataxia and a history of cat-scratch, clinicians should consider MFS as diagnostic hypothesis, in order to start rapidly the correct treatment.
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CASE REPORT: POST-COVID-19 VACCINE RECURRENCE OF GUILLAIN-BARRÉ SYNDROME (GBS) FOLLOWING AN ANTECEDENT PARA-INFECTIOUS COVID-19-RELATED GBS

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Objectives: We report on a unique combination of post-COVID-19 vaccine GBS that occurred months after a para-infectious COVID-19-related GBS.

Materials and Methods: A 57-year-old man was admitted to our Neurology Department with fever, arthromyalgia, and mixed neurological symptoms. Molecular test for SARS-CoV-2, CSF analysis, electrophysiological and serological studies were performed.

Results: Nasopharyngeal swab PCR for SARS-CoV-2 was positive, and COVID-19 pneumonia was diagnosed. The patient developed right-side seventh cranial nerve palsy, distal paresthesias in the four limbs, flaccid tetraparesis and autonomic dysfunction, with access to ICU care. CSF analysis (albuminocytological dissociation) and electrophysiological studies supported the diagnosis of GBS. GD1b IgM seropositivity was found. An IVIg course prompted almost complete recovery. Six months later, the patient received the first dose of Pfizer/BioNTech vaccine. Five days later, he developed feet hypoesthesia, distal lower limb weakness and ataxic gait. GBS diagnosis was confirmed by CSF and electrophysiological studies. Seropositivity for GM3/4, GD1a/b, GT1b IgM was detected. An IVIg course prompted complete recovery.

Discussion: Guillain–Barré syndrome (GBS) is an immune-mediated polyradiculoneuropathy that can have infectious episodes and vaccinations as triggers. The mass vaccination campaign against SARS-CoV-2 yielded several cases of post-COVID-19 vaccine GBS, which prompted the search for a possible causal link. This is difficult to demonstrate, as temporal association does not imply causation. However, an epidemiological investigation, calculating the observed-to-expected ratio of post-vaccine GBS, raised potential safety concern for GBS following receipt of Ad26.COV2.S COVID-19 vaccine. COVID-19 vaccination in patients with previous para-/post-COVID-19 GBS, especially whether they result seropositive for ganglioside antibodies, deserves reappraisal. In our patient, post-COVID-19 vaccine GBS was characterized by a so far never reported combination of IgM to GD1b and to other disialosyl gangliosides, which might reasonably be a result of molecular mimicry and hyper-stimulation of the immune system. Furthermore, anti-idiotype antibodies of the IgM class, might have contributed to autoimmune-mediated phenomena initiated with the SARS-CoV-2 infection, and reignited by the vaccine. Our case should be contextualized as an extremely rare event but warns about GBS recurrence after COVID-19 vaccination and suggests that seropositivity for ganglioside antibodies could be a marker of this risk in patients with antecedent SARS-CoV-2-associated GBS.

Conclusion: This case adds to other previously reported observations suggesting a possible causal link between SARS-CoV-2 and GBS. Molecular mimicry and anti-idiotype antibodies might be the underlying mechanisms. Future COVID-19 vaccinations/revaccinations in patients with previous para-/post-COVID-19 GBS, especially whether seropositive for ganglioside antibodies, deserves a reappraisal.
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LATE-ONSET RIBOFLAVIN-RESPONSIVE MULTIPLE ACYL-COA DEHYDROGENASE DEFICIENCY (MADD) MIMICKING POLYMYOSITIS: THE FIRST ITALIAN REPORT OF A NEW ETFDH GENE VARIANT

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Aims: We report a new electron transfer flavoprotein dehydrogenase (ETFDH) gene variant in a case of late onset-Multiple acyl CoA dehydrogenase deficiency (MADD) presenting as polymyositis.

Materials & Methods: To clarify diagnosis we performed biochemical tests on muscle and plasma samples, muscle magnetic resonance (MRI) and muscle biopsy while the genetic defect was detected by next generation sequencing (NGS) and the impact of mutation on ETFDH folding was evaluated using bioinformatic tools.

Results: A 44-years-old Italian male developed rapidly progressive fatigue, shortness of breath for long distances, myalgias and chewing difficulty in association with a relevant weight loss and a markedly increased of CPK (9 times normal). Neurological examination showed dropped head, lumbar hyperlordosis, anserine walking, mild hypotrophy of the gluteal muscles with hyposthenia at the level of the neck extensors (3.5/5), iliopsoas (4.5/5), gluteus maximus and hamstring (4/5), reduced tendon reflexes. Lower limb muscle MRI showed bilateral edematous imbibition of the semimembranous, hamstring, soleus and posterior tibial muscle. Overall, his first diagnosis was polymyositis and was treated with prednisone 65.5 mg reporting clinical, biochemical and MRI imaging benefit in particular his neurological exam and CPK returned to normal. However, his muscle biopsy, carried out before starting treatment, revealed hypotrofic fibers and degenerating fibers (50%) preferentially type 1, slight increase in perimysial connective tissue and optically empty vacuolizations (Black Sudan +) and complex IV (COX) activity slightly decreased without inflammatory infiltrate. Surprisingly the histological picture was not that of an inflammatory myopathy but a lipid storage

myopathy. In addition, plasma concentrations of both medium- and long-chain acylcarnitine were increased. So a NGS panel for lipid storage myopathy detected the homozygous missense mutation of ETFDH gene on chr.4: c.1204 A>G/p.Thr402Ala.

Discussion: MADD is a very rare disease (prevalence ~9/1,000,000) in particular as a late-onset form. We reported the first Italian case of c.1204 A > G mutation in ETFDH in adult patient. In addition, the clinical presentation of our patient, mimicking a polymyositis, was very tricking and the muscle biopsy was decisive for differential diagnosis. Our patient has progressively suspended prednisone and is currently being treated with Riboflavin 100 mg/die and CoQ10 200 mg/die with benefit.

Conclusion: Our case shows that the clinical spectrum of MADD is very wide, in particular in late onset forms, and that they can also mimic a polymyositis. Therefore, it is crucial be very careful to muscle biopsy findings to avoid diagnostic mistakes.

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UNUSUAL PRESENTATION OF PRIMARY CNS NON-HODGKIN'S LYMPHOMA: A CASE REPORT

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Primary CNS lymphoma (PCNSL) is a rare form of extranodal non-Hodgkin lymphoma (NHL) that is usually confined to brain, eyes, and cerebrospinal fluid without evidence of systemic spread. It has one of the worst prognoses among the subtypes of NHL. Biopsy is mandatory for an accurate diagnosis. CSF analysis and characteristic imaging features are helpful. More than 90% of PCNSLs are non-Hodgkin's diffuse large B-cell lymphomas (DLBCL); symptoms can be extremely heterogeneous and easily mistaken for other malignancies. A classic presentation is a butterfly pattern lesion crossing the corpus callosum. Deep brain lesions such as infiltrations of corpus callosum, basal ganglia, periventricular areas, brainstem, cerebellum and ependyma, are reported in less than 40% of patients.

Objective: The aim of this report is to present a clinical case of a man with a primary CNS lymphoma.

Materials and methods: An 81-year-old immunocompetent man came to our attention in an acute confusional state with hallucinations, psychomotor agitation alternating with drowsy states. Ependyma and the ventricular district showed contrast enhancement in MRI appearing to be the center of a infiltrating-type pathological process. No parenchymal nodular or diffuse lesions were described, and the execution of a stereotactic biopic examination was considered not easy to perform.

The first diagnostic hypothesis were encephalitis or inflammatory lesions. Analysis of the cerebrospinal fluid showed pleiocitosis without evidence of virus, bacterial or funginal infection. Cytological analysis did not show atypical or malignant cells and Bone Marrow Aspiration and Biopsy were non-diagnostic. This case was rapidly managed with low doses of corticosteroids, achieving an initial improvement of cognitive and behavioural symptoms. However, after a few weeks, the patient developed hypothalamic dysfunction, hypotension, central hypothyroidism, bradycardia, hyperglycemia, electrolyte abnormalities and chronic anemization, whose origin had not been well clarified despite invasive investigations. Several other diagnostic hypotheses were pursued, including atypical Lyme disease, histiocytosis, granulomatosis and Whipple disease. MRI imaging findings and CSF analysis appeared stable for two months. Lastly a larger periependimal nodular lesion appeared.

Results: Cerebral biopsy definitively confirmed the diagnosis, but the clinical status progressively got worse until death.

Conclusion: Clinical presentation of PCNSL consists of motor and sensory focal deficits, abnormalities in mental status and behavior, symptoms of increased intracranial pressure (headaches, nausea, vomiting, papilledema), seizures, and uveitis. Cognitive and behavioural symptoms of our case could be suggestive of the diagnosis, however diencephalic dysfunction, hypothalamic-pituitary axis involvement and isolated and diffuse ependymal localization are very unusual.

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EFFECTS OF KETOGENIC DIET IN CREUTZFELDT-JAKOB DISEASE: A CASE REPORT

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Objectives: Creutzfeldt-Jakob disease (CJD) is a prion disease that typically presents with rapidly progressive neurological manifestations such as cognitive impairment and myoclonus. Ketogenic diet (KD) is a high-fat nutritional treatment leading to an increased production of ketone bodies, which are used by the brain as an alternative energy source instead of glucose [1]. KD has been shown to be beneficial in multiple neurological diseases, including epilepsy and migraine [1]. Our objective was to administer KD to a patient with CJD as complementary treatment for dystonic and myoclonic movements, which were not controlled despite an association of haloperidol, clonazepam and levetiracetam.

Methods: A classic KD with a ketogenic ratio of 4:1 was administered via percutaneous gastrostomy. A hypercaloric diet was prescribed during the first five months due to previous weight loss, followed by a normocaloric diet. Clinical evaluations and periodic brain magnetic resonance imaging (MRI) studies were performed during a follow-up of ten months.

Results: After a few weeks from the beginning of the nutritional treatment, dystonic and myoclonic movements gradually reduced. After three months, only occasional isolated minor movements of the limbs, neck or jaw were noted. Haloperidol and clonazepam were gradually stopped and

their sedating adverse effects waned. The patient started to spontaneously open his eyes; improved awareness was noted, in form of slow and irregular voluntary gaze deviation towards the examiner and grimacing and vocalizations on cutaneous stimulation. After ten months of KD, the clinical amelioration remained stable. Longitudinal brain magnetic resonance imaging showed gradual reduction of areas of diffusion restriction and appearance of diffuse atrophy. No significant adverse effects were noted.

Discussion: KD improved the control of hyperkinetic movement disorders in our case of CJD. The efficacy of KD in controlling myoclonus and other hyperkinetic movement disorders is well described in glucose transporter 1 deficiency syndrome [2]. We previously examined the efficacy of KD in the management of myoclonus and other symptoms of subacute sclerosing panencephalitis [3]. However, its efficacy in other hyperkinetic movement disorders remains to be tested. The observed improvement allowed a reduction in pharmacologic load, that was accompanied by a sustained improvement in consciousness. Overall, the clinical course appeared to be milder than usual; further studies on KD in CJD are warranted to examine the complete spectrum of effects.

Conclusion: KD may represent a complementary treatment for CJD-associated hyperkinetic movement disorders such as dystonia and myoclonus, with an excellent safety profile.

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PARAINFECTIVE AND POST-VACCINE SARS-COV-2-RELATED MYELITIS: A CASE-BASED COMPARISON

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Introduction and objectives: Myelitis is a known parainfective complication of Covid-19 infection and can follow SARS-CoV-2 vaccination. Here, we present two of such cases comparing clinical, laboratory and radiological features.

Case 1: A 40-year-old male attended our Emergency Department (ED) with Covid-19 (day-9) infection with new onset urinary retention lower limb sensory-motor weakness and a T10 sensory level. Spinal MRI confirmed subacute thoracic myelitis (T3-T8) with heterogeneous contrast uptake for which high-dose steroids were started. Cerebrospinal fluid (CSF) on day 2 showed 16 leucocytes/microL (mostly polymorphonuclear). PCR for SARS-CoV-2 was still positive on serum but negative on CSF. Clinical deterioration continued to severe upper limbs weakness, paraplegia, a T3 sensory level and a weak cough reflex despite a 5-day course of immunoglobulins. Considering the progressive course and a negative COVID swab (day 5), 6 plasma exchange sessions were arranged. On day 27, CSF showed 1 leucocyte/microL with intrathecal IgG synthesis and no blood brain barrier (BBB) dysfunction and a repeat MRI confirmed progression of myelitis with involvement of cervical segments without contrast enhancement. Eventually, clinical stability was reached after infusion of cyclophosphamide on day 31.

Case 2: An 83-year-old man presented to the ED with new-onset left leg sensory-motor deficits associated with haematuria whilst on oral anticoagulants for atrial fibrillation (AF). He had received the 3rd vaccination against COVID-19 (mRNA-based) 3 days prior. Following initial discharge, he experienced urinary retention and progressive ascending weakness. Neurological examination after 3 weeks showed paraplegia, lower limbs areflexia, an extensor plantar response on the left, anesthesia below T5 and upper limbs weakness. MRI of the spine without contrast revealed altered signal in the cord from the bulbar to the thoracic levels and around the conus medullaris, compatible with diffuse myelitis. CSF showed a mild protein increase (67 mg/dL), type 2 oligoclonal bands and BBB dysfunction. A 5-day course of high dose IV methylprednisolone (1g) followed by a tapering regimen led to a good clinical response. Spinal MRI with contrast after 20 days confirmed improvements with intramedullary enhancement suggesting persistent barrier damage. The patient was eventually discharged after 32 days with residual paraparesis.
Discussion and conclusions: Our patient with parainfective myelitis showed no evidence of BBB dysfunction, little contrast uptake on MRI and a more severe clinical course refractory to several therapies. Conversely, the post-vaccination case exhibited a more inflammatory and benign phenotype suggesting specific disease-related mechanisms and pathogenesis could account for these differences.

ATYPICAL POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME WITH HEMISPHERIC, BRAINSTEM AND SPINAL CORD INVOLVEMENT IN A PATIENT WITH ACUTE KIDNEY INJURY – A CASE REPORT

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Objectives: Posterior reversible encephalopathy syndrome (PRES) is a disorder characterized by variable clinical presentation and MRI features consisting of vasogenic oedema in parieto-occipital regions [1]. The description of cases of atypical PRES has led to reconsidering such syndrome as a complex and multifaced clinical entity [2]. Herein, we provide clinical and radiological description of a patient affected by atypical PRES.

Materials: We describe a case of a 42-year-old man, smoker, with negative clinical history, except for sporadic headaches treated with NSAIDs. Due to an acute episode of headache, vertigo, and subsequent loss of consciousness, he presented to the emergency department where high blood pressure values where reported (240/110 mmhg). He was then admitted to our neurology ward.

Methods: The patient was alert and keenly responsive, with mild deficit of left abducens and facial nerves and a remarkable tendency to retropulsion during upright stance. Laboratory tests showed renal failure (Creatinine 3.8 mg/dL, Azotemia 101 mg/dL, Na 131 meq/l, K 2.8 meq/l) and low platelet count (110.000 mm3). Brain MRI showed remarkable hyperintensity in the T2/FLAIR sequences, likely corresponding to vasogenic edema, bilaterally involving centrum semiovale, periventricular white matter, internal and external capsules, thalami, optic chiasm, both vermis and cerebellar hemispheres, the whole brainstem and the spinal cord until C6 level. Hypointensities located in the basal ganglia and cerebellum were observed on susceptibility-weighted imaging, likely corresponding to microhemorrhages.

Results: The patient was treated with intravenous nitroglycerin infusion until blood pressure normalization. He underwent haemodyalitic treatment due to worsening of his kidney failure. Serologic level of ADAMTS-13 was tested negative. Abdomen ultrasonography showed symmetric, volumetric reduction of both kidneys. The brain MRI, executed at the normalization of kidney laboratory tests and pressure levels showed remarkable reduction of the T2-FLAIR hyperintensities with total resolution in the spinal cord together with millimetric areas of diffusion

restriction likely corresponding to cytotoxic oedema. After the placement of an artero-venous fistula the patient was discharged home in good clinical conditions.

Discussion: the patient was diagnosed with atypical PRES due to hypertension in the setting of acute kidney injury and improved both clinically and neuroradiologically after the removal of the offending cause.

Conclusions: While PRES is promptly recognized due to its typical imaging features, atypical and complicated PRES are uncommon and may constitute a diagnostic dilemma, especially when clinical history and examination are poorly suggestive [3]. Patients with atypical PRES, characterized by focal hemorrhages and diffusion restriction may have a poorer prognosis and should be readily recognized.

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DO NOT FORGET CLINICAL EXAMINATION! A CASE OF OPMD WITH NEUROGENIC PATTERN AT EMG MISDIAGNOSED FOR MND

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Background: Oculopharyngeal Muscular Dystrophy (OPMD) is a late-onset myopathy caused by the abnormal expansion of GCN repeats in exon 1 of the poly (A) binding protein, nuclear 1 (PABPN1) gene. As per other poliglutamine-expansions-related diseases, the length of GNC repeats influences the disease severity, the age of disease onset and the involvement of respiratory muscles. The main symptoms at disease onset are ptosis and ocular motor abnormalities, followed by the occurrence of dysphagia and lower proximal limb weakness, with only slightly increased creatine kinase levels. Electromyogram usually shows myopatic pattern, though a coexistence with peripheral neuropathy and the presence of neurogenic pattern at electromyogram are often reported. In the latter case, mainly when symptoms are incomplete or isolated, differential diagnosis with motor neuron diseases is more difficult. Here we describe a case of a patient with dysphagia and neurogenic pattern at electromyogram addressed to our Centre with the suspicion of a motor neuron disease.

Case Reports: The patient was a 70 years old female patient who reported difficult swallowing started a few years prior and progressively worsened in time. She also noticed the occurrence of cramps and a progressive hyposthenia in lower limbs that led to gait difficulties. Her mother suffered from a similar form of dysphagia and lower limbs hyposthenia as well, never better investigated. In time, she underwent several exams, including a fiber-optic endoscopic evaluation of swallowing showing a slowness in tongue mobility and an increased amount of food aspiration, a cerebral and spine MRI resulted normal, blood test with creatine kinase dosage resulted slightly increased (196U/l). An electromyogram showed a diffuse neurogenic pattern with no acute denervation. In the suspicion of a motor neuron disease, she was addressed to our Centre for Motor Neuron Diseases in Santa Chiara Hospital, Pisa, Italy. The neurological examination revealed nasal voice, an hyposthenia in orbicularis oris, slight hyposthenia in corrugator, hyposthenia in iliopsoas, no signs of upper motor neurons involvement excluding jerk and glabellar positivity. Interestingly, she did not present ptosis.

Considering the clinical picture and the family history, we performed a DNA test for oculopharyngeal muscular dystrophy. The exam showed heterozygous GNC triplets expansion, pointing to an autosomal dominant form of oculopharyngeal muscular dystrophy.

Discussion and conclusion: Our case underline the importance clinical evaluation, that remain the pivotal element in patient evaluation. When coupled with anamnesis, clinical evaluation can even outperform instrumental exams.

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WHY ALZHEIMER PROGRESSES SO SLOWLY IN SOME PATIENTS?

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Background: Alzheimer's disease (AD) progression is heterogeneous for various reasons including resilience, cognitive reserve and genetic characteristics, still partially understood. AD is often complicated by cerebral amyloid angiopathy (CAA) that adds another variance source. We describe the astonishing case of a man who became aware of his cognitive deficit 18 years ago and who is still in its mild cognitive impairment (MCI) stage.

Case report: An 82-year-old man with 13 education years and dementia familiarity came to first visit in 2004 reporting anomia and memory problems. ApoE genetic test was ε3/ε4, and all investigations, including brain perfusion SPECT, were normal. In 2012 brain MRI showed left hippocampal atrophy and FDG-PET highlighted moderate hypometabolism in left posterior cingulate and precuneus. CSF biomarkers (December 2012) and amyloid PET (December 2013) were consistent for AD. EEG was normal in 2004 but showed moderate theta activity in anterior regions. Neuropsychological tests were normal until 2019, when mild impairment of verbal memory was highlighted. In 2020 performance decreased in attention tests, selection and attentional shifting tasks and visuospatial research tasks (TMTA, TMTB, Stroop). The Grober-Buschke test was impaired in immediate free recall, delayed recall and recognition with poor cueing effect while logical memory test was borderline. Serial brain brain MRIs between September 2020 and May 2022 showed 4 new asymptomatic microbleeds and superficial siderosis in the left parietal area, standing for probable CAA. His last MMSE score (April 2022) was 26/30.

Discussion: SCI should not be underestimated, since can represent a prodromal disease phase that we are still unable to detect with currently available neuropsychological tests. Patients with SCI at higher risk to develop neurodegenerative diseases include those with subjective decrement in memory irrespective of function in other cognitive domains, onset of SCI within the past 5 years or at 60 years and older, concern associated with SCI, persistence of SCI over time, those seek of medical help and those show cognitive decline confirmed by an observer.

Conclusions: SCI with normal assessments requires adequate investigations and follow up to identify the underlying potential cause and

conversion to MCI, since SCI can be a first indicator of neurodegenerative diseases. However, it is important to make a proper differential diagnosis, since this condition can be physiologically experienced with increasing age and is often associated with more benign causes.
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NEW DIAGNOSIS OF DEMYELINATING DISORDERS IN THE SETTING OF MRNA COVID-19 VACCINE EXPOSURE: TWO CASE REPORTS

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Background: The COVID-19 vaccines have been shown to be remarkably safe and effective, but there are rare reports of presumed post-vaccination autoimmune phenomena, including neurologic conditions as demyelinating diseases. Multiple sclerosis (MS) with onset in the setting of acute SARS-CoV-2 virus infection has been reported, but there have been only few reports of newly diagnosed demyelinating diseases following exposure to mRNA COVID-19 vaccine.
Methods: We report clinical and MRI features of two individuals who received the Pfizer and Moderna SARS-CoV-2 mRNA vaccine and developed neurological symptoms few days and a month after immunization, respectively.

Results: Case 1: a 27-year-old man with type 1 diabetes was referred to our department for subacute onset of right brachio-crural tingling paresthesias. Neurological examination showed mild strength deficit highlighted by Mingazzini maneuvers, hyperevocable osteotendin reflexes in the lower limbs with anisoreflexia and hypopallesthesia. Brain MRI showed DP and FLAIR hyperintensities in the left semioval center, corona radiata and in the isthmic area of the corpus callosum, without contrast enhancement. CSF analysis showed elevated IgG index and k index as well as alteration of brain barrier index. The same number of oligoclonal bands was found in CSF and serum. Case 2: a 29-year-old man, without comorbidities, was referred to our department for subacute onset of daily left brachio-crural tingling paresthesias and subjective vertigo. Neurological examination showed impaired tandem gait, mild strength deficit evidenced by Mingazzini maneuvers, diffusely hyperevocable osteotendin reflexes with anisoreflexia, neutral response to right plantar stimulation, hypopallesthesia and occasional urinary retention. MRI showed 3 T2 hyperintense lesions in the right nucleocapsular area and in the retro-trigonal area on both sides. CSF analysis showed elevated IgG index and k index; numerous OCBs were reported only in CSF. According to the McDonald 2017 criteria, it was possible to confirm the diagnosis of multiple sclerosis only in the second patient.

Discussion: Clinical, laboratory, and radiological findings in these two patients confirm the presence of a demyelinating process in the CNS. The association of vaccination and onset of demyelinating disorders, whether causative or incidental, cannot be determined, also because the factors, as environmental triggers, governing onset of this kind of diseases is an area of active research, with still many unresolved questions.

Conclusions: Studies on larger samples are required to further investigate any possible relationship between COVID-19 vaccines and acute CNS demyelination.
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ACUTE/SUBACUTE ONSET OF ABDOMINAL MYOCLONUS SUBSEQUENT SPINAL CORD STIMULATION

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Objective: To describe a case of acute/subacute onset abdominal myoclonus (AM) subsequent the activation of spinal cord stimulator (SCS).
Material and methods: Report of a single case of AM and retrospective examination of medical charts.

Case presentation: A 78-year-old man was admitted for acute/subacute onset of AM. Patient was diagnosed with Parkinson's disease seven years before (at the time he was treated with pramipexole 1.05 mg/die) and had spinal surgery for severe spondylosis. Five and one year earlier he was respectively implanted with a spinal cord stimulator (SCS) (leads placed at T7 level) and an intrathecal morphine delivery system (providing 1.5 mg/die) because of a severe low back pain syndrome. At the time of the hospitalisation the AM was exaggerated in supine position and wasn't affected by sensory stimuli and distraction tasks. No further focal signs emerged besides mild parkinsonian syndrome. Video EEG polygraphy excluded focal epileptic activity. Spinal RX showed the correct leads placement. Patient was initially treated with gabapentin (up to 900 mg/die) and clonazepam (up to 2 mg/die) with no significant improvement (pramipexole wasn't suspended). Of relevance, during a recharge session of the SCS, AM presented a sudden increase in amplitude and intensity; on the other hand, the AM completely resolved in few minutes without reappearing in the successive six months turning-off the SCS.

Discussion: Myoclonus is defined as rapid, brief, irregular twitching of a muscle or a group of muscles. AM is a rare form of segmental myoclonus whose aetiology may include structural or functional lesions of the spinal cord causing abnormal rearrangement of the spinal circuitry.[1] Here, we can observed a direct time correlation between SCS recharge and AM worsening first, and then the complete resolution of AM after switching-off of the device.

Conclusions: This case indicates that AM can be secondary to SCS. Muscle spasms are a rare side effect of SCS implantation already reported in literature [2,3] and are probably due to the spinal anterior horn cells hyperexcitability.
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A NOVEL DELETION MUTATION (C.1177_1182DELGCTGAT) IN SPG9A IN A YOUNG MAN AFFECTED BY SPASTIC PARAPLEGIA

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Introduction: Hereditary spastic paraplegia (HSP) is a heterogeneous group of genetic neurodegenerative disorders characterized by progressive weakness and spasticity of lower limbs. SPG9A is a rare form of HSP due to mutations in ALDH18A1 gene, which encodes for delta-1-pyrroline-5-carboxylate synthase (P5CS) with both autosomal recessive and dominant transmission.

Case presentation: Here we describe the case of a 37 years old man who presented to our clinic in June 2019 referring during the last six months a progressive motor clumsiness of right leg. He also reported a tear to the right calf, a Baker cyst on the right and a sprain of the right ankle. No motor impairment at upper limb, no bulbar nor respiratory symptoms. These symptoms had a progressive evolution. In anamnesis only appendicectomy. Neurological examination showed a normal walking except for a light steppage on the right leg, a light hypotrophy and hyposthenia of the right leg, brisk reflexes on the right part of the body, right Achillean clonus, no Hoffmann nor Babinski signs, no urinary nor intestinal problems. He underwent: blood examination (resulted normal, no HIV, HTLV infections), electroneurography/electromyography study (resulted normal), brain MRI (normal), cervico-dorso-lumbo-sacral MRI (normal medulla, no radiculopathies nor discal hernia), cerebral PET (normal except for an hypometabolism of two orbito-frontal cortical area), motor evoked potentials at four limbs (resulted normal). On the basis of these examinations, we suspected a primary form of upper motor neuron disease. Therefore, we prescribed rehabilitation (with partial improvement of gait disturbances) and we executed a genetic examination in the suspect of a rare form of HSP. We observed a mutation in ALDH18A1 gene, which is the cause of a rare form of HSP (the SPG9A). In detail, the mutation we found (c.1177_1182delGCTGAT) is a novel deletion in ALDH18A1 gene, never described in literature. An in-silico evaluation demonstrated a pathogenic role of this mutation. The clinical features of our patients are superimposable to other cases of SPG9A.

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CEREBRAL INFLAMMATORY BIHEMISPHERIC REACTION TO FOREIGN BODY IN RECENT EMBOLIZATION OF ANEURYSM OF THE CEREBRAL ANTERIOR COMMUNICATING ARTERY: A CASE REPORT

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Case description: A 65years old woman underwent endovascular treatment of an anterior communicating aneurysm using flow diverting stents and coils, without any periprocedural complications. In the first day after the treatment, the patient developed fever and a transient mild right arm weakness. However, as CT scan, blood exams, blood cultures and urine cultures resulted normal, she was discharged. Eight days later the patient reported headaches and transient episodes of weakness in her right hand, and thus she was admitted to our department for additional evaluation. MRI demonstrated aneurismal wall enhancement and multiple enhancing lesions surrounded by edema, mainly in the left cerebral hemisphere. Most of the lesions showed magnetic susceptibility foci and some of them had diffusion restriction. We considered three possible alternative diagnoses: vasculitic process, infectious-inflammatory process and multifocal foreign body reaction. Laboratory studies, transoesophageal echocardiography and a lumbar puncture all resulted normal. The brain MRI performed ten days later showed an increase in number and size of the enhancing lesions, with more extensive edema. At the same time clinical conditions were stable. The imaging finding and clinical course supported the hypothesis of a multifocal foreign body reaction. The patient underwent empiric steroid treatment obtaining clinical and imaging improvement. The three months follow-up MRI demonstrated a remarkable decrease in number and size of enhancing lesions. However, magnetic susceptibility foci were unchanged and aneurismal wall enhancement was still evident. Surveillance is ongoing.

Discussion: Although not confirmed with biopsy and histopathology, clinical and imaging evidence suggest that the patient probably experienced a foreign body reaction to hydrophilic polymer emboli from endovascular procedural equipment. Intracranial embolic foreign-body reactions are uncommon complications of interventional neuroradiology procedures, due to the separation of the polymer coat during the procedure [1,2]. Cerebral polymer complications manifest through distinct patterns of injury, including embolic phenomena, inflammatory reactions and arterial pathologies. The range of clinical manifestations can be very wide, from asymptomatic to coma and death, as documented in some cases [1,2]. MRI imaging pattern of multiple enhancing lesions with magnetic susceptibility foci and surrounding edema in the vascular territory of an index lesion, is highly characteristic, although the confirmation requires histological examination [1,2,3]. The optimal treatment has not been determined yet, although effective steroid treatment was reported in several case reports [2].

Conclusions: It is important to consider the risk of iatrogenic embolization of polymer coatings in the workup of patients presenting with newly onset symptoms after a percutaneous intravascular procedure.

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CEREBRAL VENOUS GAS EMBOLISM IN PATIENT WITH MASSIVE BLOODPNEUMOTHORAX: A CASE REPORT

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Case description: A 28 year old man with no relevant medical history was admitted to our ER for an episode of loss of consciousness with epigastric pain. A chest CT scan showed left massive hydropneumothorax with the presence of an arterial blush of the left thyrocervical trunk. After the initial positioning of a chest drainage and the intravascular embolization of the arterial blush, he underwent an emergency surgical intervention. Two chest drainage and a CVC were positioned. About two weeks after the admission, he had a sick episode with loss of consciousness. The CVC appeared open. The clinical neurological examination showed a watchful but confused patient, with difficulties in following orders and a poor and fragmented verbal fluency; bilateral visual deficit with major difficulties in movements towards left side, and weakness of the upper left limb were present. A CT brain scan resulted compatible with venous retrograde cerebral gas embolism, whereas the MRI resulted normal. The same day he was transferred to the Stroke Unit and he immediately began three sessions of hyperbaric therapy. He received hyperbaric oxygen therapy within 4 h after the occurrence of air embolism. After these sessions the CT brain control scan and the MRI resulted both normal and the neurologic clinical evaluation came back to complete normality. We therefore hypothesize that in this patient air was aspirated through the partially disconnected CV catheter, then subsequently flowed back into the cerebral venous system due to increased intrathoracic pressure.

Discussion: Cerebral venous gas embolism occurs when gas enters the cerebral venous circulation. Usually, this situation is due to procedures related errors (iatrogenic), especially from management of CVC [2]. Although it remains a rare consequence, it is potentially fatal and yet little considered in differential diagnosis of ischemic stroke in patients carrying CVC [3]. Clinical features include sudden-onset focal neurological sign, coma, epileptic seizures and encephalopathy [2]. Imaging features revealed intracranial air bubbles and cerebral ischemia or edema [2,3]. Treatment is not yet standardized, but the use of hyperbaric oxygen to assist a faster resolution of air bubbles is deemed to be pivotal [1,2].

Conclusion: Cerebral venous gas embolism is a potentially catastrophic, though uncommon, event. Radiologists and other physicians should maintain a high level of suspicion for air emboli in patients carrying CVC. A prompt recognition and a rapid advanced management, including hyperbaric oxygen therapy, are essential to ensure the best outcome for the patient.

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A CASE OF NON–ALCOHOL-RELATED WERNICKE'S ENCEPHALOPATHY

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We present a case of a 56-year-old woman admitted to the neurology department for having developed subacutely progressive strength deficit in the 4 limbs and diffuse pain, convergent squint in the left eye, confabulations and impaired state of consciousness up to compromised state of consciousness to the point of somnolence. From the anamnestic collection with the patient's sister emerged in 2002 gastric band surgery for obesity, in 2008 esophagectomy, gastrectomy, duodenostomy and jejunostomy with subsequent retrosternal plastic esophagus-colon-jejunal surgery following gastrointestinal necrosis from ingestion of muriatic acid in a suicide attempt. Approximately two weeks before coming to our attention, the patient entered the emergency room of another hospital because of multiple diarrheal discharges and was found to have severe Vit B12 deficiency and intestinal coprostasis for which she had started supplementation therapy. On neurologic examination, she presented deviated head to the right, closed eyes, divergent squint in right eye, absent speech, flaccid tetraparesis. MRI brain showed T2 FLAIR signal hyperintensity involving the dorsal portion of the bulb, the floor of IV ventricle, the periaqueductal gray matter, the medial portion of the thalamus, the mammillary bodies, the cranial portion of the cerebellar worm, the lower portion of the right cerebellar hemisphere and the cerebral cortex of the bilateral frontal convexity. EEG showed generalized nonspecific suffering. She started vitamin B1 supplementation first i.v. and then i.m. Due to the severe impairment of the clinical picture, the patient was finally transferred to the Hospice.

Conclusions: Wernicke's encephalopathy (WE)is a neurologic emergency. In 1997, Caine et al. suggested that a diagnosis of WE can be made if two of the four criteria are satisfied: eye signs, cerebellar signs, memory impairment, laboratory data of malnutrition [1]. Non-alcoholic WE can have an atypical clinical presentation and is often missed. While alcohol abuse remains the most common precipitating factor, non-alcoholic aetiologies include starvation, hyperemesis gravidarum, IV infusion of glucose before thiamine, prolonged chemotherapy, dialysis, anorexia nervosa, refeeding syndrome and gastrointestinal surgery [2]. The anamnestic collection, clinical presentation and typical magnetic resonance imaging (MRI) findings allowed us to make the correct diagnosis. The clinical case invites us to reflect on the subtle presentation of vitamin deficiencies and therefore requires attention from the clinician to set up adequate nutritional supplements for patients undergoing gastric demolition surgery, since, as in the case of our patient, even a single episode of profuse diarrhea can precipitate a severe latent deficiency state.

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AN UNUSUAL CASE OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

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We present below the case of an 85-year-old woman previously admitted on 04/03/2022 to the neurology department of another hospital for deviated oral rim and mild stenic deficit in the left hemisoma. Anamnesis included arterial hypertension, left breast K in 2017 in follow-up and anastrozole therapy, chronic lymphocytic leukemia (CLL). On this occasion she performed serial checks with skull CT showing subacute right frontotemporal ischemic lesion, stable at various controls, also confirmed with brain MRI. On 21/04 the patient was transferred to a neurofunctional rehabilitation clinic. Due to progressive worsening of the clinical picture, not explained with the previous diagnosis of acute ischemic event, she was transferred to our neurology department on 4/05.

On neurological evaluation: sleepy patient, who can be awakened on call, tends not to explore the left hemifield, hemiplegic left upper limb. Squeezes the right hand on demand. Flexes the right lower limb on the bed. She was subjected to blood chemistry tests not indicative of metabolic alterations and ongoing infectious state. MRI of the brain with gadolinium showed: signal alteration involving the superficial and deep white matter regions of the right cerebral hemisphere, the cerebral peduncle and the right hemi mesencephalon, following the ipsilateral corticospinal fascia. It extends contralaterally through the corpus callosum to invade the contralateral fronto-parietal periventricular white matter. It has no contrast enhancement after gadolinium. In relation to the clinical and neuroimaging picture, a collegial discussion was carried out with a neuroradiologist, hematologist and neurosurgeon, evaluating different diagnostic hypotheses: amyloid angiopathy with related inflammation/vasculitis, cerebral lymphoma and progressive multifocal leukoencephalopathy (PML).

Cerebrospinal fluid (CSF) presented: few mononuclear elements with a prevalence of T lymphocytes, not B lymphocytes at immunofluorescence. Presence of some small, monomorphic lymphoid elements, cytological examination. A search for the presence of John Cunningham virus (JCV) was also carried out on liquor which was positive. The HIV-1/2 antibody test gave negative results. During the hospitalization the patient presented a progressive worsening of the neurological conditions and in relation to the unfavorable prognosis the patient is moved to the hospice.

Conclusions: PML is a rare opportunistic infection of the central nervous system caused by JCV, a polyomavirus [1]. It primarily occurs in patients with immune deficiency such as HIV infection, malignancies or immunosuppressive [2]. Our patient had a history of breast carcinoma and CLL, both conditions responsible for chronic state of immune suppression, probably considerable the cause of viral reactivation.

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FIRST DESCRIPTION OF LINGUAL FOCAL MOTOR STATUS EPILEPTICUS DUE TO ISCHEMIC STROKE

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Objectives: Focal motor status epilepticus (SE) involving one half of the tongue is exceptionally rare, diagnostically challenging, and so far never described in the context of an acute stroke. We describe a case of lingual SE due to ischemic stroke, providing suggestions for diagnostic workup.

Methods: Case report.

Results: A 82-year-old man was admitted for sudden onset of right hemiparesis and motor aphasia due to acute ischemic stroke. His medical history was significant for arterial hypertension, hypercholesterolemia, hypothyroidism; he was taking warfarin for prior pulmonary embolism. Neither systemic thrombolysis (high INR values) nor thrombectomy (no large vessel occlusion on cerebral angio-CT) were performed. Three days later, he presented with subcontinuous clonic movements affecting the right side of the tongue, without palatal tremor or impaired awareness. The video-EEG showed massive muscle artifacts, without epileptiform abnormalities, rhythmic patterns or focal slowings; the brain MRI showed left frontal ischaemia. Levetiracetam 500 mg X 2 was administered orally with cessation of the SE.

Discussion: Lingual SE is extremely rare and so far never described as a consequence of a stroke. It reflects the activation of the cortical tongue representation in the contralateral primary motor cortex (epileptogenic zone). In this condition, clonic movements are not usually associated with a clear ictal pattern in the EEG. In our case, the semeiology and response to levetiracetam supported the diagnosis of SE.

Conclusions: Although exceptionally rare, clinicians should be aware of lingual SE. Semiology, correlation with neuroimaging, video-EEG (although not usually informative due to the absence of EEG abnormalities and the marked muscle artifacts) and ex juvantibus therapy with antiseizure medications should be carefully considered to differentiate this conditions from non-epileptic lingual myoclonus due to brainstem lesions (symptomatic myoclonus) or without an identifiable cause (essential myoclonus). Interpretation within the clinical context is mandatory to reach the diagnosis.

IT´S NOT MINE!": FIRST DESCRIPTION OF NON-CONVULSIVE STATUS EPILEPTICUS MANIFESTING WITH SOMATOPARAPHRENIA

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Purpose: Somatoparaphrenia is a delusion characterized by the denial of ownership for a limb or an entire side of body. It is associated with lesions in the right hemisphere, and often accompanied by left-sided paralysis and anosognosia. We describe a case of non-convulsive status epilepticus (NCSE) presenting with somatoparaphrenia. No prior case of somatoparaphrenia in SE has been reported.

Methods: Case report.

Results: A 86-year-old, right-handed woman presented with clonic movements in her left upper limb and half of the face, with head and eyes deviation towards the left. Her medical history was significant for previous ischemic stroke in the right middle-cerebral artery territory; arterial hypertension; previous breast and ovarian cancers. The symptoms ceased following intravenous administration of benzodiazepines. The CT (repeated after 48 hours) showed no acute ischemic lesions. After three days, the patient had mirror hand movements with grasping reflex on the left hand; strength and language were normal, without motor phenomena suggesting seizures. Results of head CT were comparable with prior examinations, whereas the perfusion-CT showed right-sided fronto-temporal hyperperfusion (increased regional cerebral-blood volume). The patient was unable to recognize the left arm as her own (instead, she consistently attributed it to the visiting physician), without concomitant paralysis or anosognosia. The EEG showed a pattern of epileptiform discharges on right centro-temporal regions, compatible with NCSE. Diazepam, valproate and lacosamide were unable to control SE. The patient became rapidly unresponsive and vital parameters deteriorated until death.

Discussion: The most striking symptom of NCSE in this patient was the delusional belief that the left arm did not belong to her. Clinical, neurophysiological and neuroimaging data point to symptoms arising from a right (non-dominant hemisphere) fronto-parietal epileptogenic zone.

Conclusions: Although extremely rare, even more as an epileptic symptom, somatoparaphrenia should be promptly recognized for its localizing value.

WHEN TOO MUCH BLOOD HURTS. FOCAL HYPEREMIA AND NEURONAL DYSFUNCTION ASSESSED BY MRI AND EEG IN SPORADIC HEMIPLEGIC MIGRAINE

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Objectives: Migraine with aura represents a primary neuronal event reflecting cortical spreading depression, a propagating wave of

depolarization associated with profound vascular changes. In several case reports of prolonged hemiplegic migraine, a focal hyperperfusion has been demonstrated in the brain regions corresponding to persistent aura. We discuss the paradox of a neuronal dysfunction associated with an excessive blood supply to the brain, presenting the vascular and EEG findings encountered in hemiplegic migraine and focusing on the neuro-vascular uncoupling occurring in the brain regions corresponding to prolonged aura.

Materials and methods: Case report.

Results: A 17-year-old girl with sporadic hemiplegic migraine where focal hyperemia was associated with clinical and EEG features indicative of a severe neuronal dysfunction. A first EEG performed when the patient had expressive aphasia and mild right arm weakness associated with severe left headache and vomiting showed continuous high-amplitude delta waves over the left cerebral hemisphere without epileptiform discharges. CSF was normal. MRI was unremarkable, but angio-MRI showed prominence of the branches of the left middle cerebral artery. She received prednisone 50 mg with dramatic improvement. A second EEG, performed when neurological deficits were milder, showed an amplitude reduction of the delta activity admixed with some theta waves over the left cerebral hemisphere. A subsequent standard EEG performed after a complete recovery occurred was unremarkable. A prophylactic treatment with topiramate was started.

Discussion: In our patient, the EEG findings indicative of a severe neuronal impairment associated with focal hyperemia affecting the same cerebral regions suggest that a paradoxical neuro-vascular uncoupling underlies prolonged aura. Our case confirms previous reports of focal hyperperfusion associated with persistent aura described in familial or sporadic hemiplegic migraine, despite persistent neuronal suppression in the affected brain regions. The same neurological deficit and EEG activity encountered in hemiplegic migraine occur following an ischemic stroke, hence in a condition characterized by reduced blood supply to the brain. However, in hemiplegic migraine the neuronal impairment, manifesting with the neurological deficits and slow EEG activity, is associated with focal hyperemia, suggesting a disruption of neuro-vascular coupling in the brain regions corresponding to prolonged aura.

Conclusions: In hemiplegic migraine the neuronal deficits and EEG abnormalities suggest an underlying neuronal dysfunction with functional impairment ("loss-of-function"), rather than in terms of cortical hyperexcitability. Hemiplegic migraine may be considered a vascular disorder where neuronal dysfunction is paradoxically associated with an excessive blood supply to the brain.

AARS2-RELATED LEUKOENCEPHALOPATHY WITH A PSYCHIATRIC PHENOTYPE

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Aim: To describe a patient with long-lasting neuropsychiatric disturbances, leukodystrophy and biallelic variants in the AARS2 gene.

Patient and Methods: A 68-year-old man came to our Memory Clinic because of progressive loss of autonomy in the activities of daily living and severe apathy. He had been under psychiatric follow-up for the last four decades for neuropsychiatric symptoms, namely progressive social avoidance and obsessive-compulsive behavior. He had no significant family medical history. He underwent clinical, laboratory, imaging, and molecular studies as an inpatient.

Results: At clinical evaluation, a slight wide-base gait was observed, with an otherwise unremarkable neurological examination. A thorough neuropsychological testing did not reveal any memory deficits, with a Mini-Mental State Examination score amounting to 29/30, while it unmasked a severe dysexecutive syndrome. CSF analysis showed normal cell count and protein levels; beta-amyloid and both total and phosphorylated tau levels were within normal range. A brain MRI showed extensive, symmetric, subcortical and periventricular frontal white matter abnormalities, with slight ventricular system enlargement and marked thinning of the corpus callosum, consistent with leukodystrophy features. No contrast enhancement was found. Blood biochemistry was normal, including serum arylsulfatase-A activity. Nerve conduction studies showed no abnormalities. A multigene panel for leukodystrophies unveiled the heterozygous genomic variants c.595C>T and c.2073_2075delTGA in the AARS2 gene, resulting at protein level in the aminoacidic change p.Arg199Cys and the deletion of Aspartate in position 691, respectively.

Discussion: Biallelic pathogenic variants of AARS2 may be associated to infantile cardiomyopathy, hereditary diffuse leukoencephalopathy (MIM_615889) and combined defect of oxidative phosphorylation (MIM_614096), with an autosomal recessive inheritance. The p.Arg199Cys missense mutation in AARS2 is present in the scientific databases and has been clearly described as pathogenic [1]. The p.Asp691del variant has not been identified before, and can therefore be considered as a variant of unknown significance. Segregation studies of this variant in the family were not possible, since the parents of the patient were not alive. However, the clinical and brain imaging findings in this patient, together with molecular results are suggestive of an AARS2-related leukoencephalopathy.

Conclusion: This case supports and extends previous findings that adult-onset AARS2-related disorders may present and progress for years with apparently "pure" psychiatric symptoms [2] and shows that a long survival is possible for those affected by this disease. Further studies should confirm the pathogenic role of the c.2073_2075delTGA variant.

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ORTOSTATHIC HEADACHE ASSOCIATED WITH DEEP BRAIN SWELLING AS A NEUROLOGICAL MANIFESTATION OF MARFAN'S SYNDROME: A CASE REPORT

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Introduction: Spontaneous intracranial hypotension (SIH) is an uncommon condition diagnosed in patients with orthostatic headache. The causative factor of SIH is a spontaneous loss of CSF at the spinal level caused by tears in the dura. Weakness of the dura associated with hereditary connective tissue disease is recognized to be a predisposing factor to dura laceration and subsequent CSF leakage. Marfan's syndrome (MaS) is a rare inherited disease characterized by connective tissue laxity. Spinal dura ectasia is indeed very common in patients with MaS and represents a major diagnostic criterion. In patients with SIH, however, the association with MaS is rarely reported in the literature. We describe here a young patient with positional orthostatic headache attributed to SIH as an initial presentation of MaS.

Case presentation: A 19-year-old male had a severe orthostatic positional headache for 2 years. The headache often appeared in the second half of the

day and when he sat down and bent his head to read or coughed. He had also noticed that the headache improved in the supine position. The neurological examination was normal, but a careful physical evaluation and systemic paraclinical examinations confirmed the presence of the typical alterations of MaS. The family history was positive, in fact the mother had clinical features similar to her son and had ectopia lentis. Brain MRI showed the presence of deep brain swelling and a diffuse pachymeningeal enhancement. A total spine MRI revealed the presence of multiple radicular cysts and voluminous dilatation of the lumbosacral dural sac. An MR myelogram showed a possible CSF leak at the dorsal-lumbar level. The patient underwent a nontargeted large-volume epidural lumbar blood patch, which produced an almost complete disappearance of the orthostatic headache. The patient was also referred for an adequate therapeutic evaluation of MaS.

Conclusions: This observation, although on a single patient, indicates that SIH may be the initial presentation of MaS in young patients, and suggests the importance of a general evaluation of young patients with SIH in clinical practice.

PAROXYSMAL ASYSTOLE WITH SYNCOPE MISDIAGNOSED AS EPILEPSY IN A PATIENT WITH TECTAL GLIOMA AND HYDROCEPHALUS

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Aims: Transient loss of consciousness (TLOC) is a major cause of diagnostic challenge in medicine; seizures, syncope and psychogenic non-epileptic seizures are the most common aetiologies [1]. Misdiagnosis rates as high as 30% have been reported for epilepsy, with relevant morbidity implications [1].

Material: A 35-year-old man came to our attention with a family history of arrythmia (the father had a pacemaker). In 2015, he received the diagnosis a glioma of the quadrigeminal lamina associated with triventricular non-communicating hydrocephalus, and he underwent endoscopic third ventriculostomy. In the past year, he had several stereotyped events beginning with a feeling of general discomfort and nausea followed by loss of consciousness, falling and stiffening of the 4 limbs, which recurred monthly and lasted about 30 seconds with rapid recovery. A diagnosis of epilepsy was made. He was put on levetiracetam 3.0 g/day and then lacosamide 300 mg/day without benefit.

Results: Neurologic examination and blood tests were normal. Prolonged EEG/ECG monitoring captured a typical event with initial feeling of sickness, nausea and fainting followed by TLOC of 20 seconds, generalized limb stiffening and rapid recovery without confusion. Ictal EKG showed initial bradycardia progressing to sinus arrest lasting 25 seconds, followed by rhythm resumption with sinus tachycardia. Ictal EEG showed the slow-flat-slow electrical pattern of syncope [2]. Lacosamide was immediately withdrawn, and a dual-chamber pacemaker was implanted. In the following three months no event has occurred.

Discussion: Syncope may often be accompanied by gross bilateral motor manifestations, such as limb jerks and stiffening, raising diagnostic confusion with seizures among witnesses and even trained physicians [3]. Misdiagnosis is especially dangerous considering the potential worsening effect of some anti-seizure medications on syncope [3]. In our case TLOC associated with bilateral motor-phenomena and a history of brain tumor led to a misdiagnosis of epilepsy, with potentially dangerous therapy; the absolute lack of treatment response and post-ictal confusion, indeed, prompted a diagnostic re-challenge with life-saving implications. Given the familial history of arrythmia, the associated brain-disease is seemingly incidental, and this further reinforces the cardinal role of a detailed clinical history with careful symptom-evaluation for a correct TLOC assessment, with avoidance of potentially fatal outcomes [1,3].

Conclusions: Our case reinforces the difficulty that exists in diagnosing seizure and syncope and emphasizes the need to consider cardiac causes in patients with drug- resistant epilepsy. It also highlights the unbearable EEG and ECG co-registration contribution to an accurate differential diagnosis of TLOC.

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CLIPPERS: A CHALLENGING DIAGNOSIS AND A POSSIBLE PRECURSOR OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Objective: Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is an inflammatory Central Nervous System (CNS) disorder with suspected autoimmune aetiology, predominantly involving the brainstem with a characteristic magnetic resonance imaging (MRI) appearance and clinical and radiological responsiveness to steroid therapy. Other immune-mediated, infectious and malignant causes could represent CLIPPERS-mimics up to 31% of cases, where primary CNS lymphoma represents the largest subset. Whether primary CNS lymphoma represents a CLIPPERS mimic or an early phase of CNS lymphomatoid neoplastic transformation remains subject of ongoing discussion.

Material and method: A 73-year-old man came to our attention for subacute onset of cerebellar ataxia, horizontal nystagmus on sideways look, worse on the right, diplopia on the left. Brain MRI showed punctate homogeneously enhancing lesions in the pons and cerebellum suspected for CLIPPERS. A complete diagnostic work-up, including searching for autoimmune, neurovascular and infectious diseases excluded other possible aetiologies. A total body CT scan was negative for malignancies. Treatment with high dose intravenous methylprednisolone was started, with marked clinical improvement. Then the patient was discharged home with oral prednisolone and methotrexate.

Results: 2 months after discharge the patient had clinical worsening during steroid tapering, so he was admitted again to our Unit. Brain MRI revealed increasement of contrast enhancing lesions in the brainstem, cerebellum and cervical spine. A new total body CT scan didn't evidence neoplastic lesions. FDG PET showed an hypermetabolic area at the cardia level, while subsequent gastroscopy revealed esophagitis without lesions susceptible for biopsy. Another cycle with high dose steroids, followed by an oral prednisolone taper and addition of cyclophosphamide, moved to clinical improvement until discharge.

Discussion: CLIPPERS is a recently defined autoimmune condition, whose diagnostic biomarkers and therapy guidelines are still missing. Other immune-mediated, infectious and malignant causes could mimic CLIPPERS MRI presentations, so a careful diagnosis and follow up is warranted. Relapses under sufficient immunosuppressive treatment may serve as an early indicator for CLIPPERS-mimics, especially for haematological malignancies.

Conclusion: A close clinical and radiological follow-up should be mandated in patient initially diagnosed as CLIPPERS, even if complete remission is accomplished, as most cases of primary CNS lymphoma occur within 2 years. Future studies are needed to clarify CLIPPERS biomarkers, therapy and optimal follow up.

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CASE SERIES OF ANTI-MYELIN OLIGODENDROCYTE GLYCOPROTEIN SERUM POSITIVITY: IS THE CULPRIT THE INFECTION OR THE AUTOIMMUNE ATTACK?

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Myelin oligodendrocyte glycoprotein-associated disease (MOG-AD) is an antibody-mediated inflammatory demyelinating disorder of the central nervous system also reported in the setting of several infections. Difficult may be, in such cases, to rule out simple association of the infection and myelitis instead of causation. We report two cases of MOG-AD following infectious episodes. Fluorescence-activated cell sorting was used for a quantitative detection of serum MOG-IgG (sMOG-IgG). Diagnostic workup included brain and spinal cord magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and a complete serological evaluation for the most common virus and bacteria. The first patient was a 27-year-old woman with unremarkable medical history, admitted to emergency department for progressive urinary retention and ascending paraparesis. She reported tick exposure one month before the beginning of neurological symptoms. Febrile status (38,2°C) occurred after two days of hospitalization. Brain and spinal cord MRI identified a cervico-dorsal longitudinally extensive transverse myelitis with no brain lesions. CSF analysis revealed a marked pleocytosis with polymorphonuclear predominance and intrathecal oligoclonal IgG. Serum and CSF samples were found to be IgM positive for Borrelia Burgdorferi, as confirmed by Western blot. The patient was treated with ceftriaxone (4g/day for 21 day). High-titer positive MOG-IgG were found, therefore intravenous methylprednisolone (ivMP) 1g/day for 5 days was administered, followed by every other day plasma exchange with clinical and radiological improvement. A year after, progressive SMOG-IgG negativity and complete clinical-radiological recovery were achieved and no further episodes occurred. The second patient was a 42-year-old man with history of hypertension and hypercholesterolemia, hospitalized for acute urinary retention followed by dizziness and horizontal diplopia. He reported a mild febrile status (37,8 °C) five days before the clinical onset. Brain and spinal cord MRI identified multiple T2-hyperintense lesions (supra- and subtentorial) with mild restricted diffusion suggestive for encephalomyelitis. CSF analysis showed intrathecal oligoclonal IgG. Other laboratory tests were unremarkable except for MOG-positivity. High dose ivMP was administered and clinical-radiological recovery was achieved except for persistence of mild urinary retention. Four months after the clinical episode, a decrease in sMOG-IgG titer was detected. According to medical history and microbiological results, we considered the first case as a para-infectious MOG-Ab mediated autoimmune attack and second case as a MOG-AD. The clinical overlap between post-infectious inflammatory syndromes and primary inflammatory demyelinating diseases is significant, and careful analysis is highly recommended to shape the appropriate management. Longitudinal clinical and sierological follow-up could clarify the etiology of the disease.

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CHOREA ASSOCIATED WITH JAK2V617F-POSITIVE ESSENTIAL THROMBOCYTHEMIA: A CASE REPORT

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Objective: The variant JAK2V617F is the most common somatic mutation associated with myeloproliferative disorders, such as polycythemia vera, essential thrombocythemia and primary myelofibrosis. While Chorea is a well-known neurological complication of polycythemia vera, to date, only two cases of chorea associated with JAK2V617F-positive essential thrombocythemia have been described. In addition, its pathophysiology remains unclear. We report a case of JAK2V617F-positive essential thrombocythemia- associated chorea.

Materials and Methods (case description): A 61-year-old woman was admitted to our department with a three-months history of slowly progressive chorea involving oromandibular district, left upper limb and ipsilateral foot and toes. Five years before, the patient was diagnosed with JAK2V617F-mutation essential thrombocythemia. She was treated with hydroxyurea 500 mg OD. Of interest, this treatment was interrupted right before the neurological symptoms onset. At the admission, blood cell count showed platelet 816×10^3/μL, brain MRI showed chronic vascular infarction in the right caudate nucleus, with no evidence of acute lesions. Hydrossyurea was reintroduced increasing the dosage up to 1000 mg OD, together with tetrabenazine, 12.5 mg twice daily, with clinical improvement. At follow-up, nine months later, her neurological examination was substantially improved, and platelet count normalized.

Results: Autoantibodies panel including ENA, ANA, ANCA, RF, anti-gliadin, anti-cardiolipin antibodies, anti-beta-2-glycoprotein and lupus anticoagulant resulted negative. EEG detected slow-wave activity of non-specific meaning. Brain MRI showed right caudate nucleus ischemic chronic lesion. Genetic testing for Huntington disease was negative.

Discussion: Current literature suggests that hyperviscosity and venous stasis may alter metabolic turnover of neurotransmitters in the basal ganglia, (i.e., dopamine and serotonin) thereby causing adaptive changes in local receptor expression. In our case, we hypothesize that withdrawal of hydroxyurea determined the increase in platelet count, blood viscosity and the consequent caudate infarction. However, the subacute presentation of chorea, its gradual progression, together with the impossibility to establish a temporal correlation with the ischemic lesion, rather suggest a re-arrangement at circuit level, causing the symptom onset.

Conclusions: To conclude, growing data support that chorea is a rare complication of JAK2V617F-myeloproliferative disorders including essential thrombocythemia. Although pathophysiological mechanisms are not clearly understood, the re-arrangement in the basal ganglia receptor expression, triggered by hyperviscosity, seems to play a central role.

OROFACIAL MOVEMENT DISORDER CAUSED BY PRAMIPEXOLE ABUSE

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Orofacial movement disorders (OMD) are a group of hyperkinetic extrapyramidal movements presenting dysfunctional activities on the masticatory, facial mimic, or tongue musculatures. The most common cause of acquired OMD is drug-induced dyskinesias. Our report describes a rare case of pramipexole-induced OMD in a patient with restless legs syndrome. Here we report a case of acute OMD caused by chronic DA abuse in a non-Parkinson's disease (PD) patient under treatment with pramipexole for restless legs syndrome (RLS). A 72 y.o. woman was admitted to the emergency room for the appearance, during the last week, of intermittent, involuntary muscle contractions, causing repetitive eye movements, grimacing, pursing of the mouth and lips, and writhing of the tongue with stereotyped vocalizations and sustained neck dystonia. Neurological examination otherwise normal. Her medical history included RLS, low back pain, diabetes mellitus type 2, surgical removal of a foot acral melanoma with inguinal lymphadenectomy. Her medical therapy consisted of metformin 1000 mg daily, tapentadol 150-200 mg daily, and pramipexole prescribed at a 0.18 mg daily dose to control RLS, but arbitrarily taken at 0.9 mg daily dose for 2 months, due to a self-assessed lack of efficacy. No past or current exposure to other relevant drugs was reported. The patient underwent a Computed Tomography scan of the brain resulted normal. The patient was prescribed with reduction of pramipexole to 0.18 mg daily, which resulted in the complete resolution of OMD in 4 days.

Discussion: Our report describes a rare case of DA-induced OMD in a patient with RLS due to drug abuse. The mechanism underlying LID is attributed to a specific enhancement of the direct striatopallidal pathway and to the inhibition of the indirect striatopallidal pathway, which may be particularly found in PD patients. The resulting decreased output of the internal Globus pallidus may lead to an increased activity in the motor nuclei of the thalamus. In RLS, a chronically increased dopaminergic tone may induce a postsynaptic receptor down-regulation, mostly of the indirect pathway. RLS association with PD did not receive sufficient evidence in the literature. and our patient did not show any PD-related motor or non-motor symptoms as often happens in RLS cases. Nevertheless, after excessive intake of DA, she developed symptoms that resembled LID, a typical PD complication. It is the first report of OMD following excessive intake of DA in non-PD patients. Follow-up of this patient will address the possible future development of a parkinsonian syndrome.

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A NEW GENOTYPE FOR PROGRESSIVE CORTICAL MYOCLONIC EPILEPSIES

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Background: The Progressive myoclonic Epilepsies (PME) results from heterogeneous neurodegenerative disorders, with different etiology and a great proportion of undetermined forms [1,2]. We are describing a de novo heterozygous variant of IRF2BPL in a patient with PME and a brief revision of the literature referring patients with myoclonic jerks associated with IRF2BPL variants.

Case report: The patient was born after an uneventful pregnancy and had normal psychomotor development until the age of 10 years when he began to have frequent falls, and poor motor coordination, followed at 12 years by a tonic-clonic seizure, rare massive jerks induced by intense light, and obvious action myoclonus. The EEG-EMG recording confirmed the presence of typical action myoclonus, not associated with obvious EEG abnormalities, as well the presence of a photoparoxysmal response (PPR) to intermittent photic stimulation (IPS) and of brief spike-wave discharges concomitant with bilateral myoclonic jerks when closing the eyes. The evaluation of cortico-muscular coherence revealed a typical pattern of cortical myoclonus. Brain magnetic resonance showed cerebellar vermis atrophy. Neuropsychological tests ruled out cognitive impairment. Given the electro-clinical picture, the diagnosis of PME was made, without being able to identify its genetic cause. In the following years, the seizures became frequent, little controlled by the antiseizure medication, as well as the action myoclonus, which forced him to use the wheelchair (22 years). In his thirties, he began presenting psychiatric disorders with severe sleeplessness, thoughts of suicide, and self-harm; dystonic posturing and a cognitive decline became evident. A severe dysphagia with repeated episodes of inhalation pneumonia led to death at the age of 43. We performed a whole-exome sequencing combined with variant analysis within a panel of neurodevelopmental disorders-related genes. The analysis revealed a de novo heterozygous c.471_504 del (p.Ala160SerfsTer8) variant in IRF2BPL, absent in public databases (GnomAD, ExAC, dbSNP, 1000G) and predicted to be deleterious by bioinformatic tools (SIFT, PolyPhen2, MutationTaster). This previously unreported loss-of-function variant, was defined as pathogenetic (class 5) following the ACMG Guidelines.

Conclusion: The IRF2BPL-related disorders reported in the literature began at variable ages, namely in early childhood, and commonly with neurodevelopmental delay or regression, abnormal movements, loss of speech, and variable seizure types (NEDAMSS) [3]. Our observation suggests that IRF2BPL variants can present as a typical PME phenotype and must be included in the systematic diagnostic procedures. Thus it is worth investigating these gene mutations in the presence of childhood/adolescent-onset of progressive neurological disorder with myoclonic seizures or PPR.

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COEXISTENCE OF NEUROMYELITIS OPTIC SPECTRUM DISORDER AND SJOGREN SYNDROME: A CASE REPORT

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Background: Neuromyelitis optic spectrum disorder (NMOSD) is a rare, severely disabling inflammatory disease. It may be associated with other

autoimmune diseases, including Sjogren's syndrome (SS), mainly in those patients with positive anti-aquaporin-4 antibodies (AQP4-IgG). Although SS may cause itself neurological disorders including myelitis, an association between SS and NMOSD may also be reported. Moreover, in presence of AQP4-IgG positivity and symptoms belonging to NMOSD, an association between SS and NMOSD is considered more frequent than an isolated SS causing neurological disorders. Severe respiratory coronavirus 2 (SARS-CoV-2) may cause a wide spectrum of neurological manifestations as well, including myelitis. Here we describe a case of an elderly woman with SS who, during a possible Sars-Cov-2 infection, developed transverse myelitis and tested positive for AQP4-IgG.

Case report: A 75-year-old female with SS came to our attention for the occurrence of left iliac and low back pain later followed by paresthesia and left lower limb hyposthenia. A spinal MRI revealed a wide intramedullary lesion extended from D7 to D12, with slight contrast enhancement. Interestingly, she tested positive at SARS-CoV-2 swab test, no further confirmed at the following swab tests performed. A brain MRI and complete CSF exams resulted normal, while serum AQP4-IgG resulted positive. In the suspicion of inflammatory transverse myelitis, intravenous steroids were attempted, but after a first clinical and radiological improvement, the patient reported a new decline in her neurological symptoms. She then was treated with immunosuppressive therapy (Rituximab), with a subsequent disappearance of neurological symptoms.

Discussion: Although the association between NMOSD and SS is well recognized, the underlying pathogenic mechanisms are still unclear. AQP4-IgG are supposed to play a primary role since, when present in SS, they are associated to an increased amount of relapses and a more aggressive disease course. In particular, AQP4-IgG are supposed to cross-react against AQP5 that are widely present, for example, on salivary glands. This may contribute in explaining the association between NMOSD and SS. Furthermore, in our case the uncertain positivity for SARS-CoV-2 concomitant to disease onset is matter of debate, since neurological disorders including NMOSD after SARS-CoV-2 infection have been reported in the literature.

Conclusions: Our case confirms the possible association between NMOSD and SS in elderly people previously reported in Literature. This association must be kept in mind in order to avoid misdiagnosis, especially considering that an early immunosuppressive therapy is effective in disease control.

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OPTIC NEURITIS AS ISOLATED MANIFESTATION OF BALÓ CONCENTRIC SCLEROSIS: A CASE REPORT

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Objective: To describe a peculiar case of Baló concentric sclerosis (BCS), characterized by clinical-radiological dissociation.

Materials and Methods: Case report.

Results: We describe the case of a 33-year-old man without significant medical records. Family history was positive for Multiple Sclerosis (MS) (his mother). About a month after the third dose of anti-COVID19 vaccine, he reported acute visual loss in his left eye (LE), associated with pain, worsened by ocular movements and reduced colour vision. A few days later, because of persistent symptoms, he was admitted to the ophthalmologic emergency room. Evaluation demonstrated a compromised visual acuity (4/10) in the LE, with associated relative afferent pupillary defect (RAPD). Visual evoked potentials from the LE showed low amplitude. He was diagnosed left optic neuritis and treated with iv high-dose steroids (methylprednisolone 1 g/day for 5 days) with little residual symptoms. The ophthalmologic follow-up, a few days after the end of the steroid course, showed left visual acuity improvement (8/10). Two months after symptom onset, he came to our attention. The neurological exam was normal except for mild residual visual blurring, reduced colour vision and RAPD in the LE. Brain MRI revealed mild hyperintensity of the left optic nerve and multiple bilateral hemispheric white matter lesions, mainly with periventricular distribution, characterized by the peculiar BCS morphology. Spinal MRI excluded spinal cord involvement. There was no gadolinium enhancement. Optical coherence tomography showed retinal temporal thinning in the LE. CSF analysis showed a mild increase in total proteins (72 mg/dl), the presence of CSF-restricted oligoclonal bands, a K-index=32.67. Anti AQP4-IgG and anti MOG-IgG were negative. The diagnosis of Baló disease was made. Four months after onset he had not experienced further relapses, despite no disease modifying therapy (DMT) had been started.

Discussion and Conclusions: BCS is a rare inflammatory disease of the CNS whose pathogenesis has not yet been fully elucidated1. The significant clinical variability raised the debate whether BCS could be a subtype of MS rather than an independent entity, or even only a histological pattern of demyelination [1]. Due to its rarity, there is no consensus on therapeutic management, neither with regard to acute attacks nor to the use of DMTs [1,2]. Further studies on a large cohort, possibly obtained creating a disease registry, are mandatory to shed light on BCS nature, prognosis and therapeutic options.

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RECURRENCE OF INFRATENTORIAL-PREDOMINANT POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

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Purpose: Posterior reversible encephalopathy syndrome (PRES) classically refers to a reversible subacute neurological disorder often appearing in the setting of renal failure, hypertension, cytotoxic drugs, autoimmune disorders, and haemoglobinopathies [1]. Brain MRI typically shows confluent T2/FLAIR hyperintense cortico-subcortical lesions predominantly involving the bilateral parieto-occipital regions, consistent with vasogenic edema. Restricted diffusion and intracranial haemorrhage are detected in

up to 30% of cases [2]. Moreover, phenotypes of Infratentorial-Predominant Posterior Reversible Encephalopathy Syndrome (IP-PRES) have been reported [3]. PRES is considered a reversible and monophasic disorder. Here, we present a case of recurrent PRES with predominant involvement of infratentorial structures.

Materials and methods: In 2021, a 49-years old patient was admitted to the Emergency Department of the Santa Maria della Misericordia Hospital for headache, right hemiparesis and hypertensive crisis. During the hospitalization, the patient had a generalized epileptic seizure followed by aphasia and progressive reduction of consciousness. Because of the neurological deterioration, an electroencephalogram (EEG) and brain MRI were performed. After 1 year, the patient returned to our institution for recurrence of headache, aphasia, bilateral visual impairment and GCS of 11 associated with an increase of blood pressure (210/120). In the Emergency Room, brain CT and MRI were performed.

Results: During the first episode, brain CT detected a left caudate haemorrhage. EEG showed a diffuse slowing of cerebral activity without epileptic abnormalities. Brain MRI detected multiple bilateral subacute ischaemic lesions associated with massive brainstem vasogenic edema, compatible with IP-PPRES. Moreover, the final diagnostic work up reported also an hypertensive renal and cardiac disease and an heterozygotic sickle cell trait. During the second admission, brain CT and MRI evidenced a cortical left temporoparietal haemorrhage and a left occipital acute ischaemic lesion associated with massive brainstem vasogenic edema, compatible with a relapse of IP-PRES. In both conditions, a sickle cell crisis or other etiologies for PRES were excluded. Neurological conditions gradually improved with antihypertensive therapy.

Discussion: The presence of ischaemic and/or haemorrhagic lesions in the context of a typical PRES is described in up to 30% of cases. Moreover, some cases of isolated or predominant involvement of the infratentorial structures are reported. To the best of our knowledge, few cases of recurrent PRES have been described and none of them with predominant involvement of the infratentorial regions.

Conclusions: PRES is a transient neurological disorder which can present in the setting of severe hypertensive disease with recurrent episodes and prevalent involvement of the infratentorial brain structures.

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MULTIPLE MYELOMA AND BILATERAL ISCHEMIC STROKE: A CASE REPORT

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Aim: Solid tumors, haematological malignancies and stroke are highly prevalent conditions in the elderly. Apart from a casual association between malignancies and stroke, a direct correlation is well known, due to different pathophysiological mechanisms, from paraneoplastic thrombophilia to side effects of chemotherapies. We report a case of bihemispheric ischemic stroke in a subject with multiple myeloma and discuss possible relationship.

Case report: A 65 years old woman had a recent diagnosis of multiple myeloma, with bone and renal involvement, with therapeutic regimen of bortezomib plus dexamethasone. Two months after the diagnosis, about two hours after bortezomib infusion, she acutely developed aphasia and right hemiparesis. She arrived to E.R. at 18.16 (4 hours after stroke onset). Neurological examination confirmed presence of expressive aphasia and right hemiparesis (NIHSS: 6). A CT scan did not show acute infarct, and ASPECT score was 9. Considering chronic renal impairment, low NIHSS and delayed presentation to the ER, MRI and angio-MRI was performed, to verify possible therapeutic window. There were multiple supra- and infratentorial small ischemic lesions with both restricted diffusion and FLAIR hyperintensity, without FLAIR/DW mismatch, and no intracranial vessel occlusion. The patient was thus excluded from thrombolysis and thrombectomy. Subsequent investigations (transthoracic echocardiography, 24-hours-Holter ECG, supraortic and transcranial duplex, together with bubbles test) couldn't find any cardiac or vascular embolic source. Blood tests showed low platelets count (between 120 and 150 10^9/L, stable compared with previous values), mild reduction of fibrinogen and ATIII, with slight elevation of FDT (3400 ug/L – VN 0-500) and ACA IgG (23.6 U/ml – VN 0-12). Paraneoplastic thrombophilia was thus suspected, yet other embolic sources, or a correlation with bortezomib couldn't be excluded, thus anticoagulation with AVK was introduced.

Discussion: Cryptogenic stroke are frequent in patient with cancer, up to 50%, and tend to be associated with high D-dimer levels and infarctions in multiple vascular territories. Moreover, stroke risk seems to be increased immediately after cancer diagnosis, also in hematological disorders, in which cerebral infarction seems to be more frequently in different vascular territories. Nonetheless, there are no specific diagnostic features which can distinguish paraneoplastic from different embolic sources of stroke, and ethiological relationship with bortezomib remain possible, as already described in the literature.

Conclusions: This case highlights the importance of a complete diagnostic workup in patients with stroke and cancer, in particular multiple myeloma, as it has deep consequences in diagnosis and treatment choices.

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SPORADIC FATAL INSOMNIA PRESENTING WITH NARCOLEPSY AND RBD: A CASE REPORT

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Introduction: Sporadic Fatal Insomnia (sFI) is a rare prion disease, due to accumulation of abnormal, misfolded prion protein (PrPsc) in thalamic neurons. To date, few cases have been described in literature. Here we report the first case of sFI with sleep disorders such as narcolepsy and REM behavior disorder (RBD) at onset.

Case report: A 63-years-old man was referred to our hospital with 6-months history of progressive sleep disturbances, characterized by

nocturnal insomnia with RBD, and daytime sleepiness with frequent episodes of cataplexy suggestive for narcolepsy. His past medical history was unremarkable. In the last couple of months, he developed multidomain cognitive impairment and behavioral disturbances such as irritability, disinhibition, persecutory ideation, and hyperphagia, and mild extrapyramidal syndrome with rigidity and bradykinesia. At hospital admission, he performed a brain MRI showing mild diffuse cortical atrophy and white matter hyperintensities suggestive of cerebral small vessel disease. Brain 18FDG-PET revealed thalamic and mesencephalic hypometabolism, and the electroencephalogram registered a normal background activity with bilateral fronto-temporal focal slow waves and no epileptic seizures. We initially hypothesized a possible Lewy-Body dementia due to patient' clinical features of cognitive disorders, RBD and extrapyramidal signs. However, due to atypical clinical onset and 18FDG-PET picture, we also had him undergo a lumbar puncture detecting normal levels of proteins and cells, onconeural antibodies and Alzheimer's-biomarkers, including total tau, phosphorylated tau and beta-amyloid. Surprisingly, RT-QuIC (Time Quaking-Induced Conversion positivity assay) revealed the presence of PrPsc in cerebrospinal fluid suggestive of prion disease. In the following month, patient' cognitive and motor picture worsened. He repeated a brain MRI revealing multifocal regions of increased cortical signal intensity, and a polysomnographic registration showing marked alteration of the sleep structure, including the lack of the physiological atonia during REM periods. Genetic analysis did not detect any PRNP mutations. Based on the clinical, instrumental and biological findings, we made a diagnosis of sFI. In a couple of months, the patient became bedridden and dysphagic and he died for ab ingestis pneumonia.

Conclusion: Sleep disorders are frequently associated with dementia and atypical parkinsonisms. We described a rare case of sFI, presenting with narcolepsy and RBD at onset. The differential diagnosis between rapidly-progressive dementias can be challenging because of the wide heterogeneity and/or overlapping of clinical features. The detection of the PrPsc in CSF plays a key role in the differential diagnosis between prion diseases and other dementias, such as Lewy-Body disease.

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LATE ONSET MYASTHENIA GRAVIS: A CASE REPORT OF ATYPICAL PRESENTATION

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Objectives: Myasthenia Gravis (MG) is an immune-mediated neuromuscular junction disease characterized by widespread asthenia, easy fatigue with typical worsening in the evening, and is also classified into ocular and generalized variants. The age group most affected for women is between 20 and 40 years, although there are late onset cases with a relatively worse prognosis. It is known that MG can be associated with the presence of thymoma and other autoimmune diseases and that it can cause systemic complications, including serious ones, such as myasthenic and cholinergic crises. Diagnosis of MG is based on clinical, neurophysiological, serological and pharmacological criteria.

Materials and method: A 78-year-old woman came to the ER at our hospital with a two-week subacute onset of asthenia, easy fatigue, dysphagia, dysarthria, dysphonia, bilateral eyelid ptosis and recent dyspnoea.

Results: Neurological examination: hypostenic gait, bilateral eyelid ptosis with worsening after gaze-up test, proximal weakness of the four limbs, dysarthria, dysphonia, fatigue. During hospitalization she underwent a total body CT scan and showed a thymoma in the mediastinal area of 30x35 mm; the neurophysiological study and the serological test confirmed the hypothesis of MG (decremental response to the Repetitive Stimulation Test and presence of high titre anti-AchR antibodies). During hospitalization, routine laboratory tests revealed a progressive and significant increase in all the indices of muscle necrosis and inflammation in correlation with a worsening of dyspnoea and bulbar symptoms, but in the absence of ECG changes, echocardiographic and angiographic lesions. Only a CardioRM detected a focal myocarditis of the apical lateral wall. The patient was subjected to therapy with Pyridostigmine, high-dose steroids and IVIG for five days, with almost complete resolution of the symptoms.

Discussion: Among the systemic autoimmune manifestations that can complicate the course of MG, myocarditis is undoubtedly one of the most critical, although its incidence does not exceed about 2% of cases. Several reviews on this association have shown that elderly women with thymoma are at the greatest risk of developing myocarditis, with a mortality of up to 42%.

Conclusions: The clinical case described underlines the importance of not underestimating a rare but fearful complication of the course of MG, such as myocarditis which can be successfully treated because it responds to the most common immunosuppressive / immunomodulating therapies.

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A LIFE-THREATENING, NOVEL MUTATION, DELIVERY INDUCED, CARBAMOYL PHOSPHATE SYNTHETASE-1 DEFICIENCY ENCEPHALOPATHY TREATED BY DECOMPRESSIVE CRANIECTOMY

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Objective: To discuss the most severe clinical pictures of adult onset urea cycle disorders and their complex, multidisciplinary treatment.

Methods: Case report and review of literature.

Results: A 39 years old puerpera presented agitation, confusion, behavioral alterations, and gradually consciousness impairment. For these reason underwent brain CT and MRI, extensive laboratory tests, lumbar puncture that resulted unremarkable, while EEG showed widespread slow wave activity. Admitted to intensive care unit, in the suspect of dysimmune encephalopathy, was treated by ev immunoglobulins, with further neurological deterioration. A control brain MRI showed diffuse bihemispherical FLAIR and DWI hyperintensities, without gadolinium enhancement, consistent with citotoxic edema. These findings were associated to clinical signs of intracranial hypertension, thus an intracranial pressure of 70 mmHg was detected; according to this a large frontal bilateral decompressive craniectomy was performed. Critical reappraisal and supplementary analysis of anamnestic, clinical and diagnostic results pointed out a significant hyperammonemia (400 ug/dl). In light of this, an extensive aminoacids dosage and genetic tests were performed, founding double heterozygosity, novel, Carbamoyl phosphate synthetase-1 mutations, precisely related to urea cycle disorder. After specific treatment (stop protein intake, intravenous glucose and electrolytes, intravenous L-arginine and sodium benzoate, B6 and B12 supplementation, continuous veno-venous hemofiltration), despite negative prognostic factors (coma duration, intracranial pressure) the condition of the patients gradually improved, achieving normal consciousness, language comprehension, voluntary motor activity), so that she was referred to rehabilitation unit.

Discussion and Conclusions: Adult onset of urea cycle disorders, despite rare, represents a life-threatening under-estimated condition. During decompensations, hyperammonemia is neurotoxic, leading to severe symptoms and even coma and death if not treated rapidly. Moreover, a lack of prompt diagnosis can expose patients at high risk of inappropriate and hazardous treatment, with a poor outcome. Revising these clinical scenarios highlights the need to raise awareness and improve management of these treatable conditions.

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A NOVEL VARIANT IN TBCD GENE ASSOCIATED WITH DISTAL MOTONEURONOPATHY AND CORPUS CALLOSUM HYPOPLASIA

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Case Report: A 17 years-old female presented with exercise intolerance and leg weakness upon effort from childhood. On history she had mild intellectual disability (IQ:59) and bilateral surgery for pes equinus. Her parents were consanguineous (first-degree cousins). The maternal aunt suffered from severe intellectual disability and motor impairment from infancy. A mother's first cousin was affected from autism and pes planus. Neurological examination showed mild distal weakness, hypotrophy in intrinsic muscles of the hand and in distal leg muscles, without visible fasciculations. Hoffman and Babinski were absent. No sensory or coordination impairment was noted. Reflexes were normal in upper limbs, absent in lower limbs. The patient was followed up till age 22; progressive worsening of segmental strength at distal limb muscles was noted. Her respiratory function is unaffected, she doesn't show bulbar involvement. She never presented seizures.

Methods: NCS reported a slight reduction in cMAP amplitude, still in normative range. EMG showed sporadic fibrillations potentials and PSW; MUP were of high amplitude and long duration, with sporadic polyphasic potentials. Decreased motor unit recruitment was observed. MEP revealed a prolongation in the peripheral motor conduction time. A second neurophysiological study after4 years revealed a quantitative reduction in cMAP amplitude. Cervical MRI was unremarkable, whereas brain MRI showed thin corpus callosum. Treatable conditions were excluded. Slight elevated CK values were found (176 U/L); to exclude a multisystem condition, transthoracic cardiac, abdominal and thoracic ultrasound, plus eye examination were performed, without revealing any pathologic condition. Genetic testing for SMN1 and SMN2 was normal. NGS panel revealed a homozygous point mutation c.881G>A in TBCD gene, resulting with a codon substitution p.R294Q, confirmed by Sanger sequencing. CADD score was 25.40. Genetic testing throughout the family is still ongoing.

Discussion and Conclusion: Mutations in tubulin-specific chaperon D (TBCD) have been reported in early-onset progressive neurodegenerative disorder. This gene is primarily involved in tubulin heterodimer assembly pathway: its defects are known to cause a spectrum of diseases ranging from epileptic encephalopathy, microcephaly, motor disorders [1]. Mutations at R942Q have been implicated in an atypical case of SMA associated with corpus callosum hypoplasia [2]. We describe a variant in TBCD gene, c.881G>A, which was previously reported in heterozygosity in a patient with intractable focal epilepsy and developmental delay [3]. This mutation results in alteration of protein conformation which may affect the protein function. Finally, this case strengthens the genotype–phenotype relationship between TBCD-mediated tubulinopathy and infantile neurodegenerative disorder.

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A CASE OF ANTI-PF4 ANTIBODIES IN CEREBRAL VENOUS THROMBOSIS AFTER BNT162B2

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Cerebral venous thrombosis (CVT) is a rare adverse event reported in post-marketing surveillance of Covid-19 vaccine. Two main coagulation syndromes associated with vaccine-related CVT have been described: "vaccine-induced immune thrombotic thrombocytopenia" (VITT) and "vaccine associated-thrombosis" (VAT). VITT differs from VAT for evidence of thrombocytopenia (platelets count less than 150 x 103 μL), antibodies against platelet factor 4 (PF4) and high mortality. Larger cohort studies gathering CVT after Covid19-vaccines showed VITT only following adenovirus-based vaccine while more rarely VAT without thrombocytopenia or anti-PF4 antibodies may follow mRNA-based vaccine. We report a case of VAT following BNT162b2 (Pzifer-Biontech) where anti-PF4 antibodies have been detected despite normal platelets. A 24 years-old male in good health developed a "thunderclap" headache six days after the first dose of vaccine with initial response to analgesic treatment (CT brain was negative). A couple of weeks later he complained of chronic mild occipital and vertex headache. After 38 days he was admitted to neurological ward for headache and visual loss with

papilledema. A cerebral MR angiography confirmed a CVT involving the right sigmoid sinus and internal jugular vein. Low molecular weight heparin was started, then shifted to fondaparinux the day after when a positive ELISA test of anti-PF4 was found. Specific platelet activation assay was not performed. Extensive coagulation work-up was unmarkable and platelet counts were normal all over the hospitalization stay. Patient improved and was discharged after 20 days with anticoagulant therapy. Anti-PF4 antibodies seem to have a major role in the pathogenesis of VITT, instead their relevance in VAT is still debated. It is already known that anti-PF4 antibodies may be founded in 5,6% of an healthy cohort after BNT162b2 vaccine with negative platelet activation assay. CVT following mRNA vaccine emphasizes the possibility of a spectrum of immune-mediated platelets disorder rarely triggered by covid-19 vaccine. Despite the supposed non-pathogenetic role of anti-PF4 antibodies in VAT, Lippi et al suggest that human cells transfected by mRNA-based vaccine can produce some forms of SARS-CoV-2 recombinant spike protein which may activate platelets via spike protein-ACE2 interaction in a very small proportion of vaccine recipients. Additional studies are necessary to understand if mRNA vaccines against Covid19 could rarely cause CVT without thrombocytopenia and the underlying mechanism.

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AN EVIDENCE OF RITUXIMAB EFFICACY IN ILD-ASSOCIATED ANTI-SRP NECROTIZING MYOPATHY: A CASE REPORT

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Objectives: Necrotizing autoimmune myopathy (NAM) is a rare skeletal muscle autoimmune disorder characterized by subacute bilateral proximal muscle weakness and marked elevation of serum creatine kinase (CK) levels. NAM can be divided into three groups based on the presence of muscle specific antibodies (MSA): Anti-signal recognition particle (SRP), anti-HMGCR, and seronegative. Anti-SRP antibodies can be associated with extramuscular involvement including pulmonary manifestations [mainly interstitial lung disease (ILD)]. We present a case of anti-SRP positive NAM with severe ILD and mild myopathy.

Materials: A 58 years old male patient with two-year history of dyspnea and lung fibrosis diagnosis came to our attention following the occurrence of intense myalgias, mild lower limbs weakness and CK elevation (x10 ULN). Muscle biopsy was compatible with a NAM diagnosis and anti-SRP antibodies were found in patient serum.

Methods: We started oral prednisone at 1 mg/Kg dosage with a progressive tapering after two months. Following the severe pulmonary involvement [Forced Vital Capacity (FVC) 58%, Diffusing Capacity of Lung for Carbon Monoxide (DLCO) 42%], we decided to start Rituximab as steroid sparing agent. Results: Two months after the first infusion of Rituximab, patient reported an improvement in respiratory function and resistance, with a reduction of CK to normal level. Last pulmonary evaluation (after 4 years from first rituximab infusion) showed a persistent functional amelioration (FVC 80%, DLCO 64%) with normal CK level and no muscle weakness.

Discussion: Anti-SPR myositis typically presents a significant muscle involvement with severe proximal and axial weakness. Despite relative frequent, extramuscular manifestations rarely occurs in case of mild muscular involvement. Here we present an atypical case with a severe ILD (firstly diagnosed as fibrosis) and a mild muscolar involvement who had a brilliant response to Rituximab. When dealing with ILDs, autoimmune connective tissue disese should be considered and it may be useful to perform a full autoimmune screening, also assaying MSA.

Conclusions: When facing severe extramuscular involvement in patients with myositis, a more aggressive therapeutic approach including the use of monoclonal antibodies, such as rituximab, could lead to a better clinical outcome.

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A CASE OF NORSE (NEW ONSET REFRACTORY STATUS EPILEPTICUS): DIAGNOSTIC AND THERAPEUTIC CHALLENGES

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NORSE (New Onset Refractory Status Epilepticus) is a rare and severe disease of unknown etiology, probably autoimmune, in patients with no previous epilepsy. It manifests initially as a refractory status epilepticus, but the evolution towards super-refractory status is frequent. We describe the case of a 21-years-old woman with a very long duration NORSE. The diagnostic workup excluded an infectious, tumoral or autoimmune origin. Therapy for autoimmune encephalitis and various combinations of antiepileptic drugs and anesthetics were used. Serial EEG prolonged registrations were performed during the period in ICU and several different patterns were seen. Finally, the clinical situation ameliorated and the girl was admitted to the neurological unit about forty days later. Some neuropsychological deficits (especially in memory and attention) and focal seizures remained with the need of several antiepileptic drug. NORSE has high mortality in the short term and often unfavorable outcome in the long term (especially concerning neurocognitive domains and the development of farmacoresistant epilepsy). Aetiology is often unknown and an autoimmune origin is frequent. A prompt and intensive treatment with antiepileptic drugs, anesthetics, and autoimmune terapies such as steroids, plasmapheresis, endovenous immunoglobulin is mandatory. The EEG shows some recurrent patterns and the role of continuous registration is essential for guiding treatment. Probably, several different mechanisms are implied in the origin of seizures in these patients.

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ONEIRIC STUPOR IN A 77-YEAR-OLD MAN WITH DOUBLE ANTI-HU/ZIC-4 ANTIBODIES POSITIVITY AUTOIMMUNE ENCEPHALITIS & SENSORY NEURONOPATHY: A CASE REPORT

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Objectives: We present a case of Sensory Neuronopathy (SNN) and Autoimmune Encephalitis (AE) associated with Oneiric Stupor (OS) in a patient with coexistent anti-Hu/Zic-4 antibodies.

Case Report: A 77-year-old male suffered a subacute onset of paraesthesias and tactile, pinprick and thermal hypoestesia firstly in the upper limbs then extended to lower limbs and face with asymmetrical distribution. Neurological examination also showed absent deep tendon reflexes and severe sensory ataxia. Two months later the patient developed hallucinations, disorientation to time and place, amnesia for recent events, proximal myoclonias and marked somnolence. The neurophysiological study highlighted absent SNAPs in lower limbs, absent or markedly reduced amplitude SNAPs (<30% LLV) in upper limbs and abnormal Blink Reflex. CSF examination showed mild pleocytosis (7 cells/mm^3) and anti-Hu/Zic-4 positivity (tested positive also in serum). Contrast-enhanced Brain Magnetic Resonance Imaging (MRI) was unremarkable. Cromogranine was elevated in serum (x3 ULV), Whole Body CT was negative for heteroplastic lesions. Diagnosis of Sensory Neuronopathy (SNN) and Autoimmune Encephalitis (AE) anti-Hu/Zic-4 related was made. It was performed a video-EEG registration that showed no epileptic activity but highlighted the disruption of the sleep-wake cycle with short periods of REM sleep arising from a state of wakefulness. This pattern was associated with episodes of dream enactment whereby the patient performed movements mimicking the content of his dream such as dressing or washing and was also able to recall the oneiric scene upon awakening when asked. Such clinical ed electrophysiological features are compatible with Oneiric Stupor (OS). The patient underwent a therapeutic course with intravenous immune globulin and then high-dose glucocorticoids without benefit. Unfortunately, he eventually died for infectious pneumonia.

Discussion: SNN and AE are classically associated with anti-Hu antibodies. Sleep disorders are underrecognised in patients with AE, although they're well-described in patients with specific subtypes of AE (IgLON5, LGI1 and Caspr-2, tested negative in our case). Anti-Hu is associated with Central Hypersomnolence, while sleep disorders are not reported for anti-Zic4. OS represents a condition characterized by the recurrence of stereotyped gestures such as mimicking daily-life activities associated with the reporting of a dream mentation consisting in a single oneiric scene. It arises in the context of a completely disorganized sleep structure. Usually reported in Agrypnia Excitata, it has never been described in AE.

Conclusions: To our knowledge this is the first case of OS associated with anti-Hu/Zic-4 antibodies AE.

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A NOVEL GRN MUTATION IN AN ITALIAN PATIENT WITH NON-FLUENT VARIANT OF PRIMARY PROGRESSIVE APHASIA AT ONSET: A LONGITUDINAL CASE REPORT

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Objectives: Progranulin gene (GRN) mutations are major causes of frontotemporal lobar degeneration. Here we report the clinical presentation and evolution of a case with a novel GRN mutation and non-fluent language disturbances.

Materials and Method: A 60 years-old Caucasian right-handed woman was admitted to the Neurology Unit of the Azienda Sanitaria Locale of Vercelli. Her disturbances had one-year onset and were characterized by phonemic paraphasias, agrammatism, anomias, deficits in repetition and comprehension of sentences. Mild disturbances in computing calculations, verbal memory and executive functions were also present. She reported positive family history for cerebrovascular diseases. During hospitalization, she underwent neurological and neuropsychological examinations, positron emission tomography (PET) and cerebrospinal fluid (CSF) sample. At the hospital discharge she was addressed to San Raffaele Hospital in Milan, where she underwent blood sampling for genotyping, a 3T MRI scan, and a comprehensive neuropsychological assessment. These latter visits were carried out again after six months.

Results: Genotyping revealed a new GRN p.H340Tfsx21 mutation. Comprehensive neuropsychological assessment, performed shortly after the first hospitalization, showed a worsening of speech and comprehension deficits, as well as the appearance of apraxia of speech, orofacial apraxia, and difficulties in the attribution of others' intentions and emotions. PET showed a pattern of hypometabolism in the left fronto-insular, fronto-temporal and temporo-lateral regions and in the basal-ganglia (left>right). The first MRI scan reported left sylvian-perisylvian and fronto-opercular atrophy and prevalent left frontal periventricular white matter hyperintensities (WMHs). CSF analysis showed slightly increased total tau with normal phosphorylated tau and amyloid β levels. At that time, she received a clinical diagnosis of nonfluent variant of primary progressive aphasia (nfvPPA). After six months, language deficits worsened (including also single-word comprehension deficits), together with attention and executive functions. She presented also with apathy, aspontaneity, hyperorality and preference for sweet foods. MRI examination performed after six months revealed a progressive atrophy in the left frontal-opercular and temporo-mesial region.

Discussion: The new GRN p.H340Tfsx21 mutation resulted in a case of nfvPPA characterized by fronto-insular, temporal and striatal hypometabolism and atrophy, typical frontal asymmetric WMHs, and a fast progression towards a widespread cognitive and behavioral impairment, which reflects a frontotemporal lobar degeneration.

Conclusions: This is the first report of the occurrence of the GRN p.H340Tfsx21 mutation in PPA. Our findings extend the current knowledge of the phenotypic heterogeneity among GRN mutation carriers.

Funding: European Research Council (StG2016_714388_NeuroTRACK); Foundation Research on Alzheimer Disease.

THE IMPORTANCE OF (VIDEOEEG) IN THE DIFFERENTIAL DIAGNOSIS BETWEEN EPILEPSY AND PSYCHOGENIC NONEPILEPTIC SEIZURES: A CASE REPORT

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Aims: The purpose of this abstract is, through a case report, to give a cue on the importance of Video-Electroencephalogram (VideoEEG) in the differential diagnosis between epilepsy and psychogenic nonepileptic seizures (PNES).

Case presentation: A 56 years-old man with a 3-years-long story of seizures characterized by atypical clinical presentations and normal Electroencephalogram (EEG) came to our attention during April 2019. The seizures had presented with phosphenes and fine tremors to the four limbs. In some cases those events were characterized by impared awareness. Occasionally the seizures occurred after the sudden awakening from sleep by an heart-pounding sensation. The patient referred that he was going through a stressful time of his life at the seizure onset. The 56 years-old man was firstly treated with Levetiracetam and Benzodiazepines without the reduction of seizure frequency. Because of the unsuccessful treatment with anti-seizure medications (ASM) and the absence of interictal abnormalities at the EEG, PNES were suspected. Thus, a therapy with lorazepam and paroxetine was started. Although the therapy changes, the frequency of seizure seizures was unmodified; a continuous videoEEG monitoring was performed. During the 3-days-long VideoEEG the patient manifested many episodes of seizures, all during awakeness and with electroencephalografic correlation (presence of generalized sharp waves, polyspikes and spikes-and-slow-waves complexes). While the seizures occurred he was treated with benefit firstly with intravenous benzodiazepines and then with valproic acid. The patient was discharged from our clinic with a frontal epilepsy diagnosis and he is still in treatment with valproic acid and he has never had seizures again with a full remission of symptoms.

Discussion: The case reported shows the pitfalls of PNES diagnosis. In patients with the clinical suspicion of PNES to perform a prolonged videoEEG monitoring is mandatory to make exclusion diagnosis. Misdiagnosis of PNES and epilepsy could lead to therapeutic mistakes. Differential diagnosis between psychogenic nonepileptic seizures and frontal lobe seizures requires particular care and self-reports are often unreliable and video/EEG recording is generally required for diagnosis.
Conclusion: This case report shows how VideoEEG could be a clarifing exam in complex symptom's scenarios such as a needful method to discern between epileptic seizures and PNES.

THIRD CRANIAL NERVE PALSY WITH PUPILLARY INVOLVEMENT FOLLOWING AN INTERNAL CAROTID ARTERY DISSECTION IN ITS CERVICAL SEGMENT: A CASE REPORT

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Background: Third cranial nerve (oculomotor) palsy is classically divided in "surgical" and "medical" palsy depending on whether the pupil is respectively involved or spared, with a considerable overlap. Parasympathetic fibers controlling miosis lie at the periphery of the oculomotor nerve, the first to suffer in case of compression, while somatic fibers are located centrally and are more likely to sustain microvascular disease complications. Other less common causes of oculomotor palsy have been reported.

Case Report: A 59-year-old man presented at the emergency department complaining of double vision. Two days before his arrival, during an intense physical exercise he felt a sudden discomfort in his right eye; subsequently he noted progressively worsening diplopia without pain. He had a history of ischemic stroke due to a left internal carotid artery (ICA) dissection twenty years before, fully recovered. On admission his vital signs were within the norm. His neurological examination was positive for diplopia present in primary gaze and accentuated by upright gaze, mild right eyelid drooping and mild right pupil mydriasis. Direct and consensual photomotor reflex was present bilaterally, oculomotion and visual field appeared normal and other cranial nerves were spared. He was admitted in the Neurology Department starting a double antiplatelet therapy. An ultrasonography of the cervical vessels resulted normal and a non-contrast brain CT showed no signs of acute vascular lesions, as confirmed later by MRI. A CT angiogram of head and neck pointed out a small grade I dissection in the C2 segment of the ICA. His symptoms improved and he was discharged home with a single antiplatelet therapy.

Discussion: This right third cranial nerve palsy presents with intermediate characteristics between "surgical" and "medical" palsy. The diagnostic investigations did not highlight any of the classic surgical or medical causes: the only abnormality found was the ICA dissection. A rare cause of oculomotor palsy is indeed carotid artery disease, particularly dissection [1]. Being the site of the dissection too far from the carotid sinus (where ICA and oculomotor nerve run in proximity) to cause compressive nerve damage, the palsy is likely due to nerve hypoperfusion caused by embolization from an intramural hematoma or reduced blood flow to the vasa nervorum, as the distal tract of the oculomotor nerve is irrorated by branches of the cavernous segment of the ICA. Lastly, it cannot be excluded a nerve infarction with atypical pupillary involvement with a concomitant incidental finding of ICA dissection.
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STROKE RISK FROM DIAGNOSTIC 'BUBBLE STUDY' IS LOW BUT REAL. PARADOXICAL AIR EMBOLISM AFTER AGITATED-SALINE CONTRAST INJECTION: CASE REPORT AND LITERATURE REVIEW

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'Bubble study' (BS) methods are commonly used to detect intra and extracardiac right-to-left shunts in cryptogenic stroke workup. BS is rapid, inexpensive and generally considered safe, thus it is frequently over-requested in clinical practice in patients with other more likely causes of stroke. Patent foramen ovale (PFO) is found in ≈ 25% of adults; distinguishing between incidental and pathogenic findings can be challenging and screening the right patients may be of valuable help. We describe a 71-year-old woman admitted for multiple bilateral ischaemic lesions. After full recovery, left hemiplegia acutely occurred immediately after diagnostic transthoracic echocardiography with BS. This case and the review of literature illustrate that cerebral ischaemic events via air embolism can occur associated to diagnostic BS. Previous single reports and small case studies are mostly outdated and lack exhaustive clinical descriptions. The summary of reported cases from the literature show TIA

and stroke via air embolism occurring only in patients with a right-to-left shunt and immediately or within minutes after saline-contrast injection. Interestingly, including our patient, 3 out of 13 patients who suffered BS-related ischaemic events had a pulmonary shunt (23%) and a fourth patient had PFO and a possible pulmonary shunt (raising the possible pulmonary shunt rate to 30.7%). Considering that pulmonary shunts are significantly more uncommon than intracardiac shunts such as PFO, these data suggest greater TIA and stroke BS-related risk in patients with pulmonary shunts. The estimated stroke risk rate is low, however, a multicenter study or register on a very large cohort of patients is needed to determine the actual stroke incidence from paradoxical microbubble embolization and to analyze the predisposing factors. In conclusion, BS is a valuable diagnostic procedure, but clinicians should be aware of the possible, albeit uncommon, severe complication risk occurrence, and request it only with a proven indication.

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RECRUDESCENCE OF MYOCARDITIS AFTER COVID-19 VACCINE IN PATIENT WITH PREVIOUS MYOCARDITIS AND PARAINFECTIOUS GUILLAIN-BARRÉ SYNDROME RELATED TO INFLUENZA A H1N1

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Background: According to the US Centers for Disease Control and Prevention, an increasing number of cases of myocarditis and pericarditis after mRNA COVID-19 vaccine has been reported. Most cases are seen in male adolescents and young adults, typically within several days from COVID-19 vaccination (Pfizer-BioNTech or Moderna), more commonly after the second dose.

Case report: Here we describe the case of a 63-year-old female who developed myocarditis 14 days after the first dose of the Pfizer-BioNTech mRNA vaccine. Two years before the patient developed a myocarditis in conjunction with a parainfectious Guillain-Barré Syndrome (GBS) related to influenza A H1N1.

Discussion: Several mechanisms have been proposed to explain the correlation between myocarditis and COVID-19 mRNA vaccines. The mRNA vaccines may give rise to a cascade of immunological events leading to aberrant activation of innate and acquired immune system, triggering pre-existing dysregulated pathways. Another potential mechanism is the so called "molecular mimicry", that can be responsible of a cross-reaction between the spike protein of SARS-CoV-2 and self-antigens. This mechanism can be triggered by infections and also by vaccinations. In our case, the patient had an history of a previous myocarditis related to influenza A H1N1 complicated by the onset of GBS in a parainfectious manner, as can be highlighted by the short time elapsed between the onset of the flu symptoms and the onset of the neurological manifestations. These immune phenomena could indicate the presence of an aberrant immune response characterized by a dysregulated cytokine expression and an abnormal activation of immunologic pathways.

Conclusions: Owing to its temporal relationship, we can speculate that the vaccine may have triggered a pre-existent dysfunctional immune response manifesting as an exacerbation of myocarditis.

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CEREBROVASCULAR COMPLICATIONS IN RCVS: 2 CLINICAL CASES AND REVIEW OF LITERATURE

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Introduction: Thunderclap headache (TCH)[1] is a severe headache linked to aneurysmal subarachnoid hemorrhage (SAH); anyway, reversible cerebral vasoconstriction syndrome (RCVS) has emerged as the most frequent cause [1] of TCH in patients without aneurysmal subarachnoid hemorrhage. RCVS is a clinical-radiological entity characterized by recurrent TCH and multisegmental cerebral vasoconstriction, reversible within 3 months. Stroke complications occur in 7-54% [2].

Materials: Case 1: A 56-year-old woman presented to our ER with recurrent episodes of TCH. Lab tests and brain CT scan resulted negative. After two days SAH was evident at brain CT. Cerebral angiography (DSA) showed segmental narrowing of right middle cerebral artery, left posterior cerebral artery, and anterior cerebral arteries. Case 2: A 38-year-old man with a history of cocaine-abuse developed TCH; after a week he developed aphasia and alexia; Brain CT scan documented left temporo-parietal hypodensity. DSA showed vasospasm of left middle cerebral artery. Angiographic differential diagnosis included primary angiitis of the CNS and RCVS.

Results: Other causes of TCH were excluded in both cases; and RCVS diagnosis was made.

Discussion: We presented two cases of RCVS with recurrent TCH. TCH can be associated to SAH (30%-34%) [1] and ischemic stroke (6%-39%) [1]. SAH is usually mild, localized in superficial cortical sulci near convexity [3]. Ischemic stroke typically occurs in watershed zones of cerebral hemispheres. A major characteristic of RCVS is that complications tend to occur at different times after disease onset: SAH mainly occur during the first week, ischemic complications occur during the second or even the third week after headache onset [3]. Triggers for RCVS as postpartum state, exposure to vasoactive substances (medications or illicit drugs) are described in literature, but it would be useful to find predictive factors for stroke in RCVS.

Conclusions: RCVS is generally a benign and self-limiting disorder; early diagnosis in cases of isolated headaches enables proper management and might reduce the risk of eventual stroke.

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SPINAL CORD STIMULATION MAY IMPROVE GAIT & COGNITION IN HEREDITARY SPASTIC PARAPLEGIA

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Objective: Hereditary Spastic Paraplegia (HSP) include various sporadic and hereditary neurodegenerative disorders, characterized by progressive spasticity and weakness of lower limbs, possibly associated to additional features. We report a case of complicated hereditary spastic paraplegia referred to our unit for the treatment of spasticity. We recommended a test of cervical spinal cord stimulation. High frequency (10000Hz) SCS improved not only motor but also cognitive performances

Material: We report a male HPS patient in his 40s, showing mental retardation associated with language impairment, dysarthria, increased urinary frequency. After an initial trial with 80Hz stimulation, the patient referred some motor improvement, but unpleasant paraesthesiae limited the usefulness of neuromodulation. The recently proposed 10000Hz stimulation does not induce paraesthesiae, so we decided to test HF-SCS.

Results: Three months after treatment with electric chronic high-frequency cervical spinal cord stimulation (HF-SCS), he showed an amelioration of motor symptoms (lower limbs spasticity and gait), dysarthria, cognitive functioning (language and constructive praxic abilities) and urinary symptoms (decreased urinary frequency). Single-photon emission computed tomography (SPECT) showed a postoperative increase of cerebral perfusion in right frontal cortex and temporal cortex bilaterally.

Discussion: In our patient, HF-SCS might have induced an activation of ascending neural pathways, resulting in changes in activity in various cortical areas (including sensory-motor cortical areas), which may give rise to a modulation of activity in spared motor descending pathways and in neural networks involved in cognitive functions, including language. Although further studies in patients with HPS are needed to clarify whether HF-SCS can be a suitable treatment option in HSP, our observation suggests that HF-SCS, a minimally invasive neurosurgical procedure, might induce beneficial effects of on various symptoms of such orphan disease.

Conclusions: HF-SCS improves motor as well as language and cognitive performances without inducing disturbing paraesthesiae in a case of complicated hereditary spastic paraplegia.

PREGNANCY IN ANTI-SRP-POSITIVE IMMUNE-MEDIATED NECROTIZING MYOPATHY: OUTCOMES IN TWO PATIENTS AND IMPACT ON THE DISEASE COURSE

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Objectives: Immune-mediated necrotizing myopathy (IMNM) is a type of idiopathic inflammatory myopathy (IIM) characterized by myofiber necrosis and the frequent presence of two different muscle specific antibodies (MSA): anti signal recognition particle (anti-SRP) and anti-HMGCR. Anti-SRP positive IMNM is clinically characterized by a severe muscle weakness, possible occurrence of dysphagia and common extra-muscular involvement. As in other autoimmune diseases, pregnancy represents a clinical challenge, since it produces hormonal and immunologic changes potentially influencing the disease course. We retrospectively evaluated the pregnancy outcomes of anti-SRP positive patients included in our myositis cohort.

Materials and methods: From 2015 to 2022, 174 IIM patients were tested for the presence of MSA. 26 patients resulted positive for anti-SRP antibodies, 6 of whom were women. Two patients got pregnant after IIM diagnosis with 5 total pregnancies.

Results: Case one is a 20-year-old woman with an aggressive disease since diagnosis. Treatment history included cyclosporine, intravenous immunoglobulin and rituximab in association with corticosteroids. She had four pregnancies over time. The first one occurred while the disease was well-controlled; pregnancy continued uneventfully except for an increase in serum creatine phosphokinase in the third trimester. Her second pregnancy occurred after one year of stability and was complicated by an early clinical exacerbation, followed by a late abortion. Shortly after miscarriage, a severe disease flair was reported. Three years later, while clinically stable, her third pregnancy occurred and resulted in a second abortion. No modifications in disease activity were reported this time. Her last pregnancy occurred four months later and was uncomplicated. Case two is a 26-year-old woman treated with a single cycle of rituximab as first-line steroid sparing agent. Afterwards, she maintained clinical stability and gradually suspended corticoid therapy. She had a single, uncomplicated pregnancy, two years after therapy discontinuation.

Discussion: The description of pregnancies occurring in women diagnosed with anti-SRP myositis is only anecdotal, as most of the cases reported generically refer to polymyositis. As in other published case series, pregnancy outcome seems to depend on the level of activity of maternal disease. One the other hand, the occurrence of a disease flare after an abortion has not been described so far. The sudden disruption of the immunologic tolerance associated with pregnancy and maternal exposure to fetal antigens may be considered as precipitating factors.

Conclusions: Our cases show different effects, even in the same patient, of the mutual interaction between pregnancy and anti-SRP myositis in different phases of the disease.

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SLEEP-RELATED BREATHING DISORDERS IN MSA: A CASE REPORT

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Objectives: We report a case of a patient with asymmetric akinetic-rigid parkinsonism associated with REM sleep behavior disorder (RBD) and nocturnal laryngeal stridor.

Materials: A 69-years-old woman came to our outpatient clinic for clumsiness and micrographia, with onset three years before. Over time,

she developed hypophonia with an increase in vocal pitch, rigidity on the right side, bradykinesia, and postural instability with a tendency to fall. On physical examination, she showed, especially on the right side of the body, plastic rigidity, impairment in motor dexterity, tremor at rest, postural and kinetic tremor. In addition, she presented slowness of gait with short steps, reduced arm swing, anterocollis, and absence of postural reflexes. A cerebral DaTscan SPECT revealed a bilateral impairment of the dopaminergic system (especially on the left). A brain MRI scan demonstrated lenticular hemosiderin deposits and atrophy of the cerebellar folia. Polysomnography diagnosed obstructive sleep apnea syndrome (OSAS) and REM sleep without atonia (RSWA).

Methods: The patient was admitted to our hospital and underwent routine laboratory tests, fiberoptic laryngoscopy, head-up tilt test, neuropsychological tests, lumbar puncture and video-polysomnography.

Results. The laboratory workup showed normal findings. CSF chemical, microbiological and immunological analyses and neurodegenerative biomarkers were unremarkable. The additional CSF search for IgLON5Ab was also negative. The neuropsychological tests were normal. The head-up tilt test showed neurogenic orthostatic hypotension. The fiberoptic laryngoscopy demonstrated the presence of vocal cords adduction palsy. The video-polysomnography showed periodic limb movements disorder (PLMD), reduction of the heart rate variability, REM sleep behavior disorder (RBD) and nocturnal laryngeal stridor. According to 2022 MDS-MSA criteria, we defined a "clinically established" MSA.

Discussion: Multiple System Atrophy (MSA) is a neurodegenerative synucleinopathy characterized by autonomic failure, akinetic-rigid parkinsonism or cerebellar syndrome, and sleep and breathing disorders, in varying combinations. Its clinical features can mimic other hypokinetic movement disorders or cerebellar syndromes, so initial misdiagnosis is frequent. The RBD is a highly-specific feature of α-synucleinopathies. The laryngeal stridor is a highly-specific hallmark of MSA and an independent poor prognosis predictor.

Conclusion: The diagnosis of MSA should be considered in patients with a history of sleep-related breathing disorders, such as laryngeal stridor. In this case, we remark on the role of video-polysomnography as a supporting tool for MSA diagnosis, fundamental for detecting RBD and laryngeal stridor, both negative predictors of disease course.

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COMPLEX COGNITIVE AND BEHAVIOURAL CONSEQUENCES OF A FOCAL LESION OF THE RIGHT CAUDATE NUCLEUS

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Objectives: To describe a cognitive-behavioural picture due to the lesion of uncertain aetiology of the right caudate nucleus.

Materials and Methods: This is the clinical case of a 58-year-old Italian woman with no previous medical history, who presented with progressive confusional state, attention deficit, and memory impairment.

Results: At assessment, the patient appeared alert, poorly oriented in time but oriented in space, sometimes confabulating, without any focal neurological deficits. Brain-MRI showed a non-enhancing T2 hyperintense lesion at the level of the head of the right caudate nucleus (CN), not conclusive for unambiguous interpretation. She underwent lumbar puncture: oligoclonal bands were observed, while microbiological tests for neurotropic agents and haematological tests were negative. Neuropsychological tests initially showed normal performances, except for a mild reduction in working memory. Intravenous corticosteroid treatment was carried out, with no benefit. In the following months, serial brain MRIs confirmed unchanged the lesion. Contrary to a stable radiological picture, the patient developed behavioural disorders characterised by a reduction in initiative and in affective output towards family members, hyperphagia, and, above all, increased interest in religious practices. She didn't show disinhibition or mood swings. After 14 months from the onset, she presented poorly collaborative, severely disoriented, therefore it wasn't possible to perform the complete neuropsychological battery. Pharmacological attempts with olanzapine and amantadine didn't involve any clinical changes. The 18C-Fluorodeoxyglucose-PET scan showed reduction in glucose metabolism in the right CN and, unexpectedly, the right temporal pole. After four years, the neuropsychological evaluation showed a widespread disturbance of the cognitive functions (memory, praxis, attention, visual-spatial analysis, language, executive functions).

Discussion and Conclusions: CN can be affected in several diseases, such as cerebrovascular, neurodegenerative, neoplastic and demyelinating diseases. The most frequent symptom in patients with lesion of the right CN due to ischemic stroke is abulia. CN is the first and the principal brain structure affected in Huntington's diseases, which is a hyperkinetic movement disorder associated with neuropsychiatric features, predominantly irritability, depression, and/or disrupted social relationships, cognitive impairment and dementia. The isolated lesion of the right temporal pole has already been associated with the absence of emotional response to family members, maintaining normal recognition. It has previously been shown that striatal subregions are functionally linked to cortical networks rather than discrete portions of cortical regions. Regarding our patient, we could speculate that the hypomethabolism at the level of the right caudate nucleus and right temporal lobe could reflect a network pathology.

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THE ALIEN LIMB

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Background: Sporadic Creutzfeldt-Jakob disease is a neurodegenerative disease leading to death in a very few months. It can manifest with different kind of symptoms, making difficult the diagnosis at first sight. A definite diagnosis is possible only with anatomopathological confirmation.

Case presentation: We describe a case of Sporadic Creutzfeldt-Jakob disease presenting with a cortico-basal syndrome as first symptom. The

patient came to our attention for some motor difficulties in the right hand and a dysarthric speech. At neurological examination we noticed an alien limb syndrome with apraxia/ataxia involving the right hand, without any lack of strength. Moreover, a scanned speech emerged, without a clear aphasia disorder. First diagnostic studies (EEG and MRI) were almost normal or non-specific, with some epileptic anomalies in the left parietal lobe. After three weeks of hospitalization, the clinical, neurophysiologic and neuroradiologic picture, changed from a very lateralized cortico-basal syndrome, involving the right hand, to a complex syndrome characterized by bilateral ataxia-apraxia, myoclonus, axial rigidity, and difficulties in postural changes. Moreover, the patient, left to herself, revealed a sort of palilalia, with repetition of syllables and meaningless words. The second EEG revealed a classical pattern of bilateral periodic triphasic waves of a 1-1.5 Hz frequency. The second MRI showed FLAIR hyperintensity in different cortical and subcortical regions leading to a probable diagnosis of Creutzfeldt-Jacob disease [1]. After two months and a half since the beginning of first symptoms our patient died. The very same day we received the result of CSF analysis with a positive RT-QuIC test.

Conclusions: Around 23 cases of Creutzfeldt-Jakob disease presenting as cortico-basal syndrome have been described in literature, and only 6 of them manifested the alien limb syndrome as first symptom [2]. Our case shows how an early detection of Creutzfeldt-Jakob disease could be insidious, because of a variable first clinical presentation. Indeed, classical symptoms, such as cognitive impairment, myoclonus, etc., can appear later. Furthermore, typical pattern in diagnostic examens can be absent at the beginning. A very rapid progression of clinical examination and diagnostic investigations is a red flag that should direct the diagnostic hypothesis towards a Creutzfeldt-Jakob disease.

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EFFICACY AND TOLERABILITY OF PERAMPANEL AS A FIRST ADD-ON IN A PATIENT WITH LATE- ONSET MYOCLONIC EPILEPSY IN DOWN SYNDROME (LOMEDS): A CASE REPORT

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Purpose: Late-onset myoclonic epilepsy in Down syndrome (LOMEDS) is progressive epilepsy characterized by the development of myoclonus, tonic/clonic seizures, and gradual cognitive and functional decline in patients with Down syndrome (DS) over age 40. The clinical course of LOMEDS is similar to other progressive myoclonic epilepsies, with gradual worsening in antiseizure treatment response. In this report, we analyze the use of Perampanel (PER) as adjunctive therapy in a patient with LOMEDS.

Methods: We describe the case of a 52-year-old man with a diagnosis of LOMEDS, who suffered from persistent daily myoclonic episodes since the age of 46. Over the years, myoclonus frequency increased, and some episodes were also associated with sudden falls and minor body trauma. Neurological clinical examination showed a marked impairment in speech fluency and mild bradykinesia. An ASM treatment with Levetiracetam (LEV) was started, then discontinued due to the onset of psychiatric manifestation and replaced with Valproic Acid (VPA), which was ineffective. Thus, adjunctive therapy with Perampanel (PER) 2 mg/die was started.

Results: Low dose of PER determined a significant reduction in myoclonic seizures and a modification of seizures' semiology with the disappearance of falls. A progressive improvement in the patient's daily life independency was also reported. No adverse effects were recorded.

Conclusions: The present report describes the potential efficacy and tolerability of PER low dose as adjunctive therapy in the treatment of myoclonic seizures in a patient with LOMEDS.

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ADVERSE EFFECT OF ANTI-TNF THERAPY: A CHALLENGING CASE OF CRYPTOCOCCAL MENINGITIS

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Objective: We describe a case of cryptococcal meningitis in an otherwise immunocompetent 50 year-old-patient receiving TNF inhibitor therapy.

Materials and methods: The patient, affected by psoriatic arthritis treated with adalimumab and generalized epilepsy from adolescence, was admitted in our emergency department for confusion, dizziness and seizures. On neurological examination the patient presented with mild ptosis, generalized weakness, mild facial weakness, hypoacusia. The patient subsequently developed a non-convulsive status epilepticus, mild fever and pneumonia. He was intubated and ventilated and admitted in the Intensive Care Unit. The patient underwent a CT and MRI scan of the brain, a cerebrospinal fluid (CSF) analysis (PCR for virus identification, bacterial and fungal culture test, ACE test, autoimmune screening test, and onconeural antibodies test, serology for atypical bacteria.

Results: Brain TC scan was negative while MRI scan showed a granulomatous meningoencephalitis with leptomeningeal contrast enhancement and basicranium involvement. ACE test was negative, as PCR for viruses and culture test for bacteria, fungal and mycobacterial infection in the CSF (repeated three times). VDRL and serology for atypical bacteria were also negative, as the autoantibody panel and onconeural antibodies. Suspecting a granulomatous aseptic meningitis as a complication of TNF-blockers therapy, high doses of steroids were administrated, with marked improvement of the symptoms and regression of the brain MRI alterations. After steroids dose escalation, the patient started to worsen with seizures, nystagmus, ocular misalignment and worsening of consciousness. A brain MRI scan was performed again and detected multiple parenchymal lesions in cortical and subcortical regions with signal restriction in DWI, with particular involvement of the brainstem, compatible with vasculitis. The patient developed an acute hydrocephalus and an external ventricular derivation was positioned. CSF analysis was performed from the derivation and cryptococcus was finally identified. Unfortunately, even with specific therapy, the patient died.

Discussion: Cryptococcus infection is not very common and may cause a meningitis in immunocompromised patients, with typical granulomatous lesions and multiple cranial nerve involvement. In our patient the therapy with TNF-blockers caused immunosuppression, causing both a granulomatous meningitis and a subsequent infective vasculitis.

Conclusions: This patient is emblematic because he presented a granulomatous meningeal involvement, that firstly improved after steroids, misleading the diagnosis. Only CSF analysis from external ventricular derivation was able to detect the fungus. With the spreading of immunosuppressive therapies for several autoimmune diseases, it is important to consider fungal meningeal infections even if the CSF analysis from lumbar puncture is negative.

INTRAVENOUS IMMUNOGLOBULINS AND CIDP: A RARE CUTANEOUS SIDE EFFECT

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Introduction: Intravenous immunoglobulins (IVIGs) are purified products derived from human plasma containing 95% IgG with biologically Fc-dependent effector activity. They cure dermatologic, neurologic, hematologic, and immunologic conditions. The adverse events related to IVIGs administration vary from mild (flu-like symptoms, headache, cardiac arrhythmia, hypo-hypertension) to serious event (vascular thrombosis, neurological and renal impairment) and occur in 40% of patients. Moreover, side effects may be immediate or delayed up 2 weeks after Ig termination and can occur at first infusion or after repeated infusions. IVGs-related dermatological reactions are nearly 6% of the total side-effects. They can develop immediately or up 14 days after infusion and require topic or systemic therapy. We report a case of a rare cutaneous reaction, studied and confirmed by skin biopsy.

Materials and Methods: A 57-year-old male was affected by Chronic Idiopathic Demyelinating Polyneuropathy (CIDP) from 20 years. He underwent steroid therapy and IVIGs Cycle (1/year) at standard dose (0,4 gr/kg/die for 5 days) for 15 years; then, because of diabetes mellitus and coronaric disease, he shifted to immunosoppressive therapy with Micofenolate plus IVIGs cycles with good response. Recently, for a fast disease-worsening he underwent to repeated cycles of IVIGs. One week after terminating the second cycle, he developed itchy lesions on the palm of his hands and sole of his feet. On physical examination there were crops of deep-seated blisters on the palms and soles, on an erythematous background, sometimes traumatized by scratching. IgE assay was normal and prick test with decreasing IVIGs dilutions (max 1/10) was negative. Palmar lesions biopsy showed spongiosis with an epidermal lymphocytic perivascular infiltrate. Clinical and pathological findings were consistent with a diagnosis of dyshidrotic eczema (DE). Topical corticosteroids (betamethasone 0.1%) fastly improved and resolved the lesions. A third IVIGs-cycle (2 months later) caused an earlier (on day 2° of the cycle) relapse of the cutaneous lesions.

Discussion: IVIGs therapy is a milestone of CIDP-treatment; its wide use may present immediate or delayed cutaneous side effects which may be related or unrelated to immunological mechanisms. DE is an infrequent and not serious dermatologic side-effect of IVIGs therapy, but its relapse and worsening during repeated cycles of IVIGs deserves attention and acknowledgement. A negative prick test excludes allergic-immunologic reaction and a skin biopsy, particularly if close IVIGs administration becomes mandatory to make an appropriate diagnosis, to reassure the patient and the clinician, and to properly treat the annoying lesions.

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A CASE REPORT OF FAVA SYNDROME IN A YOUNG WOMAN CARRYING PIK3CA GENE MUTATION

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Background: FAVA (Fibro-Adipose Vascular Anomaly) syndrome, first described by Alomari in 2014, is an extremely rare pathology (approximately 20 cases report-ed in the literature) characterized by fibrofatty infiltration of muscle (mainly in the lower extremities), unusual phlebectasia with pain and contracture of the affected ex-tremity [1]. Usually, it occurs in young females (median age, 12-17 years) but has been described also at birth or early adulthood [2]. FAVA is usually sporadic and frequently caused by a somatic mutation involving PIK3CA (Phosphatidylinositol-4,5-bisphosphate 3-kinase) gene, which activates mammalian target of rapamycin (mTOR) pathway, known to promote angiogenesis and lymphangiogenesis [3].

Case report: A 34-year-old woman was referred to our Unit in January 2022; the neurological exam showed overgrowth and weakness in the left lower limb with left foot drop and gait imbalance. The physical abnormalities were already present at birth, but weakness progressed very slowly over the years. Indeed, she became a par-alympic athlete, although she had to stop when she was 30 due to the impairment of her physical performance. An electroneuromyography of the lower limbs, per-formed at the age of 20, showed neurotmesis of left external popliteal nerve at the fibular head. At the age of 32, a musculoskeletal ultrasound of the lower limbs showed bilateral fibrous infiltration of biceps femoris, medial gastrocnemius, tibialis posterior and peroneal muscles; an MRI of the pelvis revealed muscle atrophy with diffuse fatty infiltration of gluteus minimus, gluteus medius, iliac and vastus lateralis muscles. A muscle biopsy of the vastus lateralis muscle did not show histologic evidence of fibrofatty infiltration, while genetic testing on the muscle sample demonstrated PIK3CA gene mutation, in particular a missense mutation at codon 542. In contrast, a previous genetic test of PIK3CA mutation performed on saliva, skin and blood samples was negative.

Conclusion: We hereby describe a new, peculiar case of FAVA syndrome. Relevant atypical features lie in the discrepancy between the slow progression of the motor function impairment up to the age of 30 and the relatively rapid progression of mus-cle atrophy. Another atypical feature is the absence of the characteristic fibrofatty infiltration at the histopathological examination of the muscle biopsy despite the presence of the PIK3CA gene mutation. This suggests that histological alterations are not mandatory for the diagnosis of FAVA syndrome, which should be considered as a differential diagnosis when evaluating vascular abnormalities in the lower limbs.

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CREUTZFELDT -JAKOB DISEASE PRESENTING AS NEW ONSET REFRACTORY NON CONVULSIVE STATUS EPILEPTICUS IN A RECENT SARS-COV-2 INFECTION: A CASE REPORT

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Background: Creutzfeldt-Jakob disease (CJD) is a human prion disease generally characterized by rapidly progressive dementia and myoclonus. CJD frequently mimics a wide range of potentially reversible or treatable disorders. Seizures are an uncommon finding in CJD (approximately 15% of patients) and only exceptional cases of non-convulsive status epilepticus (NCSE) have been reported in the literature.

Methods: We describe clinical, EEG, cerebrospinal fluid (CSF) and neuroimaging findings of a confirmed case of sCJD, characterised by a progressive aphasia initially diagnosed as NCSE.

Results: A 68-year-old woman with a history of hypertension and diabetes and a recent SARS-CoV-2 infection underwent a routine EEG for transient aphasia. EEG showed rhythmic sharp waves on left temporal regions, suggesting nonconvulsive status epilepticus. She had positive nasopharingeal swab for SARS-Cov-2. Despite the treatment with valproic acid, phenytoin, levetiracetam and later perampanel there were no changes in the EEG pattern and clinical status. Brain magnetic resonance imaging (MRI) revealed restriction of diffusion on left temporal and frontoparietal cortical areas and subtle hyperintensities in both nucleocapsular areas and a few areas of the cerebral white matters. Routine CSF results were normal. Due to suspected encephalitis post covid infection, intravenous immunoglobulin therapy was started, without clinical improvement. An impairment of level of consciousness and aphasia was progressively observed associated with the subsequent appearance of right hemiparesis. Positive 14-3-3 protein in the cerebrospinal fluid, confirmed a diagnosis of CJD and the patient died after 40 days from admission.

Discussion: Our case and the rare case reports in literature [1] show that the diagnosis of CJD should be considered in patients presenting with rapidly progressive aphasia or decline in mental status associated with ictal EEG pattern or NCSE.

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AUTOIMMUNE BRAIN ENCEPHALITIS AFTER ADMINISTRATION OF TWO VACCINES

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Objectives: Severe acute respiratory syndrome coronavirus two (SARS-CoV-2) is a pathogenic coronavirus that was discovered in later 2019 and has caused a pandemic of acute respiratory disease, named 'coronavirus disease 2019 (COVID-19)', which can lead to systemic complications. From the beginning of the pandemic, global efforts have been focused on developing vaccines for COVID-19 prevention, which have been distributed worldwide. However various complications have been reported so far, among which neurological ones include seizures, Guillain Barrè, autoimmune encephalitis. (1). We report a case of autoimmune encephalitis following contemporary administration of anti SARS-COV2 and influenza vaccines.

Materials and Methods: A 73 years –old caucasian woman received the third dose of the COVID-19 Vaccine Moderna mRNA -1273 and quadrivalent influenza vaccine in the same day. In the following two days she experienced side effects such as malaise, localized pain, fever which lasted one day. After six days from vaccine administration neurological condition worsened with appearance of expressive aphasia, bilateral ideomotor apraxia and agraphia without meningism. Her medical history was unremarkable.

Results: Electroencephalogram revealed fronto-temporal bilateral epileptiform activity while lumbar puncture with cerebrospinal fluid (CSF) revealed pleocytosis of 61 leukocytes (mononucleated cells)/μl with elevated protein levels (61 mg/dL, reference range: 15-45). Brain magnetic resonance was normal particularly excluding stroke, herpes encephalitis, brain tumors. FILMARRAY™ Meningitis/Encephalitis Panel for common pathogens that cause central nervous system infections (including viruses, bacteria and yeast) in CSF resulted negative. Blood exams resulted all normal except for erythrocyte sedimentation rate (42 mm, reference range: one-32) and C reactive protein (5.3 mg/L, reference range: <5.0).

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CAVERNOUS SINUS SYNDROME AS THE FIRST PRESENTING SIGN OF METASTATIC CHOLANGIOCARCINOMA

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Objectives: Cholangiocarcinoma is poorly treatable and highly lethal adenocarcinoma of the hepatobiliary system. The incidence of brain metastases was 0.15%, 0.47% and 1.4% in three large case series [1]. Cavernous sinus syndrome (CSS) refers to any disease involving the cavernous sinus. It is characterized by ophthalmoplegia, proptosis, chemosis, but also trigeminal sensory loss and Horner's syndrome [2]. We report the case of a 56-year-old Caucasian woman evaluated due to partial Horner syndrome, periorbital and retroorbital unilateral moderate-to-severe headache involving the frontal and temporal regions.

Materials and Methods: Brain magnetic resonance imaging revealed thickening of the cavernous sinus because of the presence of abnormal

soft tissue isointense on T1, hypointense on T2, with homogeneous enhancement after contrast. She was treated with glucocorticoids (intravenous Methylprednisolone and oral Desametasone) considering the hypothesis of Tolosa - Hunt Syndrome, but without improvement in pain and neurological signs.

Results: After three weeks chest computer tomography was performed, revealing multiple bilateral round nodule compatible with metastases. Abdomen computer tomography showed adrenal and liver metastases, which were biopsied revealing a moderate to poorly differentiated adenocarcinoma, consistent with cholangiocarcinoma, with immunostains positive for cytokeratin (CK)7, CK20, CK19, CDX2. Brain magnetic resonance imaging pattern after one month resulted similar to the former. CA 19.9 resulted >12.000 (normal value <37), gamma-glutamyltransferase (68 UI/L) and total bilirubin resulted mildly elevated (1.87 mg/dl). At present time hypofractionated stereotactic radiotherapy (3-30 Gray) has been planned to apply to the brain lesion such as chemotherapy treatment (gemcitabin oxaliplatin- GEMOX).

Discussion: The previously reported neuro-ophthalmologic presentations of cholangiocarcinoma include one case of a clival mass and sixth cranial nerve palsy, one case of metastasis to the medial rectus muscle and diplopia, two cases of metastasis to the occipital lobe and homonymous hemianopia, and one case of a hypercoagulable state-related stroke and homonymous hemianopia [3]. There have also been two reports of cholangiocarcinoma metastasizing to the orbit presenting with eye pain, one of a combined hepatocellular carcinoma/cholangiocarcinoma metastasizing to the retina and vitreous and an isolated sixth cranial nerve palsy, which was the harbinger of a brain metastatic sellar/suprasellar mass [1].

Conclusions: This case can be considered peculiar due to clinical presentation (cavernous sinus syndrome) and the difficulty in performing differential diagnosis with Tolosa Hunt Syndrome (similar both in clinical presentation and neuroradiological pattern, but not improving after three weeks of continuous steroid treatment). It also underlines the importance of differential diagnosis in patients with atypical headache.

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CEREBELLAR BOTTOM-OF FISSURE DYSPLASIA: TWO CASE REPORTS

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Objectives: Cerebellar bottom-of fissure dysplasia (BOFD) is a novel entity that has been introduced to delineate the neuroimaging findings of a cerebellar gray matter pattern that was firstly described in 2015. Etiology was unknown and a malformative nature of BOFD was suspected. Cerebellar BOFD was differentiated from bottom-of-sulcus dysplasia^ (BOSD), because it was usually multiple, didn't have a "tail" into the white matter, and were preferentially located within the inferior and lateral aspects of the cerebellar hemispheres. In addition, cerebellar BOFDs were not epileptogenic. We report two cases of a 50 years-old Caucasian woman and man with a brain MRI pattern suggestive for cerebellar bottom-of fissure dysplasia. Neurological exam was normal. Familial and medical history were unremarkable.

Materials and Methods: She was evaluated due to persistent left ear pain and dizziness, for which she performed brain magnetic resonance imaging (MRI) showing right thickened cerebellar folia with cerebellar asymmetry of sulci and ipsilateral atrophy without contrast enhancement or high-signal intensity on diffusion-weighted imaging (DWI) sequences, stable at follow-up after one year. A 50 years-old man from Albany was evaluated due to persistent tension-type headache. Neurological examination was normal while MRI showed bilateral BOFD among semilunar lobules.

Discussion: Wright et al in 2020 evaluated twenty-three children with MRI imaging findings of focal T2 prolongation in the cerebellar gray matter and immediate subjacent white matter at the depth of the fissures. They found stereotyped pattern attributable to cerebellar watershed injury due to the following reasons: 1) location at the deep borderzone between the cerebellar artery vascular territories, 2) association with a classic watershed pattern of supratentorial cortical injury, 3) frequent acute-phase diffusion restriction with expected evolution across time, and 4) frequent late foliar volume loss with fissural prominence. De Cocker et al found the same results in 138 cerebellar infarcts observed in 70 different patients. They concluded that the depth-of-fissure sign, which is best appreciated in the coronal or sagittal plane, is an easy MRI imaging sign to diagnose cerebellar infarcts in all stages and applies to adults in addition to children but more studies are needed.

Conclusion: Both our patients doesn't present known risk factors for cerebrovascular disorders and both of them don't present neuroradiological elements attributable to cerebellar watershed injury. They don't have risk factors for cerebrovascular disorders. In both of cases we support the malformative hypothesis for BOFD. However MRI follow-up will be performed.

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LONGITUDINAL EXTENSIVE TRANSVERSE MYELITIS (LETM) AFTER SARS-COV2 VACCINE ADMINISTRATION

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Objectives: Severe acute respiratory syndrome coronavirus two (SARS-CoV-2) is a pathogenic coronavirus that was discovered in later 2019 and has caused a pandemic of acute respiratory disease, named coronavirus disease 2019 (COVID-19), which can lead to systemic complications. From the beginning of the pandemic, global efforts have been focused

on developing vaccines for COVID-19 prevention, which have been distributed worldwide. However various complications, among which neurological ones, have been reported so far. Vaccine related longitudinal extensive transverse myelitis (LETM) is rare (estimated acute myelitis is approximately 1.739/per million people). Early diagnosis and treatment of LETM can benefit the recovery and prevent recurrence. We report the case of a 60 years-old Caucasian woman who developed LETM after third dose of SARS-COV2 Vaccine.

Materials and Methods: She was evaluated due at our emergency ward due to acute paraparesis with bilateral lower limbs sensory involvement and neurological bladder started about seven days after administration of vaccine (Moderna mRNA-1273) anti SARS-COV2. She hadn't noticed any reaction after previous two doses of vaccine. Her medical history was unremarkable. Infectious disease of central nervous system was ruled out by the cerebrospinal fluid (CSF) analysis and virus culture while CSF study revealed intrathecal oligoclonal bands synthesis. SARS-COV2 PCR and swab resulted negative. Brain magnetic resonance imaging (MRI) with contrast of the whole spine was performed revealing intramedullary-enhancing lesion over the spinal cord from T2 to T5 segments. Blood immunological and coagulation exams resulted all normal. The patient received pulse therapy with 1000 mg of methylprednisolone daily for 5 days and had a dramatic improvement in the limb weakness such as sensory symptoms.

Discussion: Acute transverse myelitis is a neurologic condition characterized by bilateral lower extremity weakness, sensory loss and bowel and bladder dysfunction. Whereas the time of onset may be hours to days, the time to either partial or complete recovery may require months. Variable etiologies have been recognized even sometimes it can be idiopathic. LETM is a very uncommon condition, even rare after vaccine administration. However, some studies have reported acute myelitis occurrence following administration of other vaccines, including diphtheria, tetanus toxoids and pertussis vaccine and many others. Case reports have also been reported after SARS-COV2 vaccines administration.

Conclusion: Clinicians should be aware of possible adverse events potential dependent on vaccines administration, in order to be able diagnose and promptly treat them, even if benefits of vaccination still outweigh the associated risks.

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POSSIBLE PHACE (PACE) SYNDROME IN AN ADULT: CASE REPORT

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Objectives: PHACE syndrome (posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities/coarctation of the aorta, eye anomalies) is characterized by large infantile hemangiomas (IH) of the face, neck, and/or scalp that are associated with developmental defects [1]. Over 300 cases of PHACE syndrome have been reported, and it is considered one of the most common neurocutaneous vascular disorders in childhood [2,3]. We report the case of a 75 years-old caucasian man who recently received diagnosis of possible PHACE syndrome.

Materials and Methods: Our patient was evaluated due to worsening of gait with recurrent falls. His medical history was positive for neurocognitive development delay, psychosis, left ear hearing loss. Neurological examination showed slowing down of articulatory movement with monotonous and "scanning speech", upper limbs bilateral intention tremor, bilateral dysmetria and adyadocokinesis, marked ataxic gait, lower limbs hypotrophy with hypopallesthesia and areflexia. No facial or neck hemangioma were present.

Results: He performed brain magnetic resonance showing left cerebellar hemisphere, basilar artery and left vertebral artery hypoplasia, multiple cavernomas involving right pontine tegmentum (Zabramski II), left temporo-occipital and right frontal lobes (Zabramski III). On the basis of 2016 consensus criteria and considering the presence of 2 major criterias without IH, diagnosis of possible PHACE syndrome was performed [1].

Discussion: A multidisciplinary group drafted initial diagnostic criteria which were stratified into 2 categories: (1) PHACE syndrome or (2) possible PHACE syndrome (3). Major and minor criteria were determined for the following organ systems: cerebrovascular, structural brain, cardiovascular, ocular, and ventral/midline. Definite PHACE requires the presence of a characteristic segmental hemangioma or hemangioma ≥5 cm on the face or scalp plus 1 major criterion or 2 minor criteria. Possible PHACE requires the presence of a hemangioma ≥5 cm on the face or scalp plus 1 minor criterion. In our case basilar artery hypoplasia with agenesis of left vertebral artery associate with ipsilateral cerebellar hypoplasia could be considered as two major criteria which could allow us to perform diagnosis of PHACE syndrome.

Conclusions: We report a rare case with diagnosis of possible PHACE (or PACE considering the absence of cutaneous hemangioma) in an adult with cerebellar signs and neurocognitive impairment. We think that clinicians, especially neurologists, should consider diagnosis of PHACE syndrome when evaluating patient with cerebral and cerebellar malformations, even without cutaneous hemangioma. We also suggest that the presence of multiple cavernous manifestations should be included among additional PHACE diagnostic criteria.

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INSPECTING PROGRESSION TRAJECTORIES IN AMYOTROPHIC LATERAL SCLEROSIS BY USING PROCESS MINING: A PILOT STUDY

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Objectives: Process Mining (PM) is a a family of techniques that supports the analysis of operational processes starting from data recorded by an information system and structured as Event Log. The mined processes can be used to detect evolution clusters or inspect how patient characteristics affect progression. The main objective of this study is to develop PM-based models of ALS progression by analyzing clinical history in real-world patients. Specifically, we aim to implement a methodology that, starting from a retrospective collection of clinical information, allows us to investigate how disease trajectories evolve.

Material and Methods: We used two Process Discovery methods, namely the Directly-Follows Graph and the CareFlow Miner, in order to characterize population disease trajectories. We obtained data from two databases which are the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) dataset and a real-world database (ALS-BS) including data from patients followed-up in two tertiary centers of Brescia. Data on functional abilities progressively impaired were collected using the ALS Milano-Torino staging system (MITOS). We investigated the progression trajectories, transition probability and timing between events.

Results: The ALS-BS dataset (n = 43) showed similarities to PRO-ACT in terms of patients' sex (p=0.123), age (p=0.034), weight at baseline (p=0.019) and disease duration and progression (p=0.201). In PRO-ACT the observed follow-up was shorter (407.06 ± 175.27 days in PRO-ACT vs 931.49 ± 627.49 in ALS- BS) but overall disease duration was similar (1063.03 ± 456.22 vs 1063 1241.67 ± 722.13). In contrast, FVC (82.2 vs 96.47, p<0.01) and total ALSFRS-R (30.12 vs 36.12, p<0.01) measured at the first visit were significantly higher in ALS-BS datasets. We analyzed the average time required to reach the impairment of various functional domains. The transition from the walking to communication impairment took 200 days in PRO-ACT and 230 days in ALS-BS dataset (p=0.66), the transition to respiratory involvement was longer in ALS-BS (250 and 420 days respectively, p=0.08) and the four-domain impairment occurred 100 days later in ALS-BS. BS cohort showed a longer median time to reach each functional impairment, although not statistically significant, possibly due to the small number of patients in the cohort.

Discussion and Conclusion: We preliminarily demonstrated that PM could provide an overview of the evolution of two different ALS populations. Future work will consist in the inclusion of more events in the trajectories, such as the administration of nutritional/respiratory support, to reach better description and projection of the disease progression.

PRKN GENE DELETION-ASSOCIATED PARKINSON'S DISEASE: LONG-TERM OUTCOME AFTER SUBTHALAMIC DEEP BRAIN STIMULATION

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Introduction: Parkinson's Disease (PD) patients carriers of Parkin gene (PRKN) mutations show good response to subthalamic deep brain stimulation (STN-DBS)[1]. However, the possibility exists that different PRKN mutations could lead to heterogeneous long-term outcomes. To date, no STN-DBS follow-up longer than 5 years in PRKN-mutated patients are reported.

Objectives: To report the 15-year follow-up after STN-DBS of a PD patient presenting a compound heterozygous deletion of exons 3 and 11 of the PRKN gene.

Case report: In 1993, a 39 years-old male reported the onset of tremor in his left upper and right lower limbs; he was diagnosed with PD one year later, and levodopa was started; during the following ten years, he reported a good motor symptoms control, with only a mild modification of levodopa intake and introduction of pramipexole. In 2005 he developed disabling motor fluctuations and dyskinesia; entacapone was started, but immediately interrupted for visual hallucinations. The genetic diagnosis was made in 2006. In 2007 he was implanted with bilateral STN-DBS, with a marked improvement of motor symptoms, motor fluctuations, and activities of daily living. Levodopa equivalent daily dose decreased from 1125 to 850 mg. After six years, he reported mild motor fluctuations, which improved after stimulation parameters and oral treatment modifications. After ten years he showed mild diphasic dyskinesias, right foot dystonia, postural instability (with occasional falls), and pathological gambling, which disappeared after pramipexole discontinuation. Since 2018 (11 years after STN-DBS) he developed a single-domain (executive functions) MCI. In April 2022, fifteen years after DBS implantation, motor symptoms and fluctuations are still well controlled with levodopa/benserazide 200 mg 6-times a day, and stimulation set at 3.3 V, 60 usec, 130 Hz bilaterally; he reports mild dysphagia, symptomatic orthostatic hypotension, and MCI (MoCA score 26/30). MDS-UPDRS scores are: 21 (part I), 18 (II), 30 (III), and 8 (IV).

Conclusion: More than 40% of PRKN mutations result from structural variants of one or several exons.[2] About half of the changes affect the region spanning exons 2–4, with deletion of exon 3 being the most frequent mutation. Although heterozygous deletions of the PRKN gene in early-onset PD patients are widely described,[3] no reports of STN-DBS outcomes are available for compound heterozygous deletion of exons 3 and 11. Our case, with the longest follow-up available from STN-DBS in PRKN-associated PD confirms the good long-lasting outcome, with a marked improvement in motor symptoms/fluctuations and no significant worsening of cognitive profile.

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A CASE OF MULTIPLE SCLEROSIS RELAPSE DURING SARS-COV-2 INFECTION – WHAT SHOULD WE DO?

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Introduction: Immunosuppression and immunodeficiency are among the most significant predictors of COVID-19 severity [1]. Although the impact of long-term immunosuppressive treatments is still debated there are several evidences of an increased risk of death in patients treated with high-dose corticosteroids during SARS-CoV-2 infection [2].Herein we describe a case of Relapsing Remitting Multiple Sclerosis (RRMS) patient treated with teriflunomide in which the presence of a disease relapse during SARS-CoV-2 infection put us at a crossroads: treat the patient with high dose corticosteroids exposing her to an increased risk of developing severe COVID-19 or wait for a negative nasal swab and then treat?

Case: A 53-year-old woman affected by RRMS in treatment with teriflunomide without other medical conditions, EDSS 0, presented at the emergency department for subacute onset numbness and weakness on the left side of her face, and hearing loss. Given the high probability of a relapse, we decided to begin treatment with high-dose corticosteroids. Before starting the infusion, during the routine covid-19 nasal swab, the patient tested positive for asymptomatic SARS-CoV-2 infection. In order to avoid the possible evolution towards an aggressive form of COVID-19 secondary to high-dose corticosteroid treatment, we decided to treat the patient with Paxlovid (nirmatrelvir/ritonavir) administered twice a day for 5 days before starting corticosteroids. Immediately after the antiviral therapy, neurological symptoms started to regress and the patient refused administration of corticosteroids.

Discussion: This is the first described case of an MS relapse during SARS-CoV-2 infection. The use of high-dose intravenous or oral corticosteroids for MS relapses is a well-established treatment indicated in all the acute MS exacerbations that result in neurologic symptoms and increased disability. Nevertheless, several studies have suggested the harmful effects of high-dose corticosteroids in COVID-19 patients [3]. EMA recently approved Paxlovid as a therapy for COVID-19 adult patients who do not require supplemental oxygen, but who are at increased risk of a severe course of the disease. The drug is generally well tolerated but, in a few cases, can produce mild liver damage. Our case forced us to make a decision; we chose to treat the patient with Paxlovid before the administration of corticosteroids in order to reduce the risk of progression toward a more severe form of COVID-19.

Conclusion: In our case, given the limitation due to the decision of the patient to refuse the corticosteroid infusion, we propose a possible approach that can be pursued by clinicians who might face similar situations.
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GALCANEZUMAB IN UNREMITTING SUBTYPE OF HEMICRANIA CONTINUA: A CASE REPORT

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Introduction: Hemicrania Continua (HC) is a rare disorder belonging to the trigeminal autonomic cephalalgias (TACs) together with Cluster Headache (CH) and SUNCT. Recent studies showed that HC shares pathophysiological mechanisms with migraine, especially the activation of the trigeminal vascular system and the CGRP signaling pathway. Anti-calcitonin gene-related peptide (CGRP)/CGRP-Receptor (R) monoclonal Antibodies (mAbs) are the first specific therapy for migraine. Among this, Galcanezumab also showed efficacy in episodic CH at higher dose than migraine, although currently scanty data are available regarding its use in other forms of TACS. In literature a case of HC and a case of SUNCT were reported to respond to Galcanezumab. Here, we report a case of a woman with resistant HC responding to off-label treatment with Galcanezumab.

Case Report: A 28-years old woman was affected by HC, unremitting subtype, according to ICHD-3 criteria. She got a beneft with Indomethacin 100 mg/die but relapse after its discontinuation. She tried several pharmacological prophylaxes (amitriptyline, topiramate, gabapentin and propranolol) with no effect. A partial response was obtained with Flunarizine, but with significant weigh gain. Considering the poor tolerability and efficacy of canonic treatments and the significant deterioration of daily functioning due to headaches, we decided to administer Galcanezumab, with an initial loading dose of 240 mg followed by monthly dose of 120 mg (doses indicated for migraine). At 3 months follow-up she reported a progressive improvement in headaches frequency, with only 2 headache days/month. No adverse side events were referred.

Discussion: This first Italian case suggests that Galcanezumab could be successfully used in HC prophylaxes at dose indicated for migraine and with low side effects compared with traditional oral medication commonly used for primary headaches. Furthermore, our results seem to confirm the possible role of CGRP pathway in HC pain onset and manteinance.

Conclusion: According to the limited data currently available, this case supports the hypothesis that CGRP plays a key role in TACs. Further studies are needed to clarify if anti-CGRP/R mAb can be routinely used in HC prophylaxis, at least in resistant patients.
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AN 85-YEAR-OLD WOMAN WITH ACUTE-ONSET DYSARTHRIA: STROKE OR MYASTHENIA?

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Introduction: Stroke is the leading cause of disability worldwide with an incidence of 670-990 cases per 100.000 persons among those aged > 65 years [1]. Myasthenia Gravis (MG) is a rare disorder with an incidence of 1/100.000 in general population, but more than one third of all cases in the over 65 year-olds (Very Late Onset MG) [2]. Estimation of MG underdiagnosis is elevated in elderly individuals, especially aged over 80, in whom stroke constitutes a frequent chameleon for less common diseases [3.]

Case report: An 85-year-old woman, known for hypertension and a recent hospitalization for aphasic Transient Ischemic Attack (TIA), presented at the emergency room because of dysarthria occurred on awakening. Neurological examination confirmed dysarthria and no other neurological signs, in particular normal muscle strength without fatigability and normal single breath test. Urgent cerebral CT scan was negative for new parenchymal lesions. TIA or minor stroke was not excludible: thrombolysis was not indicated because of timing, a double disaggregant therapy with aspirin and clopidogrel was introduced. During the successive observation, the neurologist noted that dysarthria completely resolved when the patient was silent for at least 20-30 minutes and reoccurred,

gradually worsening, after continuous prolonged talk. Myasthenia Gravis with bulbar acute onset was suspected and confirmed by a neurophysiological study indicative of a postsynaptic disturbance of neuromuscular transmission and positive Antibodies to the Acetylcholine Receptor. Clopidogrel was stopped while Piridostigmine was introduced with significant clinical improvement.

Discussion: We report the case of an 85-year-old woman with history of hypertension and TIA presented at the emergency room for a sudden-onset dysarthria, initially treated as acute cerebrovascular event and successively diagnosed as very late onset Myasthenia Gravis. In this situation, the key for diagnosis redirection was a longer and comprehensive neurological examination that allowed the demonstration of a fatigability-related dysarthria. Prompt consideration since the emergency setting of MG in isolated bulbar symptoms is fundamental, because stroke management often impose quick decisions about indication to effective but potentially risky treatments1. On the other hand, MG could rapidly get worse and early identification prevents further deterioration and administration of unnecessary drugs [1-2].

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NEUROSARCOIDOSIS AS A RARE AND REVERSIBLE CAUSE OF HYDROCEPHALUS: A CASE REPORT

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Introduction: Neurosarcoidosis occurs sintomatically in 5-10% of patients with sarcoidosis and it is complicated by hydrocephalus in 10% of the cases [1].

Case report: A thirty year-old man developed vertigo, headache and hypoacusia. Brain and spinal cord MRI evidenced white matter hyperintense lesions, nodular leptomeningeal enhancement along the skull base and the spinal canal, enhancement of the second cranial nerves and the cauda aequina. Cerebrospinal fluid analysis showed lymphocytosis with elevated CD4/CD8 T-cell ratio, oligoclonal bands and negative microbiological tests. Body imaging evidenced lung and mediastinal lymphadenopathies histologically defined as non chaseating granuloma. All the investigations finally supported the diagnosis of probable neurosarcoidosis and excluded limphoprolipherative or infectious diseases. The patient initially recovered with prednisone, but subsequently he developed intense headache, slowdown and seizures. A new MRI showed lateral ventricular dilatation, periventricular seepage and contrast enhancement of ependima at foramina of Monro and Luschka and cerebral aqueduct. Prompt administration of high-dose intravenous methylprednisolone, levetiracetam and acetazolamide allowed a rapid recovery sparing neurosurgical intervention. Then introduction of methotrexate ensured clinical and radiological stability.

Conclusion: We report a case of sarcoidosis presented as aseptic meningo-encephalo-radiculitis complicated by hydrocephalus. Diagnostic assessment of neurosarcoidosis requires, as in our case, numerous systemic and neurological investigations to demonstrate granulomatous inflammation and to exclude other aetiologies [2-3]. Treatment is empiric and starts with prednisone [3], not enough in our patient. High dose metylprednisolone and the following maintenance with methotrexate determined regression of a potentially life-threating condition and prolonged stability.

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CLINICAL FEATURES OF A CASE OF CHOREA-ACANTHOCYTOSIS ASSOCIATED WITH A RARE VPS13A MUTATION

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Objectives: Chorea-acanthocytosis (ChAc) is a rare AR neurodegenerative disorder caused by loss-of-function mutations of the vacuolar protein sorting isoform 13A gene (VPS13A), which comprises 73 exons and is located on chromosome 9q21. The gene encodes for a protein termed chorein, an essential player in the membrane homeostasis in different cell organelles. [1] The VPS13A gene variants reported include missense, nonsense, frameshift, duplication, deletion, and splice-site mutations. [2] Onset of the disease is usually in adulthood, and it follows a progressive course. Here, we report on ChAc patient with a complex phenotype, genetically characterized by an infrequent homozygous VSP13A mutation.

Case Report and Methods: A 36-years-old man presented with a years-long progressive history of hyperkinetic movements, tics, dysphagia, and gait disturbances. There was no family history of neurological diseases, and the parents were not consanguineous. The past history revealed febrile convulsions when he was 3-years-old and, more recently, epileptic generalized seizures, now under control with levetiracetam and lacosamide. Because of slight stepping and dyskinetic gait, with increased CK, he underwent EMG/ENG, which documented polyneuropathy. Furthermore, he suffered from depression, social withdrawal, phobias, and obsessive behaviour. An unusual finding was the presence of an advanced cataract and early-onset severe myopia. MRI confirmed a discrete bilateral caudate atrophy; Blood counts and biochemical and CSF workups were negative, besides elevated serum CK. A blood smear has not been performed yet. The complexity of symptoms raised the suspicion of a Neuro-Ac, prompting genetic testing that demonstrated a homozygous variation c.9276-2A>T in the VSP13A gene by exome sequencing and multigene analysis. This mutation belongs to the class IV ACMG.

Results and Discussion: We have presented a case of an AR ChAc caused by a homozygous mutation of the VPS13A gene. The c.9276-2A>T mutation is an intronic splice site variant in the intron 70 and is

localized at a conserved nucleotide position. Therefore its potential pathogenicity is high. This variant is so rare that it is absent from the gnomAD database of control subjects. Our patient is the second case reported with this mutation. He showed a complex ChAc phenotype associated with the contemporary presence of unusual ophthalmologic disorders.

Conclusion: We have described a ChAc patient from non-consanguineous parents associated with an infrequent VPS13A intronic mutation, likely affecting mRNA splicing. These findings support the need for regular genetic screening in patients with complex neurological phenotypes, like neuroacanthocytosis syndromes, to reduce misdiagnoses and enable appropriate genotype/phenotype correlations. [3]
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NON-INFECTIOUS ENCEPHALOPATHY WITH RECURRENT STROKE-MIMIC EPISODES

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Objectives: To describe a 65-year-old man with stroke-mimicking events presenting a cognitive deterioration and radiologic findings of lepto- and pachi-meningitis at the MRI.

Methods: A 65-year-old man came to our attention in the emergency room because of the acute onset of anomic aphasia with no signs of recent ischemic lesions and no signs of major vessels occlusion to the CT-scan and CT-angiography. Given the low-grade NIHSS, fibrinolysis wasn't performed and he was admitted in Stroke Unit. During the last year he had multiple episodes of acute neurologic deficits that required hospitalization and various head CT scans never documented acute ischemic lesions. In the last episode DAPT was started. He was in treatment also with antipsychotic for depressive-psychotic disorder and with Levetiracetam for a post-traumatic epilepsy because of a car accident 2 years ago. During the stay in Stroke Unit, the man presented inconstant focal neurological signs associated to marked cognitive impairment (MMSE 16.4/30). The electroencephalogram showed only a frontal intermittent rhythmic delta activity (FIRDA). The MRI demonstrated pachy- and lepto-meningeal thickening and impregnation.

Results: The CSF evaluation showed hyperproteinorrachia, barrier damage without oligoclonal bands and no signs of infection. Onconeural antibodies were negative. The Total-Body CT showed interstitial thickening, but no signs of malignancies. Extensive blood workup to detect coexisting immunological disorders revealed Rheumatoid Factor 135 UI/L (<15), ESR 95 mm, and Anti-citrullinated peptide antibody 52.6 AU/mL Therefore, it was formulated a diagnosis of high-activity Rheumatoid Arthritis (RA) with systemic involvement. The pulmonary interstitial disease and the meningitis were linked to the RA and a targeted treatment was started. After three months of therapy with Prednisone and Methotrexate the patient could walk unaided, spoke fluently and without anomic difficulties. The neuropsychological evaluation showed a marked improvement in all fields (MMSE 27.86). In the following months he no longer needed hospitalization for neurological acute events. The last MRI after 3 months of therapy showed a reduction of the meningeal lesions and the resolution of the pachymeningeal contrast-enhancement.

Discussion, Conclusion: A rare CNS complication of Rheumatoid Arthritis is Meningitis. The diagnosis of Rheumatoid Meningitis is made when the MRI shows thickening and/or contrast-enhancement of the meninges, and blood tests and CSF analysis exclude the presence of infections, malingnancies or other autoimmune diseases. The clinical manifestations can mimic many neurological disorders making the diagnosis difficult. The correct recognition of this disorder is essential to avoid treatment delay.
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CHOREA AND BASAL GANGLIA HYPERMETABOLISM AS INDICATORS OF APS AND PROBABLE-APS

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Objectives: Chorea is a rare manifestation of Antiphospholipid Antibody Syndrome (APS). It has been hypothesized a direct non-thrombotic interaction of APL antibodies with neurons of the dopaminergic nigro-striatal pathway. This interaction could determine membrane depolarization that would result in chorea as clinical manifestation. Several clinical manifestations of the APS have been excluded from the diagnostic criteria of the syndrome, including neurological. These manifestations have been included in a separate category viz "Probable APS" since they could predate the development of actual thrombosis. Long-term therapy of these patients with either antiaggregant or anticoagulant might have to be considered.

Materials: A 77-year-old-woman was admitted for subacute onset of choreiform movements affecting the limbs of the left side of the body, associated with a mild slowdown of ideomotor processes and impairment of speech. Her medical history revealed one miscarriage at the fourth month and a full-term pregnancy.
Methods: In the hypothesis of APS, lab analyses revealed high titres of aCL, abeta2GPI and LAC antibodies, the absence of complement consumption and prolonged aPTT combined with in-range platelets level. Brain MRI showed a mild chronic vasculopathy. 18F-FDG PET scan showed a hyper-metabolism of the basal ganglia.

Results: Based on the high aPL titre, FDG-PET hyper-metabolism of the basal ganglia and lack of MR-ischemic findings suggestive for thrombosis, a diagnosis of Probable-APS was made. A symptomatic treatment with haloperidol was started, determining complete remission of the motor symptoms, that persisted at a 12-week follow-up evaluation. In parallel a preventive treatment with aspirin was started, in absence of further thrombotic complications.

Discussion: Movements disorders associated with hypermetabolism of the basal ganglia can be features of APS and Probable-APS. We hypothesize a role of 18F-FDG PET in the diagnostic process to assess basal ganglia hypermetabolism, since brain MRI alone would prove inconclusive or negative. In absence of a medical history characterized by thrombotic events, such assessment would support a Probable-APS diagnosis, thus allowing to start an appropriate preventive treatment (with either antiaggregant or anticoagulant) anticipating thrombotic complications, such as cerebral infarction, as a consequence of the transition to overt APS.

Conclusions: This case report outlines the importance of aPL titres assessment in patients with choreiform disorders and the role of 18F-FDG PET in the diagnostic process, since even in absence of a thrombotic medical history, such assessment would support a Probable-APS diagnosis, thus allowing to start an appropriate preventive treatment (with either antiaggregant or anticoagulant).

MILD ENCEPHALOPATHY WITH REVERSIBLE SPLENIAL LESION (MERS): A RARE ETIOLOGY OF A RARE SYNDROME

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Introduction: Mild encephalitis/encephalopathy with reversible splenial lesion (MERS) is a rare clinico-radiological syndrome generally presenting with mild central nervous system symptoms such as consciousness disturbance, seizures and headache recovering within a month. MERS is also called reversible splenial lesion syndrome (RESLES) or, according to the MR features, cytotoxic lesions of the corpus callosum (CLOCCs). MERS can be triggered by infections, antiepileptic drugs, malignancy, subarachnoid hemorrhage, metabolic abnormalities, trauma and other causes. Adult- onset MERS is relatively rare. Here we describe a case of MERS associated with covert HIV positivity.

Case report: The patient was a 24-year-old male without any relevant disease history. He presented to our ER for drowsiness, disorientation and slurred speech with onset after prolonged sun exposition. Neurological examination did not show focal abnormalities nor meningeal signs. Blood pressure and body temperature were normal. He underwent lumbar puncture for CSF examination which was normal. Film array on CSF for common encephalitis and meningitis viruses was negative. He tested negative at nasopharyngeal swab for SARS-COV2 and other respiratory viruses. Brain MR showed diffuse corpus callosum and corona radiata high-signal-intensity on T2, FLAIR, and DWI sequences and decreased ADC of the lesion on ADC maps without contrast enhancement. MR angiography was normal. Laboratory examination showed only mild linfopenia. HIV screening resulted positive for HIV-RNA dosing. EBV and JCV RNA on CSF was negative. Patient quickly improved and after 3 days neurological examination was normal. He repeated brain MRI two weeks later which showed a dramatic improvement of previous findings. Patient was discharged with a diagnosis of MERS and followed by the HIV outpatient clinic.

Discussion: MERS is divided into two types according to the lesion location. MERS type I, the typical form, mostly involves the midline of the splenium of the corpus callosum, while MERS type II generally presents also symmetrical lesions in the cerebral white matter or in the anterior aspect of the corpus callosum as in our patient. Moreover, MR features in our patient are typical of a CLOCCs which is the radiological-based definition of MERS. MERS can occur in the context of infections including influenza virus, rotavirus, mumps virus, Mycoplasma pneumoniae, Legionella pneumophila and SARS-COV2 but HIV has never been described as a trigger of MERS.

Conclusion: MERS is a rare clinico-radiological syndrome associated with a variety of causes. Among these, HIV can represent a rare infectious etiology that clinicians should always consider in the diagnostic pathway.

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EVOLUTION OF POLYSOMNOGRAPHIC FEATURES IN A PATIENT WITH CASPR-2 ANTIBODY-ASSOCIATED LIMBIC ENCEPHALITIS

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Background: Antibodies to neuronal surface protein contactin associated protein like 2 (CASPR-2) are related to a broad spectrum of disorders, including Morvan's syndrome, limbic encephalitis (LE) and acquired neuromyotonia. Hallmarks of these syndromes are sleep disorders such as insomnia, REM behavioral disorders, agrypnia excitata or hypersomnia. We describe here the evolution of the polysomnographic (PSG) pattern in a patient with CASPR-2 LE related insomnia.

Clinical Case: A 63-year-old man referred to our Department with a 1-year history of epileptic seizures, mnesic deficiency, mood changes with increased anxiety and irritability and, most of all, with a remarkable daytime sleepiness (23/24 Epworth Sleepiness Scale). Medical history was silent except for vocal cord leucoplakia surgically removed 2 years earlier. Brain MRI did not show significant abnormalities. The first polysomnography showed Total Sleep Time (TST) of 4 hours and 47 minutes: REM sleep was undetectable; NREM sleep was highly fragmented and undifferentiated, with the absence of vertex sharp waves, K complexes and sleep spindles. There was no clear organization in sleep cycles and only two longer periods of sleep were recorded (one in the morning and the other at night), of 64 and 72 minutes, respectively. Laboratory investigations showed positive anti CASPR-2 antibodies in both serum and liquor. CSF analysis showed increased IgG index. Brain PET showed slight reduction of cortical metabolism in the right mesial temporal lobe and upper parietal regions, with increased uptake of striated nuclei. Based on these results, patient was treated with Solumedrol 1 g / day for 5 days, followed by administration of IVIG 2 gr/kg once a month for three cycles. After the treatment patient referred mnesic and mood improvement while daytime sleepiness gradual decreases. The fourth IVIG administration was interrupted for an adverse event and at that time we performed a second polysomnography. This showed a slight improvement: we observed a reorganization in cycles with the reappearance of REM sleep (7% of TST) and of sleep physiological figures, with N2 representing 51.5 % of TST. A new polysomnography is planned after 1 year.

Discussion and conclusion: In a treated patient with CASPR-2 antibody-associated limbic LE, PSG showed recovery of sleep structures in parallel with a remarkable general clinical improvement of the patient, who returned to normal working activities. PSG studies may provide interesting data to increase the awareness regard this rare condition and to better understand the role of CASPR2 in CNS.

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ALTITUDINAL HEMIANOPIA AS PRESENTING SYMPTOM IN MULTIPLE SCLEROSIS: A CASE REPORT

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Introduction: We describe an atypical visual defect as a first symptom of multiple sclerosis (MS).

Case: A 23 years-old woman developed blurred right eye (RE) vision and a pulsatile right temporal headache lasting a few days, followed by an acute painless RE field inferior defect described as a "white band". Her medical history was relevant for estrogen-progestin contraception and episodic headache. A vascular disorder was suspected. Ophthalmological evaluation, including perimetry and fundoscopy, confirmed a RE inferior altitudinal hemianopia. Brain MRI showed multiple small lesions compatible with an inflammatory demyelinating disease, MR angiography was unremarkable. Oral methylprednisolone was started 10 days after onset, followed by visual improvement. At admission, neurological examination showed only RE red desaturation. VEPs and OCT were compatible with right optic neuritis (ON). Lab tests excluded coagulopathy, infective and autoimmune antibody-mediated disorders. Serology for MOG and aquaporin-4 was negative. CSF oligoclonal bands (pattern 2) were positive. According to MRI and CSF results she was diagnosed with MS and started a first line disease modifying drug.

Conclusion: Altitudinal hemianopia (AH) is commonly associated to optic nerve ischemia, vasculitis or compression. Neuromyelitis optica can also present in up to 40% of cases with AH. In our patient AH was the presenting symptom of MS. Other two similar cases have been described so far. Altitudinal visual defects require an extensive work-up to differentiate demyelinating disorders including MS from vascular diseases, especially in young patients without vascular risk factors and history of coagulopathy, for the important clinical, therapeutic and prognostic implications.

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INTRACRANIAL HYPERTENSION ASSOCIATED WITH IGG4-RELATED AUTOIMMUNE PANCREATITIS. IS IT A DIFFERENT SIDE OF THE SAME COIN?

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IgG4-related disease (IgG4-RD) is a systemic inflammatory disorder that can affect many organs and is characterized by increased serum IgG4 levels. Autoimmune pancreatitis is one of the most common IgG4-RD inflammatory disorders and was the first IgG4-RD inflammatory disease reported in the literature. Recently, intracranial hypertension (IH) has been described as a clinical manifestation of IgG4-related hypertrophic pachymeningitis and cerebral venous thrombosis1. We report an interesting case of IH associated with elevated serum IgG4 levels and autoimmune pancreatitis.

Case Presentation: A 24-year-old woman had been complaining for a month of severe headache with nausea and vomiting that worsened with supine position, associated with diplopia. Brain MRI demonstrated distention of the periocular subarachnoid space and flattening of the posterior sclera. Cerebral MR venography (MRV) revealed bilateral transverse sinus stenosis (BTSS), indicating altered intracranial venous outflow. Cerebrospinal fluid (CSF) analysis was normal. One-hour lumbar CSF pressure monitoring by spinal needle2,3 showed elevated opening pressure and mean pressure (247 mmH2O and 282 mmH2O, respectively), with a maximum peak of 330 mmH2O and the presence of abnormal CSF pulsations (B waves)2. A complete blood test showed elevated levels of lipase and amylase, 262 IU/L (n. v. 13-53) and 245 U/L (n. v. 13-60), respectively. The serum concentration of IgG4 was elevated, 1.540 g/L (n.v. 0.08-1.40). A cholangio-RM was performed, which showed enlargement of the cephalic portion of the pancreas without any sign of obstruction of the duct of Wirsung.

Discussion: Occurrence of IH in patients with IgG4-RD has been rarely reported. It is probably due to hypertrophic pachymeningitis and venous flow abnormalities secondary to IgG4 infiltration. Moreover, it has been suggested that inflammatory mediators can increase CSF viscosity reducing CFS uptake and altering CSF flow dynamics. Pachymeningeal thickening and enhancement are characteristic MRI findings, but these signs may be mild or absent in the early phases1.

Conclusions: To our knowledge, this is the first case of IH during IgG4-related autoimmune pancreatitis. The exact mechanism leading to IH in IgG4-RD patients still remains debated. Here we would like to emphasize the importance of early diagnosis of IgG4-RD presenting with IH to avoid delays in initiating appropriate treatment.

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CAROTID WEB: A RARE CAUSE OF ISCHEMIC STROKE IN A YOUNG AND HEALTHY PATIENT

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Background: Carotid web is characterized by a shelf-like projection into the lumen of the proximal cervical internal carotid artery without evidence of calcification. By altering the hemodynamic distal to the web it can cause flow stasis and remote embolization of fibrin-based clots, representing a potential and uncommon cause of embolic ischemic stroke. Carotid webs may be missed or misinterpreted because usually they don't produce significant stenosis and can mimic arterial dissection, non-calcified atherosclerotic plaque, or intraluminal thrombus.

Case report: A 45-year-old man presented on March 2022 aphasia with sudden onset during the night. The day after, because of the persisting of the symptomatology he presented at Emergencies

Department. CT scan showed a left temporal ischemic lesion and CT angiography revealed a stenosis in the M3 segment of the left middle cerebral artery. Later he was admitted to our Neurological Service. His past medical history was silent revealing only a mild smoking habit in the absence of cerebrovascular risk factors. To disclose the aetiopathogenesis of this ischemic stroke he underwent cardiological exams including echocardiography, cardiac telemetry monitoring and 24h Holter ECG which didn't show any abnormalities. Extensive blood analysis including the immunological and coagulation screening test were unremarkable. Also the transcranial color-coded sonography including bubble test, underwent few days after, was normal. However, the carotid ultrasound showed at the level of the left internal carotid a shelf-line linear filling defect, atypical for atherosclerotic plaque and more suggestive of carotid web. Brain MRI with angiography confirmed the left temporal-parietal ischemic lesion and the left middle cerebral artery M3 segment stenosis. A reevaluation of CT angiography disclosed the presence of carotid web into left internal carotid. Doppler ultrasound study of renal artery showed no sign suggestive of fibromuscular dysplasia. The patient started antiplatelet therapy in secondary prevention waiting for the left internal carotid artery stenting. Furthermore, due to an intensive speech rehabilitation, the patient achieved an almost complete recovery.

Conclusion: The diagnosis of carotid web is often puzzling and needs the use of different exams due to the rarity of the pathology. It should be considered in those cases of embolic ischemic stroke, typically in young patients with otherwise cryptogenic cerebrovascular accident.

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RISK OF INFECTIOUS DISEASE IN THE CNS IN PATIENTS TREATED WITH IBRUTINIB: THE CASE OF AN ABSCESS OF ASPERGILLUS

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Background: Ibrutinib is an oral tyrosine kinase inhibitor approved for the treatment of Waldenstrom's macroglobulinemia. Although considered to be less immunosuppressive than conventional immunochemotherapy, the prevalence of invasive fungal infections among these patients appears to be higher than expected.

Case report: An 83-years-old woman presented to the Emergencies Department in February 2022 for a progressive and generalized weakness, asthenia, and headache. Head CT scan showed a right frontal hypodensity with perilesional edema in the white matter; chest X-ray suggested an interstitial pneumonia. She was admitted to our Neurological Service. Her past medical history consisted in Waldenstrom's disease diagnosed in November 2021 treated at first with low dose of steroid then associated to Ibrutinib 140mg TID form January 2022. A month later, due to the development of an iatrogenic atrial fibrillation and asthenia, Ibrutinib was discontinued. A total body CT scan showed a reduction of the known mediastinal lesion and confirmed the interstitial pneumonia associated to a pleural effusion. An oropharyngeal candidiasis and a peripheral neuropathy associated at burning paresthesia were also disclosed. Extensive blood analysis revealed a severe lymphopenia, anti-toxoplasma antibodies pattern was IgM negative and IgG positive, angiotensin I-converting enzyme and HIV were negative. Brain MRI showed a single right frontal lesion characterized by ring enhancement and central necrosis with diffuse peripheral vasogenic edema; spectroscopy didn't depict a pic of choline. CSF examination: citochemical analysis revealed a proteinorrachia without pleocytosis; the research of HSV, EBV, JC virus, cryptococcus, HHV 6 and HHV8 was negative. A fungal etiology was suspected, and the positivity of galactomannan antigen supported the diagnosis of aspergillosis; therefore, a target therapy with Voriconazole 6mg/Kg/die was started. Unfortunately, few days later, the patient died due to respiratory failure. Post-mortem autopsy confirmed the pulmonary and cerebral aspergillosis.

Conclusion: Brain aspergillosis is associated with high mortality and is a burden on health care. It should be suspected especially in the immunocompromised patient when respiratory symptoms are present. To date is no recommendation of any specific prophylaxis although are known the aspergillosis infections after Ibrutinib therapy. The need of antifungal prophylaxis in ibrutinib recipients needs to be re-evaluated, at least for patients with additional risk factors.

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ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM) AS CLINICAL PRESENTATION OF ANTI-MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODIES DISEASE (MOG-AD) AFTER SARS COV2 VACCINATION

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Objectives: We describe the case of a 17-year-old patient developing ADEM with anti-MOG antibodies positivity in close temporal correlation with the administration of the first dose of Pfizer-BioNTech COVID-19 vaccination.

Materials and Methods: A 17-year-old male patient was admitted to our Emergency Department on 22 September 2021, presenting with right lateropulsion and imbalance on Romberg test, second-degree nystagmus in the primary gaze to the left, and urinary retention progressively evolved in 1 month. His past medical history was unremarkable. The patient received on 20th August 2021 the first dose of Pfizer-BioNTech COVID-19 Vaccine. Brain computed tomography (CT) scan was unremarkable. Magnetic resonance imaging (MRI) of the brain and spinal cord showed multiple altered-signal areas, all of about the same age, with no hypointense T1 lesions, in the subcortical white matter of both semioval centers, in both the thalami in the bulb, at the level of the left cerebellar peduncle and of the right cerebellar hemisphere, in the cervical spinal cord, in planes passing from C2 to C4, and dorsal, in planes passing

from D5 to D7. Lumbar puncture showed pleocytosis (leukocytes 40 cells/uL consisting of 90% lymphocytes), elevated L-IgG and L-IgM. Link index and Reiber index were normal. Anti-myelin oligodendrocyte glycoprotein (MOG) antibodies were positive, with titration of 1:10240, while anti-aquaporin 4 (AQP4) antibodies were negative. Oligoclonal bands were negative. The patient was treated with IV methylprednisolone (1000 mg/day for 5 days) followed by oral steroid tapering (prednisone, starting from 50 mg/die), with marked improvement of symptoms. After three weeks from admission the patient started spontaneous urination. No bladder rehabilitation was needed. Repeat brain and spinal cord MRI performed eighteen days from admission and showed improvement of radiological findings, with significant reduction in size of all altered-signal areas. At discharge, his neurological examination was normal.

Discussion and Conclusions: After a eight-month follow up (May, 2022), our patient had no signs nor neurological symptoms at his follow-up visits, suggesting that his clinical and radiological evolution was monophasic. The narrow time interval between vaccine administration and the symptom onset is indicative of an association between these two events, considering that ADEM typically occurs after two to four weeks after infections or vaccinations, and that MOG antibodies have been identified in up to 64% of children (< 18 years) with ADEM.

WERNICKE ENCEPHALOPATHY IN A YOUNG WOMAN CAUSED BY HYPEREMESIS GRAVIDARUM: A CASE REPORT

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Objective: Thiamine deficiency may lead to several neurological symptoms that include Wernicke encephalopathy (WE), an acute neurological disorder characterized by a triad of ocular movement abnormalities, ataxia, and mental confusion. Although alcoholism is the most common cause of WE, it can also develop in any patient with a nutritional deficiency state such as malnutrition, gastrointestinal disorders with malabsorption, or other less common causes. It's also been rarely seen in women with hyperemesis gravidarum. With this case report we bring attention to the symptoms of WE, also in young pregnant women who do not have a story of alcoholism.

Case report: We discuss the case of a 23-year-old pregnant woman who developed subacute neurological symptoms after being admitted to the obstetric emergency room with persistent pain in her upper belly that radiated to her back and daily vomiting. She had gait ataxia, horizontal and vertical nystagmus, bilateral abducens palsy, dizziness and diplopia on the neurological evaluation. Due to increased T2-weighted signal in the medial regions of the Thalamus and in the Periaqueductal Grey on MRI, she was diagnosed with WE and started intravenous thiamine infusion. She also developed memory issues, with fatuous behavior and indifference about her condition. The neuropsychological exam revealed an abnormal score in the verbal fluency and verbal memory assessment tests. Her neurologic state had nearly entirely improved after 6 months, but no improvements were shown in her neuropsychological evaluation.

Discussion: Although hyperemesis gravidarum affects approximately 0,5 to 3% of pregnant women, it can induce severe nutritional deficit and be a source of subtle neurological and psychiatric symptoms. The patient in this case was diagnosed with WE after suffering from hypermesis gravidarum and acute pancreatitis, two uncommon but well-known causes of WE. Treatment with an initial loading dose of intravenous thiamine followed by a lower dose improves ocular and cerebellar symptoms, but it may not be as effective in treating psychiatric and cognitive issues.

Conclusion: Wernicke encephalopathy may not be necessarily associated with alcoholism. Not many clinicians are aware of the rarest causes of WE, such as hyperemesis gravidarum. Although it is a rare complication, early diagnosis of WE is crucial, because if it's not treated with thiamine in the acute stages, it may result in permanent and irreversible neurological sequelae. Further research is needed to better understand the neuro-functional basis of the cognitive impairments in this encephalopathy.

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NATALIZUMAB-INDUCED REMISSION OF MULTIPLE SCLEROSIS-ASSOCIATED UVEITIS AND RETINAL PERIPHLEBITIS: A CASE REPORT

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Purpose: The purpose of this study is to report a case of multiple sclerosis (MS) - related uveitis and retinal periphlebitis, refractory to topical corticosteroid therapy and azathioprine, which remitted after Natalizumab was started.

Materials and Methods: A 59-years-old female was treated with intravenous Natalizumab, a monoclonal antibody indicated in the treatment of relapsing-remitting MS, which inhibits cell migration toward tissues by targeting the alpha chain of the VLA-4 integrin.

Results: The patient was diagnosed with MS when she was 50 years old and firstly, she was treated with interpheron (interrupted due to side effects), then with teriflunomide (interrupted due to ineffectiveness on disease activity) and eventually with glatiramer acetate. In March 2021, she presented with a 4-month history of progressive and bilateral decrease in visual acuity caused by intermediate uveitis. At her first examination, her best corrected visual acuity was 20/80 in her left eye while she could only see hand motion with her right eye. Fundoscopic examination and fluoresceine angiography revealed a picture of vitreitis and retinal venous vasculitis in both eyes. Topical corticosteroid therapy was ineffective while azathioprine was interrupted after one month due to hepatic intolerance. She was then prescribed Natalizumab which soon resolved intraocular inflammation, with partial yet significant recovery of visual acuity: her best corrected visual acuity was 20/50 in both eyes two months after Natalizumab was started.

Discussion: Retinal periphlebitis (RP) is a vasculitis that affects the peripheral retina in approximately 10% of patients with MS and it has been related to a more active disease [1]. MS and intermediate uveitis share similar immunopathogenic mechanisms. Treatments targeting specific aspects of immune response could be effective in acute relapses and in chronic inflammation of both these immune-mediated diseases [2].

Conclusions: This case corroborates the potential utility of Natalizumab in the treatment of MS-associated uveitis and retinal periphlebitis when other immunosuppressants are ineffective or contraindicated.

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COMPLEX MUSICAL HALLUCINATIONS AT THE ONSET OF ALZHEIMER'S DISEASE: A CASE REPORT

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Introduction: Alzheimer's Disease is the most common form of dementia, and its clinical hallmark is cognitive impairment with progressive loss of memory. Among the most frequent neuropsychiatric symptoms, the prevalence of hallucinations has been reported from 4% to 76% (median 23%), and the prevalence of auditory hallucinations is between 1% to 29% (median 12%) [1].

Case Report: We report the case of a 79-year-old woman, a former literature teacher, who came to our attention after 3 years from the start of her symptoms: she stated to hear vivid voices of jovial, happy people who sing and dance, accompanied by instrumental music, in a continuous way, all along during the 24-hours, also affecting her sleep. The sounds are reported to be more intense from the left ear, not changing to external stimulus. However, the patient was able to hear and follow conversations around her. According to her relatives, contextually to the onset of the hallucinations, she began to show cognitive impairment, with progressive memory disturbances. During the medical examination, she showed insight of her condition, telling us how intrusive and bothersome the hallucinations were. The patient has been subjected to the PET-FDG that showed a significative reduction of the glucidic metabolism in the temporo-parietal cortex's area, bilaterally, slightly asymmetric since the left hemisphere's structures were more compromised than the right ones. We then proceeded with PET-scan with Flutemetamol (18F) that showed a pathologic uptake of the tracer, all over the cerebral cortex, confirming AD diagnosis. We performed a genetic test looking for mutations of MAPT, GRN, C9ORF72, of which we have found none.

Discussion: A previous study showed that the kind of musical hallucinations experienced by patients with neurodegenerative diseases tended to resemble songs from childhood or overlearned material such as religious, patriotic, or cultural songs [2]; in our case, even if the melodies and the voices that the patient heard were not familiar to her, she told us that the latter would seem to tell her a locality's name where she spent part of her childhood, where her family still has some possessions, suggesting a not yet fully understood linkage between old memories and this phenomenon.

Conclusions: Therefore, as reported in our case, even if complex musical hallucinations are not very common, especially as the first manifestation of the disease, in presence of this symptom, Alzheimer's Disease must be included in the diagnostic work-up.
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EXCESSIVE DAYTIME SLEEPINESS AND "CATAPLECTIC ATTACKS": A NARCOLEPSY TYPE 1 MISDIAGNOSIS

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Introduction: Narcolepsy type 1 (NT1) is a rare neurologic disease characterized by excessive daytime sleepiness, uncontrollable sleep urge and cataplexy. [1] Because of low prevalence and its heterogeneous clinical presentation, NT1 is often misdiagnosed. [2] Here we report a case of a female patient who erroneously received a NT1 diagnosis, aiming to better recognize its caveats.

Case description: A 65-year-old female patient, with family history of epilepsy, and affected by depression in treatment with venlafaxine, acceded to our Sleep Center complaining severe daytime sleepiness refractory to treatment. Sixteen years before she received a clinical diagnosis of NT1, after a major episode of sudden-onset sleep while driving and referred multi-daily episodes of generalized, cataplectic-like, loss of muscular tone. At onset a standard EEG was performed, showing no noteworthy abnormalities. NT1 symptomatic treatment was started with Modafinil, Pitolisant and Sodium Oxybate. During following years her symptoms persisted, despite progressive increase in drugs dose, taking her to our attention. Firstly, an extensive anamnesis pointed out a severe excessive daytime sleepiness according to Epworth Sleepiness Scale (ESS: 19) along with severe depressive symptoms at the Beck Depression Inventory questionnaire (BDI: 34). Physical examination showed no objective neurological deficits. A complete polysomnography (PSG) revealed a slight reduction of sleep efficiency (85.3%) and normal REM latency (78.5 minutes). Our patient reached REM stage 3 times during the sleep night with physiologic muscle atonia. Cardiorespiratory polygraphy depicted severe obstructive sleep apnoea (OSA, Apnoea-Hypopnoea Index: 46.3/h and Oxygen Desaturation Index: 45.0/h) with normal average oxygen saturation. Unexpectedly we observed subclinical paroxysmal diffuse slow waves during both wakefulness and sleep. Multiple sleep latency test (MSLT) was conducted and our reached sleep in 4 out of 5 tests, with normal mean sleep latency (12.1 minutes). No sleep onset rapid eye movement periods (SOREMPs) were found. Interestingly, during MSLT were reported sequences of bilateral, synchronous and symmetrical, 3-3.5 Hz, spike-and-wave discharges lasting 3 seconds each. Finally, cerebrospinal fluid (CSF) analysis, comprehensive of hypocretin-1/orexin levels, was normal. HLA genotype was DQB1 03:01:01. Our results together with clinical history deposed for generalized epilepsy and severe OSAS. Sodium oxybate was progressively tapered off, sodium valproate and continuous positive airway pressure therapy were started effectively.

Conclusion: NT1 diagnosis based on clinical evaluation must be avoided: only objective tests, such as PSG and MSLT, are discriminatory and mandatory in order to perform a correct diagnosis, to prevent overtreatment and its consequences on everyday life. [3]
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CEREBRAL VENOUS THROMBOSIS WITHOUT THROMBOCYTOPENIA AFTER SINGLE DOSE OF COVID-19 (AD26.COV2.S) VACCINE INJECTION: A CASE REPORT

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The coronavirus pandemic is the biggest health challenge of the new millennium. Vaccination is the only weapon available to tackle the pandemic: it is estimated that about 3 billion people have received at least one dose of the available vaccines. In addition to the known adverse effects that emerged during the trial phases, some new and less common ones are manifesting themselves during the post marketing phase. One of these is vaccine-induced thrombocytopenia (VITT), responsible for diffuse venous thrombosis in the splanchnic and cerebral districts, whose pathogenesis mimics that observed in heparin-induced thrombocytopenia (HIT). However, some venous thromboses present with different characteristics, assuming a different etiology. In this article we describe a case of cerebral venous thrombosis after administration of the Ad26.COV2.S vaccine, without thrombocytopenia, paving the way for possible new causes of this pathological condition. A 45-year-old woman come to our emergency department for bilateral headache and orbital pain, occurring 8 days after administration of the Ad26.COV2.S. vaccine. The ophthalmological examination shows a bilateral papilledema. Brain MRI reveals a right temporo-insular contrast point, suggestive of venous thrombosis. The absence of thrombocytopenia and platelet factor 4 (PF4) led to the exclusion of a VITT. The patient was successfully treated with warfarin, corticosteroids and Venous thrombosis secondary to Covid vaccination is a topic of special interest. Patients with evidence of thrombocytopenia and positivity for anti-PF4 antibodies show a systemic thrombophilic pattern, with autoimmune aetiology, and are burdened by higher mortality. Thrombosis without thrombocytopenia does not have a clear etiology, but laboratory data and a good response to warfarin suggest a different pathogenesis. Future research will allow us to discover other possible mechanisms with the aim of identifying a subgroup of patients at greater risk of developing this complication.

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A SURPRISING CASE OF LATE ONSET MULTIPLE SCLEROSIS

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A 70 years-old right-handed woman was admitted to our emergency department in October 2021 for the acute onset of glove hypoesthesia of her left hand. She presented smoking habit and hypertension and reported an otherwise unremarkable clinical history. Blood tests were normal, and Brain CT was negative for acute events. The patient was thus transferred to the Neurology unit for further evaluation. The clinical neurological examination was normal except for left hand hypoesthesia, which encountered full and spontaneous recovery in few days. After specific interrogation, the patient reported a transient episode of acute visual loss 5 years earlier, which lasted few hours and for which she had underwent a Brain MRI showing multiple bilateral and confluent periventricular white matter lesions in T2-FLAIR sequences, and no contrast enhancement. She had been prescribed Cardioaspirin upon suspicion of chronic vascular leukoencephalopathy. During hospitalization she underwent a follow-up Brain MRI that revealed areas of diffusivity restriction at the corona radiate and in the right parietal lobe, with corresponding hyperintensity in T2-flair and mild gadolinium uptake. To rule out an inflammatory cause we expanded our work-up with a Column MRI and ophthalmological examination, both normal, and visual evoked potentials whose latency resulted bilaterally increased.

Additional thrombophilic and autoimmune screening, cardiac and carotid echo-color-doppler sonography and the bubble test Transthoracic Echocardiogram were all negative. Considering the severity and the topography of the lesions, the paucity of anamnestic elements suggestive of inflammatory pathology and the absence of cardiovascular risk factor to justify ischemic aetiology, both NOTCH3 gene analysis and lumbar puncture were performed. CSF cell count was normal, with 48.00 mg/dl proteins and absence of virological markers. The patient was discharged in good conditions. After a few weeks, oligoclonal bands were identified in the CSF, and the analysis of NOTCH 3 was negative thus excluding a diagnosis of CADASIL. Then, the patient was diagnosed as having a probable paucisymptomatic late onset multiple sclerosis.

Discussion: This case highlights the importance of good anamnestic history taking. It also shows how inflammatory diseases and in particular multiple sclerosis should be considered in the differential diagnosis of white matter lesions when appropriate, even in age groups where vascular aetiopathogenesis seems to be more plausible and statistically frequent.

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AN ATYPICAL ADRENOLEUKODYSTROPHY: A CASE REPORT

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Introduction: X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal fatty acid beta-oxidation disorder, caused by mutation on the ABCD1 gene on Xq28, that results in accumulation of very-long-chain-fatty-acids in all body tissues and demyelination of the white matter.

Case Presentation: A 44 year-old man came to our attention in 2021 for worsening of a previous speech disorder, appeared in 2020 after an head trauma, and a new-onset cognitive impairment. He had a progressive gait disorder started in 2004. Two out of his four brothers suffered from spastic paraparesis. Neurological evaluation reported fluent aphasia, verbal reiteration, bilateral lower limbs dragging, hypertonus, brisk tendon reflexes, clonus and bilateral extensor plantars. MRI showed bilateral and asymmetric hyperintense signals in the parieto-temporal-frontal subcortical white matter, splenium of the corpus callosum and bilateral internal capsules. MR spectroscopy demonstrated a choline spike. Routine blood tests, autoimmune screening and cerebrospinal fluid were normal. A demyelination peripheral neuropathy was present on electrophysiological testing.

Brain biopsy showed a lymphohistocytic inflammatory infiltrate and reactive gliosis. Clinical, familiar, radiological and biopsy findings raised

the suspicion of an inherited leukoencephalopathy. The diagnosis of adrenoleukodystrophy was confirmed by identification of a pathogenic mutation in the ABCD1 gene: c.1847C>T.

Discussion: The main phenotypes of ALD are: Addison-only (isolated adrenal insufficiency), Adrenomyeloneuropathy-AMN (a distal axonopathy characterized by progressive spastic paraparesis, sensory ataxia, sphincter dysfunction, impotence and pain), CerebralALD-CALD (presenting with rapid cognitive and neurological decline, dementia, ataxia, seizures, behavioural changes and death). Patients are asymptomatic at birth. Symptoms in male patients are usually adrenocortical insufficiency in childhood and AMN in adulthood. Infections or head trauma may trigger the onset of cerebral-ALD. Brain MRI typically shows bilateral and symmetric hyperintense signals in the corpus callosum and parieto-occipital-frontal white matter. Elevated VLCFAs are biomarkers of X-ALD and the diagnosis can be confirmed by sequencing of the ABCD1 gene. Our patient developed typical symptoms of AMN in lower limbs, even though he suffered from a demyelinating neuropathy and not from an axonal one, as the majority of patients. After years an insidious cognitive decline appeared. Brain MRI showed a demyelinating disease but the pattern was atypical, describing asymmetrical disease.

Conclusion: We described a case of an adult man who presented clinical features of cognitive deterioration and an atypical AMN with unusual findings brain-MRI of X-ALD. In such cases, a family and personal history, and radiographic images are fundamental to suspect the diagnosis and to provide a timely genetic counseling.

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CANCER DETECTION AFTER 9-YEAR COURSE OF LAMBERT-EATON MYASTHENIC SYNDROME

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Objectives: To describe a patient with paraneoplastic Lambert-Eaton myasthenic syndrome (LEMS) in whom the interval between the onset of neurological disease and tumor detection was as prolonged as nine years.

Materials and Methods: Neurophysiological examination included needle electromyography (EMG), nerve conduction studies, low-rate and high-rate repetitive nerve stimulation. Onconeural antibodies (Abs) were detected with tissue-based assay on mouse brain and confirmed with line blot (Euroimmun). Voltage-gated calcium channel (VGCC) Abs were tested by radioimmunoassay (RIA). Tumor screening was performed with chest contrast-enhanced CT scan and [18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET).

Results: A 61-year-old man presented with a 3-month history of lower limb proximal weakness subsequently progressing to upper limbs, associated with dysphagia, xerostomia and erectile dysfunction. Neurological examination revealed absent deep tendon reflexes and post-exercise facilitation. LEMS was diagnosed on the basis of signs of presynaptic neuromuscular transmission defect on EMG and positive P/Q-type VGCC Abs (188.06 pmol/L, normal range < 80 pmol/L). At diagnosis, the Dutch-English Tumor Association Prediction (DELTA-P) score was 4, meaning a high risk (93.5%) of small-cell lung carcinoma (SCLC). FDG-PET/CT scan showed no malignancy. An integrated chest FDG-PET/CT scan was repeated after 3 months and then every six months, with negative results. Two years after LEMS onset, the patient developed a clinical picture consistent with limbic encephalitis (LE) with bilateral temporal slowing at electroencephalogram (EEG) and negative brain MRI. Anti-Hu Abs were detected in serum and CSF samples. The patient improved after treatment with high-dose steroids and intravenous immunoglobulin. At that time no malignancy was detected by FDG-PET/CT scan, that remained negative for the following seven years (it was repeated every six months for four years and subsequently on yearly basis). Nine years after LEMS onset, a hypermetabolic lesion of the left lung hilus, high suggestive of SCLC, associated with lymphadenopathy and lung carcinomatosis was detected. The malignancy was deemed untreatable and the patient died few months later.

Discussion and Conclusion: According to recent guidelines, cancer screening in patients with LEMS should be performed for 2 years. However, in our patient, tumour detection occurred much later, probably because tumour growth was suppressed by the host immune response. The onset of anti-Hu+ limbic encephalitis further enhanced the likelihood of SCLC association, although FDG-PET/CT scan had remained negative for other seven years. Our findings suggest that in patients with paraneoplastic diseases and very high-risk of an underlying malignancy, tumour screening with FDG-PET/CT scan should be prolonged far beyond current recommendations.

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ORGANIZATION AND IMPLEMENTATION OF A NOVEL OUTPATIENT CLINIC DEDICATED TO PATIENTS WITH UNDIAGNOSED DISEASES

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Objectives: The Undiagnosed Diseases are pathological conditions that affect people with a range of disorders and disabilities, probably caused by a genetic alteration that has not been yet identified or by an atypical phenotype of a more common disease. For these people, the lack of a definite diagnosis causes considerable diagnostic and therapeutic delays, with significant psychological, social and economic distress. In order to cope with these issues, several international initiatives have been launched, culminating in the creation in 2014 of the NIH Undiagnosed Diseases Network International. In Italy, the "Clinical Center for Diagnosis Orphan Patients" was set up in 2017 at the IRCCS Ospedale

Policlinico San Martino in Genoa, following an agreement with the "Comitato I Malati Invisibili". The aims of our Clinical Center are taking care of the patients, whose diagnosis is uncertain, critically examining the complex clinical histories, improving the diagnostic investigations, reducing the social distress, increasing the quality of life, limiting the phenomenon of diagnostic 'nomadism', reducing the high costs to the national health system of repeated investigations.

Materials and Methods: The core of our clinical activity is realized in a multidisciplinary team, at first by a screening unit composed by a neurologist, an endocrinologist, an internal physician, an immunologist; these specialists evaluate the applications received and then share decisions with a scientific committee composed by several clinical specialists. Each evaluated patient is addressed in a tailored clinical pathway according to the specific clinical picture of disease. Genetics plays a major role in extend the etiological study of these complex diseases; we perform Next Generation Sequencing of gene panels, clinical/whole exome sequencing, and clinical/whole genome sequencing. We also designed an innovative electronic clinical record, focusing on the integration of different datasets from different sources.

Results: In the first five years of activity, we received 101 applications, whose 78 have been accepted; we have visited 65 patients and arrived to a diagnosis in 14 cases. In some of these cases, the genetic exams led to the diagnosis, detecting known or unknown previously undescribed nucleotide variants.

Discussion and Conclusions: Our clinical center obtained results comparable to similar international centers. The possibility of having a diagnosis is a great opportunity for this group of subjects affected by a complex symptomatology; when a right diagnosis is reached, the patient has the possibility to "give a name to the disease", and to receive social cares and appropriate clinical treatments.

A CASE OF MISDIAGNOSED POEMS SYNDROME WITH ONSET AFTER SARS-COV-2 INFECTION AND CENTRAL NERVOUS SYSTEM MANIFESTATIONS

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Aims: We aim to describe a case of POEMS syndrome previously diagnosed as chronic inflammatory demyelinating polyneuropathy (CIDP) with onset after a paucisymptomatic SARS-CoV-2 infection and with associated central nervous system manifestations.

Methods: The case was investigated with clinical, laboratory, and instrumental examinations at the Bellaria Hospital of Bologna.

Results: A 46 years-old Mauritian man presented with subacute onset of distal bilateral weakness of lower limbs-right hand and thrombocytosis. Antiplatelet prophylaxis and treatment with hydroxycarbamide were started, and he was hospitalized in the Neurology ward of another department for further investigations. Electrophysiologic studies demonstrated chronic signs of demyelinating polyneuropathy, and CSF examination showed albumin-cytologic dissociation. Therefore, the diagnosis of CIDP was formulated and the patient underwent a cycle of intravenous immunoglobulin therapy followed by a cycle of plasmapheresis three weeks later. Both treatments had a poor clinical response. Subsequently, oral steroid therapy was initiated, with slight clinical improvement of symptoms. Eight months later, during a febrile episode the patient experienced two seizures and he was hospitalized. A pathologic fracture of the hip was found, with whole-body FDG PET showing hypermetabolism of the bone tissue. Surprisingly, an MRI of the brain showed punctiform leptomeningeal and cortical-subcortical multifocal lesions. He was discharged with suspected combined central and peripheral demielination. He was later admitted in our hospital. Serum protein electrophoresis confirmed the presence of an M component IgA lambda-type. Dermatologic evaluation revealed upper body cherry angiomas and initial signs of nail clubbing. Blood tests disclosed hypothyroidism and hyperprolactinemia, and elevated serum levels of VEGF. Electrophysiology showed severe mixed demyelinating axonal polyneuropathy; MRI did not confirm central demyelinating lesions. Diagnosis of POEMS syndrome was consequently formulated. The patient is currently a candidate for autologous stem cell transplant and has already received a cycle of cyclophosphamide.

Discussion and conclusions: This case illustrates the diagnostic pitfalls of POEMS syndrome which often lead to delayed diagnosis and treatment of the disease, if close attention is not paid to the details and to the atypical features of the presumed diagnosis of CIDP. Furthermore, although the involvement of central nervous system has been previously described, seizures are a rare and scarcely reported manifestation of the syndrome and should not exclude the diagnosis. Ultimately, the onset of the disease after SARS-CoV-2 infection is of particular interest and may represent a clue about the pathogenetic mechanism, possibly linked in this case to an infectious stimulus to the immune system.

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TRIMETHOPRIM-SULFAMETHOXAZOLE INDUCED ASEPTIC MENINGITIS (TSIAM), A CLINICAL AND RADIOLOGICAL CHALLENGE

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Objectives: Drug-induced aseptic meningitis (DIAM) has been described as an infrequent side effect of many medications, such as anti-inflammatory and immunomodulating medications and antibiotics [1,2]. In this case report we describe a probable Trimethoprim-Sulfamethoxazole Induced Aseptic Meningitis (TSIAM), completing the discussion with a review of the imaging features associated with DIAM.

Subject: We report the case of a 65-year-old woman, with no significant history except for mild seasonal asthma, who presented to our Emergency Department.

Method: Brain CT with CT angiography and perfusion CT, contrast brain MRI and EEG were performed. CSF samples were obtained through lumbar puncture, and empirical antibiotic/antiviral therapy was initiated.

Results: The patient complained of confusion, disorientation, and speech impediment upon awakening. On neurological evaluation only global aphasia was reported. In less than 24 hours we documented complete regression of her deficit. On brain MRI leptomeningeal enhancement was documented in late contrast FLAIR, compatible with meningitis. Brain CT with CTA/CTP and EEG were negative. Atypical microbial serologies were negative. The CSF analysis showed xanthochromia, with mild lymphocytic pleocytosis (136 cells, 97% lymphocytes) and elevated protein concentration (275 mg/dL); viral and bacterial PCR, and microscopic examination were negative.

Discussion: Before the current hospitalization, the patient reported recent worsening of her asthma, poorly controlled with the usual medications, for which the general practitioner, suspecting an infectious bronchitis, had suggested cotrimoxazole. After the first intake neurological symptoms showed up, then worsened after subsequent intake and rapidly regressed after hospital admission for discontinuation of the drug. These

findings, combined with other radiological and laboratory data, led us to hypothesize a TSIAM, a particular subtype of DIAM. It has been hypothesized that DIAM is mediated by a non IgE-mediated hypersensitivity mechanism, explaining its delayed onset after drug intake, and that it associates more with lipophilic drugs, such as cotrimoxazole [2]. Clinical presentation is variable, usually with speech and movement disturbances, seizures or rarely coma, while CSF analysis shows neutrophilic or lymphocytic pleocytosis and high protein concentration [1,2]. The radiological picture is usually nonspecific with leptomeningeal enhancement in post-contrast FLAIR and sometimes with white matter lesions, like other forms of aseptic meningoencephalitis [1,3].

Conclusions: DIAM, and more particularly TSIAM, are poorly understood pathological entities, with not clearly defined clinical and radiological features [1,2]. Of paramount importance, in the presence of a suspicious presentation, is to collect a precise history to highlight any drugs responsible, thus limiting invasive procedures and unnecessary treatments.

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ACUTE PAPILLOEDEMA AFTER OCULAR PRESSURE LOWERING TREATMENT: A CASE REPORT

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Introduction: Acute loss of visual acuity associated with papilloedema is a frequent reason for neurological second opinion after a first level ophthalmological examination and represent a diagnostic challenge for the clinician.

Clinical case: A 58-year-old woman, with history of arterial hypertension, obesity and dyslipidemia, presented with sudden painless visual loss in left eye three days after laser peripheral iridotomy for the prevention of glaucoma. Although ocular pressure was reported as normal at the end of the procedure, in the following hours the patient developted an ocular pressure peak in the operated eye (56 mmHg). She was treated with massive doses of acetazolamide and pressure promptly dropped to normal levels. Ophtalmological examination showed marked papilledema in the left eye with vascular congestion, normal ocular pressure, 5/10 uncorrectable visual acuity and central scotoma. Optical coherence tomography (OCT) revealed optic disc swelling with retinal nerve fiber layer thickening. The patient was referred to neurological clinic in the suspect of anterior ischemic optic neuropathy (AION). Neurological examination was unremarkable except for visual loss in the left eye. Brain and orbital magnetic resonance was negative for ischemic or inflammatory lesions, extra and intracranial EcoColorDoppler scan ruled out significant vascular disease. EcoColorDoppler of temporal artery didn't show any sign of arteritis and autoimmune and procoagulative screening were normal. Transorbital ultrasound examination disclosed a marked unilateral papilloedema without expansion of the optic nerve sheats. Having ruled out the hypothesis of AION and optical neuritis, high-dose steroid therapy was initiated with prompt recovery of visual acuity. OCT control at one week was normal.

Conclusions: To the best of our knowledge this is the third case described in the international literature of acute papilleodema due to sudden drop of ocular pressure after iriditomy. The use of ultrasound to differentiate various optic neuropathies is a promising field of application for this technique and can represented a useful tool to achieve a correct diagnosis and treatment.

NEW-ONSET REFRACTORY STATUS EPILEPTICUS (NORSE): A CASE SERIES OF A DEVASTATING BUT TREATABLE CONDITION

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Objectives: Autoimmune encephalitis and the Febrile-Infection-Related-Epilepsy-Syndrome (FIRES) account for 40% of the cases of New-Onset-Refractory-Status-Epilepticus (NORSE) [1]. We provide detailed clinical, laboratory and treatment data regarding four patients diagnosed with NORSE at the Ospedale Vito Fazzi in Lecce.

Materials and Methods: Electronic and paper medical charts and EEG database were revised to find patients diagnosed with NORSE within a 2-year period (Jan-2020 to Jan-2022).

Results: Four patients were included: three women of 24, 36 and 64 years of age respectively (patients-1, -2 and -3); a 16-year-old boy (patient-4). Nobody had history of epilepsy. Prodromal symptoms included: behavior changes, memory loss, sleep disorder and flu-like syndrome. Patients were hospitalized for a first partial or generalized motor seizure. The NORSE developed within a week from admission. Patient-1 and -3 suffered from non-convulsive-SE, whereas convulsive-SE was diagnosed in the remaining cases. EEG recordings mostly showed spike- or poly-spike-and-wave in the parietal and temporal derivations with a desynchronized and slowed background activity. Neuroimaging was normal in patient-1 and -4; patient-2 showed hippocampal hyperintensity; FDG-PET revealed temporal hypermetabolism in patient-3. Nobody had malignancy at the body scans. CSF findings were unremarkable. Antibodies testing were positive for anti-NMDAR, anti-GAD and anti-LGI1 in patients -1, -2 and -3 respectively, consistent with a diagnosis of limbic encephalitis. In patient-4 a diagnosis of seronegative and cryptogenic FIRES was made considering the history of fever. Disparate second-line anti-epileptic-drugs (AEDs) were administrated: Levetiracetam, Valproic Acid and Lacosamide in patient-1; Levetiracetam, Lacosamide and Phenytoin for patient-2; Lacosamide and Phenobarbital in patient-3; Levetiracetam and Midazolam in patient-4. Steroids were the first-line treatment (except for patient-3), followed by plasmapheresis or immunoglobulin therapy. Rituximab was administrated in patient-1 and -3 while Anakinra was used in the FIRES. Patient-1, -2 and -4 were admitted in the ICU where Ketamina, Tiopentale, Midazolam and Propofol were used (alone or in combination) to control epilepsy. Patients had a good prognosis; only the FIRES patient did not completely recover. They all are still on AEDs.

Discussion: In our retrospective study, we identified 4 patients suffering from NORSE. Despite previous cases series [2,3], in our cohort an etiological diagnosis (autoimmune encephalitis or FIRES) was made in all patients and the proportion of patients with fair outcomes at follow-up was high.

Conclusion: NORSE is a rare, devastating but treatable epileptic disorder occurring in previously healthy patients. Despite the severity of clinical presentation and progression, patients can fully recover. This motivates extensive investigations and intense treatment with AEDs and immunosuppressants when appropriate.

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CEREBRAL PALSY IN A CHILD WITH CONGENITAL HYPOMYELINATING NEUROPATHY: PERINATAL SUFFERING OR GENETIC DISEASE SPECTRUM?

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Case Report: A 7 years-old child is followed in our IRCCS for a dyskinetic cerebral palsy in history of perinatal hypoxia [1]. She is a preterm infant, born at 31st week of gestation with cesareon section due to fetal atrial flutter. At birth were also diagnosed CMV infection, pulmonary hypertension and ductus arteriosus patency, treated with Sildenafil. Brain ultrasound scanning and genetic testing (CGH-array) were negative. When she was 1 years old, Brain MRI was performed, showing signal alteration in the posterior trait of left internal capsule, in periventricular white matter and bilaterally in globus pallidus. Were also described corpus callosum thinning and myelination pattern to lower limits. Over time she developed a tetraparesis with axial hypotonia, dyskinetic movement involving particularly upper limbs and orofacial region; so specific treatment with tetrabenazine was started until the dosage of 2 mg/kg/day, obtaining partial control of dyskinetic movements [2]. She also reported a severe cognitive disability and neurosensorial hearing loss requiring cochlear implants. Based on clinical evolution, complex medical history at birth and neuroradiological finding, genetic testing was expanded with Exome sequencing: two variants of CNTNAP1 gene were found, trasmitted with compound heterozygosity.

Discussion and Conclusions: CNTNAP1 gene encodes a Contactin-associated Transmembrane Receptor (CASPR) essential in the formation of paranodal axoglial junctions in myelinated axons but also involved in the development of cerebral cortex. Its mutation causes Congenital hypomyelinating neuropathy type 3 (CHN3) but it is also associated with polyhydramnios, severe neonatal hypotonia, arthrogryposis, facial diplegia and severe motor paralysis. Magnetic Resonance could reveal signs of hypomyelination and cerebral atrophy [3]. In our patient, perinatal hypoxia certainly played a determining role in developing cognitive and motor disturbances. On the other hand, some CNTNAP1-related features, such as axial hypotonia, central hypomielination and facial diplegia closely resemble our child's phenotype. This case suggests that before to attribute Cerebral Palsy to postnatal events, it's mandatory to exclude genetic underlying causes. We need to consider that a certain medical history is not always enough to rule out other contributory factors.

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MUTUAL LINK OF LIPID MYOPATHY AND DIET: A CASE REPORT

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Lipid storage myopathies (LSMs) are a group of genetic disorders characterized by excessive and pathological lipid accumulation in multiple body organs, chiefly within muscle fibers. Patients can clinically present with a range of clinical features, but most commonly encompass a progressive myopathy with muscle weakness, myalgia, and fatigue. There are four classic LSMs with a defined genetic cause. These conditions are associated with dysfunction in intracellular triacylglycerol catabolism, mitochondrial fatty acid oxidation, or transport of carnitine, acyl-carnitines, and/or long chain fatty acids. The most body triacylglycerol is derived from sources of dietary fat. Furthermore, case reports in the literature outline the role of dietary interventions in these patients. Especially, low-fat carbohydrate-rich diet has been shown to be a beneficial therapeutic dietary strategy. On the other hand, it has been reported that the restriction of carbohydrate intake potentially exacerbating metabolic decline. We report the case of a 31-year-old woman with recurrent episodes of rhabdomyolysis associated with myalgia and weakness. At first neurological examination she complained myalgias, started in the shoulder girdle and spreaded to the lower limbs, and fatigue, muscle strength and trophism were normal. EMG showed a mild myopathic pattern with early recruitment. No familial history of neuromuscular disease was referred. At blood exams Epstein-Bar Virus (EBV) IgM and anticardiolipin antibody were detected. Therefore she was diagnosed with mild post-infectious myopathy and treated with steroid and antiaggregant therapy with full recovery. However, symptoms fluctuated repeatedly under treatment with steroid, and worsened few days prior to the current presentation. At the admission patient complained widespread myalgia, weakness of proximal limbs were detected, with a right prevalence, and fatigue. Patient reported a weight loss higher than 20% of the baseline cause to a change of dietary regimen with adhesion to a ketogenic diet, which is a high-fat, adequate-protein, low-carbohydrate diet. During hospitalization CPK increased up to 175.00 UI, EMG reported similar myopathic pattern, while EBV IgM and anticardiolipin IgM were not confirmed. TC Total Body were performed with no abnormalities. Because of worsening respiratory function patient were transferred in High-Care Medicine and treated with steroid bolus and Igev with slow improvement of respiratory function and muscular strength. Muscle biopsy was performed and muscle fibers exhibited large intracellular lipid droplets. Therefore, the final diagnosis was lipid storage myopathy. In conclusion, this report remarkes how much extrinsic factors such as lifestyle and diet, mostly restriction of carbohydrate, are likely to influence disease severity and progression exacerbating metabolic decline.

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AMPHIPHYSIN ANTIBODY ASSOCIATED WITH SYMMETRICAL MIDDLE CEREBELLAR PEDUNCLES LESIONS: AN UNUSUAL CLINICAL, RADIOLOGICAL AND LABORATORY PRESENTATION OF BREAST CANCER

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Introduction: Lesions limited to the bilateral middle cerebellar peduncles (MCPs) are uncommon and most frequently observed in cerebrovascular diseases, followed by neurodegenerative diseases, inflammatory diseases, toxic encephalopathies and lymphomas [1]. We herein report a rare presentation of anti-amphiphysin paraneoplastic syndrome with atypical clinical, neuroimaging and laboratory features.

Case Report: A 50-year-old woman with an unremarkable medical history was admitted to our Department in February 2022 because of a seven-month history of subacute and progressive weakness of the inferior limbs together with postural instability. On admission, she had an ataxic paraparesis, with bilateral exhaustible ankle clonus and indifferent plantar reflex. She underwent a brain magnetic resonance (MR) on February which showed a symmetrical hyperintensity in T2/FLAIR of MCPs, without contrast enhancement or DWI resctriction, modification that was already detectable, although to a lesser extent, in a previous brain MR performed on October 2021. Electroneurography was normal while sensory and motor evoked potentials demonstrated signs of sensory and motor pathways impairment. Cerebrospinal fluid (CSF) examination showed mild pleocytosis (14 cell, 89% lymphocytes) with normal protein level and presence of CSF oligoclonal band (OCB). On suspicion of a paraneoplastic neurological syndrome (PNS), the patient underwent an extensive workout, which revealed a right breast cancer with homolateral axillary lymphadenopathies. Histological analysis after needle biopsy unveiled the presence of carcinomatous cells with ErbB2 overexpression. Total body [18F] fluorodeoxyglucose Positron-Emission-Tomography (FDG-PET) showed some hypermetabolic foci corresponding to the axillary and breast lesions, while there was a clear cerebellar hypometabolism. As for the PNS diagnostics, no reactivity for neural antibodies was present in serum. Amphiphysin antibodies were detectable in the CSF, but not in serum (OCB indicated intrathecal antibody production), and in the tissue-based (monkey cerebellum tissue) assays, but not in line immunoblots. The patient underwent a neoadjuvant chemotherapy with trastuzumab and subsequent surgical removal of the neoplasm.

Discussion: The final diagnosis was of an "anti-amphiphysin antibody PNS in breast cancer". This is a relevant case first for the atypical neuroradiological presentation, in that few cases have been reported so far of paraneoplastic syndrome with bilateral MCPs lesions; secondly, for the laboratory features, due to the isolated CSF positivity conformational antibodies showing an amphiphysin-like pattern [2], undetectable with denaturing immunoblot techniques.

Conclusion: This case report expands the clinical, neuroradiological and laboratory spectrum of PNS associated with amphiphysin antibodies and emphasizes the utility of tissue-based assays as a complementary tool of commercial line blots.

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ISOLATED FINDING OR SYSTEMIC DISEASE?

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Polycystic kidney disease (PKD) is a genetically and clinically heterogeneous group of disorders, defined as "ciliopathies", characterized by impaired epithelial cilia formation, misguided direction of cell migration, polarized cell division and cellular differentiation, disruption of epithelial organization with subsequent cystogenesis, increased extracellular matrix production, aberrant cell proliferation, apoptosis (Halvorson CR, 2010). All over the world, PKD is among the conditions more frequently treated by peritoneal dialysis, haemodialysis and renal transplantation. A 19 years old patient came to our observation for cranial trauma, because of new onset generalized epileptic seizure. Smoke and binge drinking were reported. Familial, maternal case history of polycystic kidney was referred. Computerized Tomography showed a left posterior, subarachnoid cyst, confirmed by Magnetic Resonance Imaging. Renal microcysts were detected at echography. At discharge, we prescribed an antiepileptic drug and required genetic counseling and control of renal function at neurological follow-up. The prevalence of arachnoid cysts is 0.5–1% in the general population [Helland CA, 2010, Vernooij MW, 2007), 5.2–8.1% in patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) (Romao EA, 2006, Schievink WI, 1995, Torres VE, 1990). In our population, although there is a high percentage of renal cysts, described at echography and/or computerized tomography (111/209, 53%), the contemporary presence of arachnoid and renal cysts was detected only in 2% of the cases. However, we do not exclude misdiagnosis. Symptomatic cysts are rare and may be associated with altered development, seizures, cerebral haemorrhage and focal neurological deficits. Spontaneous rupture of meningeal cysts may cause cerebrospinal fluid leakage, intracranial hypotension, headache. Unruptured intracranial aneurysms are reported in 3% of the general population (Vlak MH, 2011) compared to 11% of ADPKD patients [Cagnazzo F, 2017]. Renal dysfunction may increase the risk of ischaemic sufferance (Aguilar MI, 2010, Fiori P, 2010). Renal failure usually occurs by the fifth to sixth decade of life. Genetic counseling is recommended. Prenatal diagnosis may be performed by chorionic villus sampling or amniocentesis. Next-generation sequencing allows simultaneous analysis of a large group of genes in a single test, at relatively low cost. Whole-genome sequencing is still an expensive tool. Ultrasound is pivotal for diagnosis and for monitoring disease progression. MRI better defines cysts features. The most powerful strategy for slowing disease progression includes lifestyle changes, salt-

restriction, low protein intake, regular exercise, maintenance of a healthy body weight, frequent water intake, blood pressure control, adequate pain control, antibiotics for urinary tract infections.

TRANSIENT ISCHAEMIC ATTACK IN SHORT BOWEL SYNDROME

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Higher rate of Paroxysmal Atrial Tachyarrhythmias and Non-Paroxysmal Atrial Fibrillation (NPAF) are detected in females compared to males, admitted for Acute Cerebro-Vascular events (ACV) (Fiori P. et al., 2022). The unexpected finding of similar rate of NPAF in no-hysterectomized compared to hysterectomized AS patients suggested that atrial disarrangement may be related to other concomitant pathological conditions (Fiori P. et al., 2022). We report a case of transient ischaemic attack in a hysterectomized, 67 years old patient. She referred thyroid nodules, hysteron-adnexectomy for uterine cancer, followed by radiotherapy, eight years ago. After this surgical intervention, she began suffering from constipation. She underwent ileal resection for occlusion five years ago. Because of short bowel syndrome (SBS), her alvus was diarrhoeic, causing severe ipokalemia. She came to our observation for vertigos, mixed aphasia, dysarthria, confusion, right upper arm pronation and dysmetria lasted one hour. Arterial Pressure 151/96mmHg; Heart Rate 95b/min; Body temperature 36,5°C; Neutrophyls 6,99 x 103 (82,8%); Lymphocytes 0,93 x 103 (11%); Fibrinogen 696mg/dl; Urea 61mg/dl; Creatinaemia 1,03mg/dl; ESR 56; CRP 56,1mg/L; Na 144mEq/L; K 2,44mmol/L; Ca 7mg/dl; hs Troponin 488ng/L; pH 7,63; pO2 114mmol/L; pCO2 28mmol/L; HCO3 29,5mmol/L; SaO2 99,6%; Foecal examination: occult blood; Oncomarkers: negative. CT scan and Magnetic Resonance Imaging with angio sequences showed a collateral finding of cerebellar arachnoid cyst. Hypotonic solution with KCL, Ca gluconate, loperamide, os, ceftriaxone, iv, were administered. Severe arrhythmias were prevented. She was discharged with the suggestion of consuming small amount of food, repeatedly, limiting fat intake. The following oral therapy was prescribed: pantoprazole, losartan, clopidogrel, canrenone, amlodipine, allopurinol, KCL R, levothyroxine, cholestyramine, 25-hydrossi-cholecalciferol. SBS is characterized by the inability to maintain nutritional homeostasis after consumption of a normal, healthy diet, because of malabsorption secondary to extensive surgical resection of the small intestine (Duran B, 2005; Parrish CR and DiBaise JK, 2017; Pironi et al., 2015). Because of higher prevalence of lactate producing bacteria, D.-lactate enantiomer may accumulate and cause metabolic acidosis and neurological disorder (D-lactic acid encephalopathy) (Joly et al, 2010, Kowlgi and Chhabra, 2015; Mayeur C, 2016). On the contrary, our patient showed metabolic alkalosis. Medical therapy restored hydro-electrolyte steady-state, avoiding parenteral nutrition and worsening of renal dysfunction. SBS patients may undergo renal failure (oxalate nephrolithiasis). Impaired reabsorption of bile acids in enterohepatic circulation and adequate liver compensation further contribute to pathological vicious circle. Trials with teduglutide are ongoing. Innovative approaches, as intestinal transplantation, artificial intestine are still at the dawn.

EARLY ONSET CEREBRAL SMALL VESSEL DISEASE DUE TO HETEROZYGOUS HTRA1 MUTATION: A CASE REPORT

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Background and Aims: Cerebral small vessel disease (CSVD) accounts for around 25% of strokes. Rare monogenic variants account for about 1.5% to 5% of lacunar stroke. We report a case of early onset CSVD due to HTRA1 mutation.

Methods: The patient, a 57-year-old man without significant vascular risk factors except for mild hypertension, had recurrent lacunar ischemic strokes since his 3rd decade, leading to vascular dementia and death. Neuroimaging, neuropsychological tests, Cerebrospinal Fluid analysis (CSF), cutaneous biopsy and genetic analysis (Next Generation Sequencing) targeted to a panel of genes for vascular leukoencephalopathies were performed.

Results: Family history was remarkable for stroke and dementia, affecting the patient's father and paternal uncle. The patient experienced his first ischemic stroke at 36 years. He then experienced several minor strokes. At 57 years the neurological examination displayed paretospastic gait, right facial deficit, polykinetic patellar reflexes, bilateral ankle clonus, mild spasticity of both upper arms, hypokinesia, urinary and fecal urgency. Brain MRI showed marked T2 hyperintensity of supraventricular and infraventricular white matter with confluent lesions, cribriform status of the basal ganglia, lacunae with hyperintense border and small subcortical microbleeds. No extra neurologic signs or symptoms were present. Neuro psychological tests showed deficits in working and recent memory, in verbal and visuospatial planning and constructive apraxia. CSF was normal. Granular osmiophilic material was absent at the cutaneous biopsy. Genetic analysis revealed an heterozygous c.496C>T, (p.Arg166Cys) missense variant in exon 2 of HTRA1 gene. The mutation was confirmed by direct Sanger sequencing.

Discussion & Conclusions: Biallelic pathogenic variants in HTRA1 cause CARASIL. Monoallelic mutations have been described in apparent sporadic, late onset CSVD and in autosomal dominant CSVD. Monoallelic pathogenic variants are clustered in two distinct regions: the linker region contributing to trimerization and the loop region contributing to HTRA1 activation [1]. The mutation found in our patient resides in the linker region and has already been described both in CARASIL and in familial dominant CSVD. Unless most patients with heterozygous HTRA1 related CSVD have the onset of symptoms in the sixth decade [2], our patient had to our knowledge the earlier age of onset described to date. Early age at onset, recurrence of strokes despite the control of risk factors and MRI pattern might prompt the clinician to look for a genetic cause of stroke. In the European population monoallelic HTRA1 variants are the 2nd cause of familial dominant CSVD, accounting for nearly 5% of cases.

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A CASE REPORT OF AN ANTI-YO MEDIATED PARANEOPLASTIC CEREBELLAR DEGENERATION

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The paraneoplastic cerebellar degeneration (PCD) mediated by anti-Yo autoantibodies is a rare cerebellar complication which occurs during specific cancers such as breast cancer, small cell lung cancer, gastrointestinal cancer and female pelvic tumors. Anti-Yo are highly specific autoantibodies targeted against a cytoplasmic antigen of the Purkinje neurons. In a limited number of women with cancer, an almost simultaneous coexistence of breast cancer and PCD anti-Yo antibodies has been demonstrated. Among the PCDs, that one mediated by anti-Yo autoantibodies has a female predominance and occurs frequently in women with gynecological malignancies over their 60s. We report an anti-Yo mediated PCD clinical case from a 58-year-old female patient with poorly differentiated infiltrating ductal carcinoma of the breast, estrogen positive, progesterone negative, Ki67 positive, Her-2 positive. In addition, the serum antibody test was specifically positive for the anti-Yo autoantibody. Moreover, previous neurological, psychiatric and autoimmune diseases were absent in her clinical history. Brain MRI analysis revealed an entire elective atrophy of the cerebellar vermis and an abnormal dilation of all the cerebellar sulci. Clinical evaluation of the patient showed co-presence of motor and non-motor cerebellar symptoms and signs. Bilateral deficits characterized by trunk and limbs ataxia, nystagmus, diplopia, dizziness and ataxic dysarthria were observed. In psychiatric assessment, depression and anxiety were noted. Neuropsychological evaluation revealed a condition ascribable to cerebellar cognitive affective syndrome, featuring deficits in executive functions, spatial cognition and visuospatial memory, as well as inappropriate behavior and moderate depression. In our analysis of the aforementioned case, we highlighted the coexistence of motor and non-motor cerebellar deficits, rarely found combined in this kind of condition. At the end of diagnostic work-up, the patient underwent various therapies, namely corticosteroids and plasma exchange for 2 weeks. In addition, the patient has been going through intensive sessions of neuromotor rehabilitation with modest improvement to date. Conclusively, further studies are needed, given the lack of early diagnostic criteria and effective therapies that reliably improve the course of cerebellar deficits.

A CLINICAL CASE OF CORPUS CALLOSUM AGENESIA: A NEUROSCIENCE MULTIDISCIPLINARY EVALUATION

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The corpus callosum (CC) is the most voluminous brain interhemispheric commissural structure in placental mammals. In humans, CC reaches its maximum complexity and size with respect to the whole brain volume. CC fibers are mainly composed of myelinated fibers and a smaller number of unmyelinated fibers, both originate from neocortical neurons of layers III, V, VI which have a heterogeneous neurochemical composition. Cytologically it is mainly composed of glial cells such as oligodendrocytes, astrocytes and few neurons. The CC is topographically subdivided into 7 regions, in which the functional distribution of the fibers is still little known. Recently, protein expression studies have shown in the CC regions a different expression profile of the regulatory proteins involved in oxidative stress and in the calcium regulatory signal. Among the most severe malformative neurodevelopmental disorders is considered the agenesia of the corpus callosum (AgCC) characterized by an almost total or residual presence of CC fibers. Nonetheless, AgCCs are often neglected or undiagnosed. Several studies demonstrated the coexistence of AgCC and other brain anomalies, however, the reciprocal influences of AgCC with other brain anomalies and the correlations between neurological and psychiatric symptoms are scantly. The goal of this clinical evaluation was to analyze the reciprocal influence of AgCC with other brain anomalies, clinical symptoms, neuropsychological functions in a clinical case of AgCC by means of a translational or morphofunctional, clinical and neuropsychological approach. The morphofunctional analysis highlighted the coexistence of other brain abnormalities, the presence of psychiatric and neurological symptoms, and the presence of neurocognitive deterioration closely related to the AgCC. The multidisciplinary analysis of this clinical case of AgCC suggest that this type of approach may play an important role in highlighting the presence of undiagnosed AgCC or CC abnormalities in certain neurological and psychiatric diseases such as multiple sclerosis, stroke sequelae prognosis, cognitive impairments, Korsakoff syndrome and autism spectrum disorders.

CLINICAL-MRI DISSOCIATION IN SPINAL CORD SARCOIDOSIS: A CASE REPORT

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Objective: To describe a rare case of longitudinally extensive spinal cord sarcoidosis incidentally disclosed during the diagnostic work-up for intermittent diplopia.

Materials and methods: The clinical presentation and diagnostic approach leading to the diagnosis of spinal cord sarcoidosis are presented.

Results: A 53-year-old man presented after one month of intermittent diplopia that resolved spontaneously. Acetylcholine receptor and muscle-specific kinase antibodies were not detected in serum. Neurological examination revealed diffuse hyperreflexia, bilateral Trömner sign and diplopia evocable after fatigability on the left gaze. Brain MRI (1.5 Tesla) was unremarkable but revealed some abnormalities in the upper cervical spinal cord. Spinal cord MRI disclosed a longitudinally extensive T2-hyperintense lesion from C1 to D1, with associated patchy gadolinium enhancement. Serum diagnostic evaluations included normal copper, folate, and vitamin B12 levels, negative testing for anti-nuclear and extractable nuclear antigens antibody, and negative testing for aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies by cell-based assay (fixed and live, respectively). Plasma levels of angiotensin-converting enzyme (ACE) were elevated (85 U/L; normal range, 19-70 U/L). Lumbar puncture showed mild pleocytosis (12 white blood cells/mm3),

elevated proteins (70 mg/dL; normal range, <40 mg/dL), and negative oligoclonal bands. An extensive diagnostic screening for infectious etiologies was unremarkable both on serum and cerebrospinal fluid. Chest CT revealed mediastinal lymphadenopathy, with associated intense FDG uptake on positron emission tomography. Endobronchial ultrasound (EBUS) with transbronchial needle aspiration (TBNA) of a lymph node revealed non-caseating granulomatous inflammation, consistent with probable neuro-sarcoidosis. The patient was followed untreated for 3 months with stability of the spinal cord lesion on MRI. After 3 months, he developed numbness in both hands and Lhermitte's phenomenon. Intravenous methylprednisolone was administered (1 g/day for 5 days) followed by slow tapering of oral prednisone (starting from 50 mg/day), with prompt resolution of symptoms and marked improvement of the spinal cord abnormalities.

Discussion and Conclusions: The diagnosis of spinal cord sarcoidosis can be particularly challenging when not accompanied by clinically overt systemic involvement. A marked clinical-MRI dissociation (i.e., extensive MRI abnormalities accompanied by only mild clinical manifestations) is a big clue for diagnosis. In our patient, the cause of the intermittent diplopia initially complained by the patient remains unclear; a granulomatous inflammation of the oculomotor nerves not detectable on MRI can be hypothesized.

BASELINE SUBTLE NEUROLOGICAL SIGNS PREDICT FUTURE IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME (ICANS) IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) TREATED WITH CAR-T THERAPY TISAGENLECLEUCEL

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Objectives: Chimeric antigen receptor T cells (CAR-T) are a new class of treatment against lymphoid malignancies. Albeit their great efficacy, significant adverse events such cytokine release syndrome (CRS) and Immune effector cell-Associated Neurotoxicity Syndrome (ICANS) are common. ICANS includes a plethora of different clinical manifestations, such as aphasia, dyscalculia, tremor, seizures, headache and stroke. Several tools have been developed to early identify and assess severity of neurological complications (e.g. CARTOX scale). Both CRS and ICANS are usually reversible if treated promptly. Aim of this study is to analyze our cohort of patients who underwent to CAR-T to better characterize clinical course and adverse events.

Materials and methods: In this retrospective case series we analyzed seven consecutive patients with Diffuse Large B-Cell Lymphoma (DLBCL) treated with CAR-T therapy tisagenlecleucel in the Hematology Unit of our hospital. Age at the treatment, ECOG Performance Status Scale, brain MRI, CRS and ICANS score, administration of tocilizumab and clinical outcome were recorded.

Results: Four females and three males treated from January 2020 to April 2022 were included in this study. Median age at treatment was 54.9 years (range: 26.4 – 68.9 years). Brain MRI was obtained from four patients before the infusion, all of them showing no significant alterations. All patients experienced grade 1 CRS (fever) within the first day after the infusion. One female patient had severe ICANS. In detail, her first neurological examination before the infusion revealed mild temporal disorientation and bilateral palmomental reflex. Six hour after infusion she started to develop fever (grade 1 CRS). The first neurological impairment was observed twenty hours after the infusion when her writing became paligraphic ("MI PIACE LA PIZZA" became "MII PIIACEE LA ZIZZZ"), configuring a grade 1 ICANS. Two hours later she was completely unable to perform the writing task and, after a few hours she became disoriented in space and time, dyscalculic and anomic (grade 10 ICANS). Tocilizumab was then administered with a complete regression of neurological signs after three hours.

Discussion: The only patient reported ICANS presented subtle alteration of neurological examination at baseline. Pathogenesis of ICANS adverse events of CAR-T and disturbances in language remain largerly unknown likely involving cytokine-mediated neuroinflammatory mechanisms.

Conclusions: Pre-treatment recognition of subtle neurological signs at bseline may predict ICANS and the need of a prompt (or maybe preventive) treatment after CAR-T therapy. Further studies are required to better understand this relationship.

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ANTI-AQUAPORIN-4 ANTIBODIES AND MULTIPLE SCLEROSIS: A DUAL PATHOLOGY OR A LABORATORY FLAW? A CASE REPORT

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Background And Aims: Both multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) are inflammatory diseases of the central nervous system with a significant clinical overlap. Despite this, their differential diagnosis is crucial since, in some cases, MS treatments may cause detrimental effects in NMOSD. Anti-aquaporin-4 antibodies (AQP4-Ab), highly specific seromarkers of NMOSD, are extremely rare in MS.

Materials: We performed Brain and Spinal Cord MRI, Physical examination, lumbar puncture, laboratory exams and Eye examination with visual field test and optical coherence tomography (OCT). We report the case of a patient with typical MS characteristics with concomitant AQP4-Ab seropositivity.

Methods: We report the case of a patient with typical MS characteristics and concomitant AQP4-Ab seropositivity.

Results: A 47-year-old woman, with a previous mild episode of left arm hyposthenia, presented with transient acute cervical pain. Neurological examination was normal, except for left arm and both legs hypopallesthesia. Expanded Disability Status Scale score was 2.0. Brain and spinal cord (SC) MRI showed multiple T2-FLAIR/DIR hyperintensities in typical MS areas (periventricular, cortical, juxtacortical, infratentorial and SC) and patterns ("Dawson's fingers", black holes, short peripheral SC lesions), as well as a small lesion in the left optic nerve, suggesting a previous subclinical optic neuritis. Eye examination, visual field test and OCT confirmed the possibility of previous optic neuritis. Also visual evoked potentials (VEPs) were altered with P100 increased latency in OS. Laboratory work-up showed intrathecal oligoclonal bands and AQP4-Ab seropositivity, while other tests, including anti-myelin oligodendrocyte glycoprotein antibodies were normal. Considering diagnostic uncertainty, a disease-modifying therapy with ocrelizumab was started. At a 6-month clinical and MRI follow-up the patient was stable.

Discussion: Our report of AQP4-Ab seropositivity with typical MS characteristics suggests either a false positive AQP4-Ab test or a coexistence of MS and NMSOD, both of which extremely rare in literature.

Conclusions: Anti-CD20 therapy could be a reasonable choice in both diseases. AQP4-Ab testing is crucial in MS differential diagnosis.
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AN ATYPICAL CASE OF ECLAMPSIA-ASSOCIATED POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

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Background: Posterior reversible encephalopathy syndrome (PRES) is a rare clinic-radiological entity that may present with non-specific clinical symptoms, namely headache, visual disturbances, seizures and altered mentation. The typical neuroimaging finding is a symmetric vasogenic edema predominant in the subcortical parietal-occipital white matter.

Case presentation: A 31-year-old pregnant woman with a history of gestational hypertension, underwent cesarean section after spinal-epidural analgesia. Later she complained about bilateral orthostatic headache so post dural puncture headache was diagnosed. Puerperium was complicated by fever associated with bilateral interstitial pneumonia (with a suspected SARS-CoV-2 etiology). Ten days after delivery, she developed a severe, frontal, non postural headache associated with hypertension (160/100 mmHg). On the following morning a generalized convulsive seizure occurred; during neurological evaluation she was conscious but very drowsy without other neurological signs. Magnetic resonance imaging (MRI) was performed and showed asymmetric hypersignal intense lesions in the cortical and subcortical fronto-parietal lobes and left temporal lobe in both the fluid-attenuated inversion recovery (FLAIR) sequence and apparent diffusion coefficient (ADC); these lesions were not recognized in diffusion-weighted imaging (DWI). There was also extensive signal abnormality in the bilateral cerebellar hemispheres and within callosal splenium; pathologic contrast enhancement was present in the corpus callosum and in left frontal cortical area. PRES was considered due to clinical presentation and neuroimaging; differential diagnosis included encephalitis (maybe related to COVID-19) and Reversible Cerebral Vasoconstriction Syndrome. Cerebrospinal fluid (CSF) analysis revealed mildly increased level of cell count (9 cells/μL, normal: <5 cells/μL, 55,6% polymorphonuclear cells), normal proteins without glucose consumption; oligoclonal bands were not detected. CSF bacterial culture was negative as well as viral panel (included herpes simplex virus type 1 and 2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus and SARS-CoV2). MR angiography was negative for vasospasm. Antiepileptic and antihypertensive drugs were administered; follow-up brain MR performed in 10 days showed complete resolution of the lesions. The patient was discharged from hospital in good clinical conditions.

Discussion: We present a tricky diagnosis of eclampsia-associated PRES. History of dural puncture and pneumonia were confounding clinical factors; atypical imaging findings (cerebellar and callosal lesions associated with contrast enhancement), on the other hand, could lead clinicians to diagnose other etiologies (such as hypoxic-ischemic injury or encephalitis).

Conclusions: Since signs and symptoms of PRES are not specific, MRI is vital for diagnosis. Nevertheless, atypical imaging findings must be known in order not to mistakenly reject the diagnosis of PRES.
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ISOLATED BRAINSTEM LESION SUGGESTIVE FOR NEURO-BEHÇET DISEASE: A CASE REPORT

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Objectives: To address the differential diagnosis of an isolated brainstem lesion suggestive for parenchymal Neuro-Behçet disease (NBD) in a young patient lacking systemic manifestations of Behçet disease.

Materials and Methods: We report on a 21-year-old girl presenting with subacute onset of headache, dizziness, dyplopia and paresthesias on the right half of the face and right upper limb. Her history was unremarkable except for recurrent aphthous stomatitis during childhood and alopecia areata. The patient underwent a thorough diagnostic work-up comprehensive of 3T brain MRI, MR spectroscopy, cerebrospinal fluid (CSF) analysis, extensive immunological and microbiological assessment, whole body imaging and specialistic rheumatological and ophthalmological referrals.

Results: Brain MRI disclosed a single T2-hyperintense lesion in the pons showing contrast-enhancement in the periphery and central area; MR spectroscopy showed a decreased N-acetylaspartate (NAA) peak. Spine MRI was normal. CSF analysis revealed pleocytosis (58 normal cells/uL, 98% lymphocytes 2% polymorphonucleocytes) and three unique-to-CSF oligoclonal bands with normal IgG index. Microbiological assessment was negative. Immunological profile only disclosed low titer ANA positivity and mild hypogammaglobulinemia. The patient was positive for HLA B*44*51. We started therapy with intravenous (iv) methylprednisolone (1 gr for 7 days) which resulted in clinical remission. Follow-up brain MRI at 1 month showed the decrease in volume of the lesion with persistent contrast-enhancement. Repeated CSF analysis showed markedly decreased pleocytosis (7 cells/uL) and no oligoclonal bands. A second iv MPN cycle (1 gr for 5 days) was administered, followed by slow oral steroid tapering. The patient remains in strict clinico-neuroradiological follow-up.

Discussion: Neuroimaging was highly suggestive for parenchymal NBD, showing a single brainstem lesion with patchy CE and decreased NAA peak in the acute phase; multiple sclerosis and other inflammatory CNS diseases were excluded by repeated CSF analysis, extensive antibody testing comprehensive of antiMOG Abs, anti AQP4 Abs, neuronal surface Abs, serum and CSF ACE and IL-6, neuroimaging showing no other lesions and normal VEPs. The patient was positive for HLA*B*44*51 but lacked other stigmata of Behçet disease (no oral or genital ulcers, negative pathergy test, no uveitis on ophthalmological examination).

Conclusions: NBD diagnosis can be challenging in patients with no systemic symptoms, and it currently depends on the exclusion of all differential diagnosis, leaving the dilemma of long-term treatment. Further characterization of NBD is needed to achieve an early diagnosis and safely start the appropriate immunosuppressive therapy.
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BRAIN PARENCHYMA SONOGRAPHY AS A USEFUL TOOL IN DETECTING PATIENTS WITH ESSENTIAL TREMOR AT RISK TO DEVELOP PARKINSON'S DISEASE: A CASE REPORT

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Objectives: Essential tremor (ET) is the most common cause of action tremor. ET patients have an increased risk of developing Parkinson's Disease (PD) during their lifetime. Single-photon emission computed tomography (SPECT) with DaT has high specificity and sensitivity, but in early stage of disease can be negative. We underline the importance of Brain Parenchyma Sonography (BPS) as a useful tool in detecting patients with ET who have developed or are at risk to develop PD in routine clinical practice.

Materials and methods: Case report

Results: A female 76-years-old patient, suffering from ET from childhood developed tremor dominant PD, in the last year. Neurological examination revealed head and voice tremor, kinetic postural and rest tremor of upper limbs, greater on the left, bilateral bradykinesia and reduction of synkinesis. Dopaminergic treatment was started with resolution of bradykinesia and improvement of tremor at rest. Brain MRI showed only mild brain atrophy; a DaT SPECT was apparently normal; a BPS revealed a bilateral hyperechogenicity of the Substantia Nigra (SN, right 0,46 cm2, left 0,33 cm2).

Discussion and conclusions: The clinical presentation leaded to a diagnosis of PD, that is more frequent in long-standing ET. The DaT SPECT was apparently negative and seemed to exclude a consistent damage of DaT presynaptic basal ganglia receptors. BPS revealed SN hyperechogenicity, detectable in more than 90% of patients with PD or at risk to develop it but not in ET. BPS may be a sensitive non-invasive diagnostic tool in doubtful clinical cases or in early stages of PD, as in this case.

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A CASE OF ATAXIA AND OPTIC ATROPHY CAUSED BY NDUFA1 MUTATION

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Background, Objective: To describe a case of NDUFA1 mutation associated with ataxia and optic atrophy.

Methods: A 43-year-old male from non-consanguineous parents came to our attention because of worsening of balance. He was full-term born, started to walk at 13 months and had language acquisition delay, needing a support teacher until age 18 (QI by WISC 79). At age 5 visual disturbance was noted, and optic atrophy was diagnosed. At 24 years he underwent brain MRI and motor evoked potentials, which were normal, electroneurography, documenting pure sensory axonal polyneuropathy, visual evoked potentials, documenting bilateral P100 absence, and lactate stress test, that was positive. Histology on muscle biopsy was normal. Genetic testing for SCA 6 was negative. Current neurological examination showed ataxic gait without need of support, positive Romberg sign, spontaneous nystagmus, severely reduced visual acuity, pes cavus and no motor deficits. The patient underwent a new brain MRI, showing thinning of optic nerves and slight vermian atrophy. Both the patient and parents underwent genetic testing through Next-Generation TruSightONE-Expanded Sequencing Panel (Illumina), filtering results for genes associated to mitochondrial diseases.

Results: Genetic testing showed the hemizygous missense mutation c.55C>T; p.(Pro19Ser) on NADH-Ubiquinone Oxidoreductase Subunit A1 (NDUFA1) gene, which was inherited from his mother. To confirm pathogenicity, previous muscle biopsy was used to evaluate by blue native gel electrophoresis activity of mitochondrial Complex I (CI), which was reduced, and reduction of diverse CI subunits by Sodium Dodecyl Sulphate-PolyAcrylamide Gel Electrophoresis.

Discussion and Conclusion: NDUFA1 codes for a subunit of CI and is fundamental for CI assembly and functioning. The same mutation was once described associated with young-onset Leigh syndrome, characterized by hypotonia, nystagmus, epilepsy and T2 midbrain hyperintensities. Our case is of interest because expands the phenotypic spectrum of NDUFA1 mutations, that should be added to causes of ataxia with optic atrophy.

NORSE AS EARLY MANIFESTATION OF RAPIDLY EVOLVING CREUTZFELD-JACOB DISEASE IN A COVID19 PATIENT: DIAGNOSTIC CHALLENGE AND PATHOGENETIC CONSIDERATIONS

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Aim: Creutzfeld-Jacob Disease (CJD) diagnosis can be challenging. Usual initial course of the disease is characterized by a subtle onset of psychiatric and neurological symptoms: in particular most patients experience depression, anxiety, nervousness, autonomic disturbances, disruption of sleep-wakefulness rhythm, gait alterations, ataxia and myoclonus.

Materials and Methods: We report the case of a 70 years old patient coming to our attention for new onset refractory status epilepticus (NORSE) in a rapidly evolving CJD during SARS-CoV-2 coinfection.

Results: In the 40 days before the ward admission the patient experienced aspecific disturbances. 40 days later a nasopharyngeal swab for SARS-CoV-2 resulted positive. An EEG was performed, showing continuous diffuse spikes, sharp waves and sharp-and-slow wave complexes, pattern consistent with a non-convulsive status epilepticus (NORSE). The clinical condition of our patient rapidly evolved in akinetic mutism and coma. Based on the clinical history of a rapidly progressive dementia with epileptic seizures, a prion disorder or an autoimmune encephalitis were suspected and a lumbar puncture was performed. Two weeks after the admission he died. The results of the RT-quic confirmed the diagnose of CJD.

Conclusions: CJD with SARS-CoV-2 coinfection could be characterized by an accelerated evolution. In this type of patients, CJD diagnosis

might be even more challenging due to the presence of uncommon presentations, as NORSE.

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AN ATYPICAL PRESENTATION OF BICKERSTAFF BRAINSTEM ENCEPHALITIS ASSOCIATED TO ANTI-GD3 AND ANTI-GT1A ANTIBODIES: A CASE REPORT

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Background: Bickerstaff brainstem encephalitis (BBE) is a rare immunologic disease characterized by subacute onset of external ophthalmoplegia, ataxia, and consciousness disturbances, most often subsequently to an infection. BBE is considered to be a variant of Guillain-Barré and Miller-Fisher syndromes, with a predominant involvement of central nervous system (CNS). Anti-gangliosides antibodies have been related to BBE, especially anti-GQ1b, even if some variability is described. Both intravenous immunoglobulin and plasma exchange are reported as reasonable treatments.

Case presentation: A 59-years-old man presented an acute onset of fever, headache with mild nuchal rigidity, 4-limb ataxia and paresthesia. The first diagnostic hypothesis was a CNS infection, with the support of cerebral spinal fluid (CSF) pleocytosis and IgM anti-Borrelia antibodies detection. The patient was treated with iv antibiotics, until the exclusion of an infectious disease with PCR analysis. Meanwhile, symptoms worsened with progressive onset of bulbar signs – dysarthria, dysphagia, facial palsy, and trigeminal dysesthesia – and consciousness disturbances. CSF resulted positive for anti-GD3 and anti-GT1a antibodies. MRI showed brainstem hyperintensity on long TR images, involving trigeminal nerve and nuclei bilaterally and right cerebral peduncle. Blink reflex showed abnormal R2 responses bilaterally, revealing a deficit in the trigeminofacial circuit. The diagnosis of BBE was done, and the patient was treated with iv immunoglobulin and corticosteroids, showing gradual improvement. After about 6 months from discharge, the patient reported a recrudescence of residual symptoms, in particular ataxic gait, and limb paresthesia. A second course of iv immunoglobulin was performed, with discrete benefit.

Discussion: We reported the case of an atypical form of BBE, because of both the absence of the complete clinical triad (i.e., absence of ophthalmoplegia) and the presence of atypical anti-gangliosides antibodies (i.e., anti-GD3 and anti-GT1a). However, cases of BBE without anti-GQ1b antibodies have already been described, and a possible relation between the type of antibody and the clinical phenotype has been proposed. More specifically, anti-GD3 antibodies have been related to ataxia, which was one of the most prominent and early symptoms in our patient. Moreover, our case is one of the few reports of recurrent or persistent disease. Indeed, BBE has always been considered a monophasic disease, but chronic forms could reasonably exist. This raises unanswered questions about the need of a chronic immunosuppressive therapy for selected patients.

Conclusions: In conclusion, our case allows to highlight the clinical and immunological variability of BBE phenotypes, and to discuss new perspective on prognosis and treatment.

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A CHALLENGING CASE OF HEADACHE AND STROKE

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Background: The primary angiitis of the central nervous system is a rare inflammatory disease that involves the brain and spinal cord vessels, leading to their destruction. The etiology is unknown, but several potential etiologic agents or mechanisms have been proposed, i.e. infectious agents, such as Varicella Zoster Virus, West Nile virus, Mycoplasma gallisepticum, and human immunodeficiency virus (HIV) [1]. The diagnosis is challenging due to the broad spectrum of symptoms, along with the nonspecificity of available investigational modalities. Brain biopsy is the gold standard to achieve a diagnosis, but its sensitivity is lowered by the difficulty to sample an involved brain area [2].

Case report: A 74 years old man presented to the Emergency Department with a new onset headache and fever. His medical record was relevant to arterial hypertension, type 2 diabetes mellitus, central retinal artery thrombosis of the right eye and West Nile encephalitis two years before. Brain CT was normal, while the CSF analysis showed a mild protein increase. An empirical treatment with acyclovir and ceftriaxone was started. The next day he developed a mild left hemiparesis and an impairment of consciousness until GCS 11. A second brain CT and a CT angiography study were normal, while the brain MRI showed the presence of acute ischemic cortical lesions in the right hemisphere. In the next few days he improved with a recovery of consciousness and of left limbs strength, but with emergence of visual and auditory hallucinations. The history of cephalalgia, fever and stroke suggested a diagnosis of vasculitis, so we performed a cerebral conventional angiography, a total body CT angiography and a serum immunological screening, which didn't show alterations. A second lumbar puncture revealed the persistence of a mild protein increase and the presence of oligoclonal bands. The patient has undergone an MRI guided brain biopsy of the right temporal lobe, including parenchyma and meninges. The brain sample revealed the presence of a massive lymphocyte infiltrate (CD3+) in the wall vessels both in necrotic and normal parenchymal areas. Moreover, wall vessels were destroyed in several stretches. A five days cycle of high doses of methylprednisolone (1000 mg/day) i.v. has been administered with psychotic symptoms resolution and the patient has been discharged with prednisolone 1 mg/kg/day. Currently, he is under monthly monitoring, receiving rituximab and prednisolone orally with dose tapering.

Conclusion: Diagnosis of PACNS is challenging and requires high suspicion to arrive at the brain biopsy.

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COVID-19 COURSE AND OUTCOMES AFTER THREE MRNA VACCINE DOSES IN MULTIPLE SCLEROSIS PATIENTS TREATED WITH HIGH EFFICACY DMTS

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Objectives: High-efficacy (HE) disease-modifying therapies (DMTs) for Multiple Sclerosis (MS), such as anti-CD20 monoclonal antibodies - i.e., Ocrelizumab (OCR) and Rituximab - may worsen COVID-19 course. Preliminary data suggest that two doses of mRNA COVID-19 vaccine (RNA-Vax) reduce the risk of breakthrough/severe COVID-19 in patients with MS (pwMS) under treatment with HE-DMTs. Little is known about the protective effect of a third booster dose of RNA-Vax in pwMS treated with most commonly used HE-DMTs, such as Natalizumab (NTZ), Fingolimod (FNG), and OCR. The aim of our study was to compare COVID-19 course and outcomes in pwMS on NTZ, FNG, and OCR after receiving the third dose of RNA-Vax.

Methods: Inclusion criteria were: >18 years old, being treated with NTZ/OCR/FNG since the first vaccine dose, diagnosis of COVID-19 after a third booster dose of RNA-Vax, not being treated with steroids within the month prior to any vaccine dose or COVID-19.

Results: 232 pwMS (63 NTZ, 106 OCR, 63 FNG) from 17 Italian MS centers were included in the analysis. pwMS on NTZ (37±9) were younger than those on OCR (42±10, p=0.026) and FNG (43±11, p=0.006); EDSS was higher in pwMS on OCR (3.0, IQR=1.5-5.5) than those on FNG (2.0, IQR=1.0-3.0, p=0.017). COVID-19 was diagnosed 65±41 days after receiving the third booster dose. PwMS on OCR compared with those on NTZ showed more frequently (p<0.02-0.001): fever >38°C (53.8% vs 20.6%), cough (67% vs 36.5%), dyspnea (18.9% vs 3.2%), longer symptoms duration (9.5±8.7 vs 6±4.6 days), use of NSAIDs (74.5% vs 52.4%), oxygen (7.5% vs 0%), antibiotics (45.3% vs 14.3%). PwMS on OCR compared with those on FNG needed more frequently the use of oxygen (7.5% vs 1.6%, p=0.002). PwMS on FNG compared with those on NTZ showed more frequently (p<0.03-0.002): fever >38°C (39.7% vs 20.6%), cough (65.1% vs 36.5%), dyspnea (15.9% vs 3.2%). There were no differences between the 3 groups of pwMS regarding: COVID-19 treatment with steroids or monoclonal antibodies, hospitalization, and full recovery or death (0%).

Discussion: Breakthrough COVID-19 after a third booster dose of RNA-Vax was more symptomatic in pwMS on OCR and FNG than those on NTZ. Nevertheless, no deaths were reported and the Covid-19 course in terms of full recovery and hospitalization rates was not different across different HE-DMTs.

Conclusions: These results support the efficacy of a third booster dose of RNA-Vax in preventing severe COVID-19 (with hospitalization/death) in pwMS treated with most common HE-DMTs.

ANTI-METABOTROPIC GLUTAMATE RECEPTOR 1 (MGLUR1) ENCEPHALITIS: A RARE CAUSE OF CEREBELLAR DEGENERATION

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Objectives: Anti-metabotropic glutamate receptor (mGluR) are antibodies against G-protein-coupled glutamate receptors that mediate excitatory neurotransmission in central and peripheral nervous system. There are 8 different types of mGluRs; few case reports and small case series have investigated the clinical syndrome associated with anti-mGluR1 encephalitis. Herein, we report a cases of anti-mGluR1 encephalitis in patient with heterologous paravertebral muscle formation and serum and cerebrospinal fluid (CSF) anti m-GluR1 antibodies.

Case report: A 68-year-old man came to our attention because of progressive imbalance with repetitive falls, associated with speech disturbance and apathy. His neurological examination revealed dysarthria, gait instability and limb ataxia (SARA 18). His past medical history was significant for weight loss, and normocytic anemia. Brain MRI showed diffuse cerebellum atrophy; spinal MRI showed heterologous tissue involving the right paravertebral muscles from L3 to S2, with intense enhancement after gadolinium, and infiltrating lamina, articular processes and pedicle of right L5 and extending in the epidural space with displacement to the left of dural sac. FDG PET showed increase uptake in the right posterior lumbar paraspinal muscles at L5 level (SUV 11.0) and diffuse uptake in osteo-medullary compartment; whereas cerebellum exhibited a widespread glycidic hypometabolism. CSF analysis revealed mild pleocytosis with a severe damage to brain barrier and systemic oligoclonal IgG. Common clinically available autoimmune encephalitis' autoantibodies and onconeural were negative on CSF and serum. Both transpedicular L5 biopsy and ultrasound-guided needle biopsy of muscle failed to identify neoplastic tissue. A course of intravenous methylprednisolone (total dose 5 gr) was administered with partial clinical improvement (SARA 14). According to medical history of subacute onset of a cerebellar syndrome, we investigated also anti-mGluR1. High title of anti-mGluR1 was detected both in CSF and serum. Intravenous immunoglobulins were started and further biopsy planned.

Discussion: According to literature, patients manifest a cerebellar syndrome accompanied by behavioural changes (apathy), subacute onset and partial response to immunotherapy. Anti-mGluR1 encephalitis are rarely paraneoplastic, being associated to prostate cancer or lymphoproliferative disorders. The patient's heterologous lesion is still under definition. Few studies exist on anti-mGluR1 encephalitis, which demonstrate a worse outcome than other more frequent autoimmune encephalitis such as anti-NMDAR or anti-LGI1. Future studies will investigate if a delayed diagnosis and treatment or the irreversible neuronal damage are responsible of worse outcome.

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BULBAR ONSET OF MYASTHENIA AND CONCURRENT ANXIETY DISORDER: A DIAGNOSTIC CHALLENGE

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Background: Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction that may be triggered by stress. We report the case of a patient with bulbar onset of MG, who was initially diagnosed as affected with anxiety disorder, and treated with psychiatric drugs that eventually worsened the picture and led her to the emergency room (ER).

Case report: A 54-year-old woman with a long history of anxiety and hypochondria presented an insidious and fluctuating onset of asthenia in July 2021. The patient, a teacher, was heavily distressed by the COVID compulsory vaccination for her work category that she has refused. She started avoiding social life and having frequent panic attacks. When asked, she referred infrequent episodes of blurred vision in the morning. In the following weeks, she experienced prominent weakness of neck and mimic muscles, without a clear modification during the day. A psychiatric and physiatrist evaluations were inconclusive. At a private consultation, she was considered neurologically normal, and an anxiety disorder was diagnosed. A second psychiatrist prescribed a drug regimen based on three different benzodiazepines. In a few weeks, the patient's conditions worsened, with onset of dysphagia, for both solids and liquids, weight loss (10kg in a month), left eye ptosis, and episodes of evening air hunger, interpreted as panic attacks. The worsening of symptoms finally led the patient to the ER of our hospital in October 2021. On ER admission, the patient was cachectic, referred important anxiety and had many dyspnea episodes with desaturation. On neurological evaluation, she had hypophonic and nasal speech, bilateral ptosis, neck weakness, diplopia after upper gaze for 30 seconds, leg weakness after 10 seconds. An arterial blood withdrawal showed respiratory acidosis with hypoxia. Due to the strong suspect of Neuromuscular Junction Disease, she underwent a repetitive nerve stimulation that confirmed the suspect. She was eventually diagnosed with MG with positivity for acetylcholine receptor antibodies and finding of a thymoma, treated with surgery and radiotherapy. She started pyridostigmine and azathioprine, with partial benefit.

Discussion and Conclusions: Our case shows how a concurrent anxiety disorder may camouflage and postpone the diagnosis of MG in patients without a clear modification of symptoms during the day. Misdiagnosing MG with anxiety disorder may have severe consequences as benzodiazepines may precipitate and aggravate MG symptoms.

HERPES VIRUSES IN THE CEREBROSPINAL FLUID AND BLOOD OF ACTIVE MULTIPLE SCLEROSIS PATIENTS: AN INCIDENTAL FINDING?

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Background: Strong evidence support the involvement of Herpes viruses (HV) in multiple sclerosis (MS) pathogenesis [1]. Herein, we observed the presence of detectable HV in the CSF of active MS patients.

Methods: Patients suspected of MS diagnosis undergoing diagnostic lumbar puncture were screened for HV in CSF with PCR. Demographical, clinical, and radiological data were collected.

Results: From May 2021 we identified three patients diagnosed with relapsing-remitting MS who tested positive for HV in CSF: HHV6, VZV, and EBV. We found no double-positivity. In all cases, a low-titer viremia of the same HV was simultaneously detectable in blood. Despite no patients having fever nor clinical or laboratory features suggestive of active infection, 2/3 were treated with antiviral drugs (ganciclovir for HHV6 and acyclovir for VZV) before high-dose steroid treatment, following infectiologist indications. All patients were female, the mean age was 44. Interestingly, 2/3 were older than expected for MS diagnosis (53, 58 years). MRI presented contrast-enhancing-lesions (CELs) in 2/3 of patients and spinal cord involvement in 3/3. MRI showed no findings suggestive of CNS infection. The mean disease duration was 10.6 days, with all experiencing a relapse in the former 15 days. Three months following diagnosis, the VZV-positive patient underwent follow-up lumbar puncture and serum PCR, both testing negative for VZV. In the HHV6-positive and the EBV-positive patients the viremia was detectable in the following months, with titers fluctuating over time. After infectiologist evaluation, 2/3 of patients started dimethyl-fumarate, without experiencing infectious events, with a mean follow-up of 8.5 months.

Discussion: The correlation between presence of HV in CSF of MS patients was variously reported in the literature. Herein, we observed the incidental finding of HV in the CSF and blood of MS patients asymptomatic for CNS and systemic infection. In our case series, all the patients were in an early phase of their disease, as testified by the short disease duration. Furthermore, all patients were close to a relapse, and 2/3 presented CELs at MRI. This is in line with previous authors who found a higher number of CELs [2] and a higher lesion load [3] in MS patients with HV detectable in CSF.

Conclusion: The presence of detectable HV in CSF of MS patients is an unusual but possible finding, without a definite impact on disease management. The possible link between HV reactivation and disease activity in MS deserves further investigation.

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ANTI-LGI1 ENCEPHALITIS PRESENTING WITH A PSP-LIKE SYNDROME AND RAPIDLY PROGRESSIVE DEMENTIA

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Aim: To describe a case of leucine-rich gliomainactivated 1 (LGI1)-antibody encephalitis presenting with a progressive supranuclear palsy (PSP)-like syndrome.

Materials and Methods: Clinical data were retrieved from hospital charts.

Results: An 83-year-old male, with a history of hypertension and COPD, presented to our attention for a 1-year history of falls, postural instability, and gait abnormalities. Standing up was associated with sudden leg jerks leading to backward leap and subsequent falls. Two months before admission, the patient developed new-onset depression, behavioural abnormalities, and rapid cognitive decline. On neurological examination, we observed a multi-domain cognitive impairment characterized by deficits in attention, episodic memory, and language. Additional features included generalized rigidity, bradykinesia, loss of postural reflexes, and a wide-based shuffling gait. Frequent involuntary movements were noted, such as multifocal myoclonic jerks and brief episodes of abnormal ipsilateral facial and arm posturing, whose semiology was compatible with faciobrachial dystonic seizures (FBDS) [1]. Brain MRI and CSF analysis were unremarkable. EEG revealed frontal intermittent rhythmic delta activity superimposed on a diffuse background slowing. Thorax and abdomen CT scans did not reveal neoplasms. CSF and serum samples were sent for autoantibody panel screening. Hospital stay was complicated by severe hyponatremia and COPD exacerbation, treated with fluid restriction, antibiotics, and intravenous methylprednisolone: common causes of hyponatremia were excluded. While on treatment, we observed a sudden neurological improvement with reduction of paroxysmal movements and partial recovery of cognitive deficits and hyponatremia. Later, autoantibody testing turned out to be positive for anti-LGI1 antibodies in both CSF and serum. The patient was discharged home with an oral steroid taper and follow-up is ongoing.

Discussion: Anti-LGI1 encephalitis may rarely present with a PSP-like phenotype and rapidly progressive dementia. LGI1 is an essential component of the voltage-gated potassium channel complex at the synaptic cleft. Investigation of mechanisms of falls [2], as well as recognition of subtle and pathognomonic features, such as FBDS, may expedite the diagnosis. Unremarkable routine CSF findings and neuroimaging, present in up to 60% of cases [3], should not preclude the diagnosis and autoantibody testing is advised in front of a compatible clinical syndrome.

Conclusion: LGI1-antibody encephalitis is a rare but treatable form of autoimmune encephalitis and should be considered in the differential diagnosis of patients with PSP-like phenotype and cognitive impairment. A high index of suspicion should be maintained despite normal ancillary tests. Hyponatremia should not be overlooked or etiologically misinterpreted and distinction with metabolic encephalopathies is essential to avoid misdiagnosis.

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COVID-19 VACCINE-RELATED GUILLAIN-BARRÉ SYNDROME IN LIGURIA, REGION OF ITALY: A MULTICENTER CASE SERIES

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Background and Purpose: Guillain-Barré-Syndrome (GBS) can follow COVID-19 vaccination, with clinical and paraclinical features still to be precisely assessed. We describe a cohort of patients who developed GBS after vaccination with different types of COVID-19 vaccines.

Materials and Methods: Patients with post-COVID-19 vaccination GBS, admitted to the six hospitals that cover the whole Liguria region, Northwestern Italy, from February 1st to October 30th 2021, were included. Clinical, demographic, and paraclinical data were retrospectively collected. Epidemiologic data about the vaccination campaign in the Liguria Region were obtained.

Results: Among the 13 patients with post-COVID-19 vaccination GBS (9 males; mean age, 64 year), 5 were vaccinated with Oxford-AstraZeneca, 7 with Pfizer-BioNTech, and one with Moderna. Mean time between vaccination and GBS onset was 11.5 days. Ten patients developed GBS after the first vaccination dose, 3 after the second dose. Acute inflammatory demyelinating polyradiculoneuropathy was the predominant GBS variant. Bilateral seventh cranial nerve involvement followed AstraZeneca vaccination in two cases. Three patients presented treatment-related fluctuations, and 4 mild symptoms that delayed treatments and negatively affected prognosis. Prognosis was poor (GBS-disability score, ≥3) in 5/13 patients, with a disability rate of 3/13.

Discussion: We outlined the clinical features of thirteen post-COVID-19 vaccination GBS patients admitted to the hospital network of the Liguria region, an area of about 1.5 million inhabitants, over a period that covers the mass vaccination campaign for COVID-19 in Italy. Our findings confirm that most post-COVID-19 vaccination GBS belong to the AIDP subtype and occur after the first vaccine dose, and sensory symptoms may represent a common feature in GBS post-SARS-CoV-2 vaccine. AstraZeneca-associated bilateral seventh cranial nerve involvement is not uncommon, as well as CSF pleocytosis. Particular clinical features of GBS, namely treatment-related fluctuations, and insidious diagnosis-delaying, mild symptoms at onset, affect prognosis and deserve prompt recognition. We compared the features of the GBS cases unrelated to COVID-19 vaccine that occurred during the same period covered by this study in the Liguria region. By comparing the two groups, there was no difference in age at onset, gender prevalence, prognosis, and mortality rate. Conversely, in the COVID-19 vaccine-unrelated GBS patients, the antecedent infectious events (p=0.001), and the AMSAN-AMAN subtype (p=0.025) were more frequent.

Conclusions: Overall, our data contribute to fill a gap in the current literature on COVID-19 vaccines and describe the treatment related fluctuation as an element of distinction.

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A CASE OF POLYNEUROPATHY IN HIS110ASN MUTATION OF TTR GENE SUCCESSFULLY TREATED WITH PATISIRAN

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Background: The amyloidoses constitute a large group of diseases in which misfolding of extracellular protein has a prominent role. The most frequent hereditary Amiloidosys is hATTR, there are about 130 point mutations known that favour tetramer dissociation. His110Asn (or His90Asn in the old nomenclature) mutation is reported in two case reports but the authors concluded that mutation is a nonpathogenic polymorphism for FAP in the Italian family investigated.

Case Report: A 56-years-old female came to our attention on April 2021 for a suspect progressive memory decay. She underwent a Brain PET with non-homogeneous pattern of hypomethabolysm. Her mother died at 50 years after a Guillain-Barré diagnosis, she had married and has 3 sons. Since the age of 35 she was treated for psychiatric symptoms (anxiety, depressive mood), and was frequently hospitalized in psychiatric ward. In 2021 she rapidly developed progressive weight loss (up to 20 kg in 6 months), diarrhea, nausea and distal paraesthesia.

Investigations: An EMG study revealed a sensory axonal polyneuropathy in upper and lower limbs, normal laboratory exams (including tumor markers, hormonal and vitamin dosage), and abdomen echography. Brain and lumbosacral MRI were unremarkable. Genetic testing demonstrated a heterozygous mutation in TTR gene (His 110 Asn) which is of uncertain significance. Hence a biopsy from salivary glands could demonstrate typical Congo red-positive pathologic deposition of amyloid fibrils.

Treatment: The patient affected by polyneuropathy FAP 1, in May 2021 started ONPATTRO infusion at dosage of 0,3 mg/pro Kg/ every 21 days.

Discussion: In this case weight loss and sensitive polyneuropathy can't be explained by nutritional deficiency, toxic, substances or iatrogenic causes. Although the His 110 Asn mutation is not clearly related to deposition of Amyloid fibrils, the positivity of biopsy lead us to start treatment with ONPATTRO. The patient gained weight (6 kg in the first 6 months and overall, 14,5 kg at 9 months follow-up), improved her symptoms of neuropathy (from 19 to 12 points on NIS-W, -37%), neurography parameters, speed on 6MWT (from 148 to 285mt, +93%) and quality of life (Norfolk scores from 95 to 60) as well as Karnofsky performance status (from 50 to 70%).

Conclusion: In conclusion, His110Asn genotype was associated to sensitive polyneuropathy with significant gastrointestinal involvement and confirmed by evidence of amyloid deposits at biopsy. This mutation should therefore be considered pathogenetic for FAP. Patients with His 110Asn genotype can benefit by RNA interference therapies.

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A CASE OF ORBITAL APEX SYNDROME IN A PATIENT WITH ARTERITIC POSTERIOR ISCHEMIC OPTIC NEUROPATHY

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Objectives: We present a case of a 70-year-old Caucasian woman, who reported sudden, painless and severe loss of vision in her right eye (RE), worse in the lower visual field, associated with binocular diplopia in all gaze direction and ptosis. She had also a quite complete external ophtalmoplegia, mild proptosis and dyschromatopsia in the RE. Direct and consensual pupillary reflexes, intraocular pressure and fundus were normal bilaterally. She had no other neurological signs, with normal left eye functions. This clinical presentation, also known as Orbital Apex Syndrome, affects the structures crossing the superior orbital fissure and optic canal (II-III-IV-VI and V-first division cranial nerves, ophthalmic vein and artery). In her medical history, she had a diagnosis of polymyalgia rheumatica (PMR).

Materials and Methods: Routinary blood tests, autoimmune screening, HBV-HCV and Borrelia serology, Quantiferon, Myasthenia-antibodies, Thyroid tests, OCT, brain CT and CTA, brain and orbital MRI with and without contrast, doppler ultrasonography (DU) of temporal regions were performed.

Results: All laboratory investigations were negative, except for increased ESR (90 mm/h) and positive LAC antibody. OCT showed bilateral and symmetrical thinning of RNFL on peripapillary inferior and temporal region. Brain and orbital MRI showed a focal enhancement of an intraorbital vessel in the retrobulbar region, suggesting an inflammatory disease. DU of temporal regions did not show halo sign.

Discussion: All available data and her PMR history lead us to a diagnosis of Posterior Ischemic Optic Neuropathy (PION), with a possible inflammatory origin. We started a therapy with IV Methylprednisolone 1g/die for 5 days, followed by an oral tapering. Patient showed a rapid and quite complete improvement of ptosis and diplopia, but only a little improvement of the visual loss. Indeed, her vision remained quite blurred, with partial dyschromatopsia.

Conclusions: PION is a very rare acute ischemic damage of the retrobulbar section of the optic nerve, much less common than anterior variant (AION). Like AION, PION is clinically characterized by acute and severe vision loss (with altitudinal distribution), without pain. PION is always a diagnosis of exclusion because the characteristic funduscopic changes of AION are not seen. PION may be due to an arteritic inflammatory condition. Indeed, about 6% of patients with Giant-Cell Arteritis (GCA) present PION[1]. Even though our patient had not other signs of GCA, she suffered of PMR, which is associated with GCA in 40-60% of cases[2].

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THE ANTI-IGLON5 CASCADE: PROGRESSIVE MULTISYSTEM DYSFUNCTION RISES SUSPICION FOR BRAINSTEM ENCEPHALOPATHY

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Objective: To report clinical features and course of a patient with anti-Long5 disease.

Material and Methods: A 73-year-old woman was referred to our Institute in February 2022. She suffered from chronic obstructive pulmonary disease. Two years before she experienced an acute sixth nerve palsy, corrected with prismatic lenses. Since early 2020, the patient had episodes of disorientation, memory loss, mood deflection and apathy, showed daytime sleepiness fluctuating in severity, and reported odd nocturnal behaviors. Slurred speech and swallowing difficulties with severe sialorrhea progressively developed, causing a weight loss of 30 kilograms. Gait instability with frequent falls and involuntary rhythmic movements of left leg and shoulders appeared initially at nighttime, then progressively worsened impairing daily activities.

Results: The neurological examination showed tongue, oropharyngeal, facial, and scapular rhythmic movements, lower limb rigidity, and hyperreflexia. Cutaneous plantar reflex was flexor. Brain and spinal cord MRI were normal. Hypnogram recording showed severe reduction in sleep efficiency, with NREM sleep increase and REM sleep reduction. Night breathing was characterized by prolonged hypoxic phases that required continuous positive airway pressure ventilation. Videofluoroscopy showed severe dysphagia due to dyskinetic esophageal contractions. Percutaneous endoscopic gastrostomy was positioned to avoid aspiration pneumonia. Polymyography revealed a complex pattern of oculo-facial and limbs myorhythmia. Cardiovascular autonomic testing showed mild systolic orthostatic hypotension. Anti-IgLON5 antibodies tested positive at high titer in cerebrospinal fluid and serum. HLA typing showed DRB1 10:01:01-03:01:01 alleles. Plasma exchange, high-dose intravenous methylprednisolone and immunoglobulins were administrated. Response to treatments was moderate with partial improvement of sialorrhea and oculo-facial myorhythmia at one month follow-up.

Discussion: Anti-IgLON5 disease is a rare immune-mediated encephalopathy. Both sexes are equally affected, with onset between the ages of 50 and 70, and median interval of 2.5 years between symptoms onset and diagnosis [1]. The clinical spectrum includes sleep disorder with parasomnia and breathlessness, bulbar syndrome mimicking motor neuron disease, PSP-like syndrome, and cognitive decline [2].

Conclusion: The variability of the clinical presentation makes the diagnosis of anti-IgLON5 encephalopathy often challenging, mimicking other neurodegenerative, autoimmune, or infectious diseases. Sleep disorder, myorhythmia and bulbar disfunction should rise high suspicion for antibody testing.

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TWO CASES OF SARS-COV-2-RELATED MYELITIS IN A LARGE NEUROLOGICAL CENTRE IN CENTRAL ITALY

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Background: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) shows a keen neurotropism and may affect both Central and Peripheral Nervous System. Among the several neurological manifestations reported, only few cases of acute transverse myelitis (ATM) have been described so far. Here we present two cases of myelitis after a SARS-CoV-2 infection that referred to our Centre in Azienda Ospedaliero Universitaria Pisana, Pisa, Italy.

Cases presentation: In the first case, a 39-year-old man came to our attention for a sudden onset of hypoesthesia started in lower limbs and acutely spread to abdominal and perianal region, associated to bladder dysfunction with urinary retention. A spine MRI showed multiple lesions extending from D4 to D5 involving the dorsal column. Complete blood test including virological and rheumatological screening, serum Anti-Aquaporin 4 and MOG antibodies as well as complete cerebrospinal fluid analysis and brain MRI resulted negative. Follow-up brain and spine MRIs did not detect any other lesions. Since the patient had tested positive for SARS-CoV-2 at nasopharyngeal swab few days prior the occurrence of symptoms, a SARS-CoV-2-related myelitis had been postulated. Interestingly, he received the third dose of SARS-CoV-2 vaccine fourteen days prior, well tolerated at that time. In the second case, a 31-year-old man came to our attention for a burning sensation in the right iliac crest with allodynia and dysesthesia, gradually extended to the right armpit and occurred a few days after having been tested positive for SARS-CoV-2 at nasopharyngeal swab. A spine MRI revealed a right posterolateral lesion extended from D10 to D11. Again, complete blood test, cerebrospinal fluid analysis and brain MRI resulted negative. Thus, a SARS-CoV-2 related myelitis had been hypothesized.

Discussion: Since SARS-CoV-2 may affect spinal cord and neural structures with different mechanisms, the precise pathogenesis of SARS-CoV-2-related myelitis is still unclear. Molecular mimicry, bystander activation or a dysregulation of the cytokine cascade triggered by viral proteins are all possible pathogenic mechanisms.

Conclusions: Among the neurological symptoms related to SARS-CoV-2 infection, ATM is not commonly reported. These two cases may contribute in shedding light on the precise etiopathogenetic mechanism underlying SARS-CoV-2 -related myelitis.

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IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME: A CASE WITH ADEM-LIKE PRESENTATION

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Objectives: We present an atypical case of neurotoxicity due to Chimeric Antigen Receptor (CAR) T cell therapy.

Materials: A 21-year-old man had been diagnosed with mediastinal large B cell lymphoma with compressive effects on adjacent parenchyma.

The patient, already treated with several chemotherapy regimens due to the relapsed and refractory behaviour of hematologic malignancy, was then treated with CD19-targeted CAR T cell therapy. Cerebral MRI and neurological examination routinely performed were unremarkable.

Method: After CAR-T infusion, he developed a severe cytokine release syndrome (CRS) for which he was treated with Tolicizumab and dexamethasone. Three days after the infusion, he started to complain diplopia in primary gaze position; he was also slightly apathetic, with decreased verbal fluency. On tenth day he presented a tonic-clonic seizure.

Results: Cerebral MRI showed multiple supratentorial and infratentorial lesions involving middle cerebellar peduncles. They were associated with cytotoxic and vasogenic oedema with variable patterns of enhancement. The patient, neutropenic, was then submitted to extended laboratory workup to rule out opportunistic infections: acute-phase reactants, blood and cerebrospinal fluid cultures were however negative. Nonetheless, a therapy with broad-spectrum antibiotics and antifungal agents had been administrated. In the suspicion of immune-mediated disorder of CNS, the patient was then treated with a high-dose methylprednisolone followed by IVIg, without benefit. Patient died sixty-two days later, also after anti-IL-1 receptor monoclonal antibodies administration.

Discussion: Immune effector cell-associated neurotoxicity syndrome (ICANS) is one of the side effects of CAR T therapy, presenting with variable degrees of encephalopathy and resolving within a few weeks, generally without neuroimaging abnormalities. Among the ICANS risk factors, previous CRS and the use of Tolicizumab have been described. Our patient presented with an atypical neurological presentation with multiple brain lesions: failure of broad-spectrum antibiotics and negative culture tests have led us to rule out an infectious hypothesis, considering our case as an unusual type of immune-mediated neurotoxicity. An inflammatory response could indeed be triggered by CAR T cells recognition of target antigen on non-pathogenic CNS-resident cells, or by the damage induced by the direct attack against the asymptomatic brain localizations of the neoplasm. The absence of clinical improvement in our patient could be partly explained by reduced efficacy of CAR T therapy caused by the introduction of immunomodulatory treatments.

Conclusions: To our knowledge, manifestations of neurotoxicity with similar clinical features to our patient are not described in literature, suggesting a "new form" of immune-mediated neurotoxicity with ADEM-like presentation.

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EXPANDING THE NEUROPSYCHOLOGICAL AND CLINICAL KNOWLEDGE ON SPINOCEREBELLAR ATAXIA 17: A CASE REPORT

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Introduction: Spinocerebellar ataxia 17 (SCA17) is a rare autosomal dominant form of inherited ataxia. Fewer than 100 families with SCA17 have been reported. The disease is caused by heterozygous expansion of a trinucleotide repeat encoding glutamine in the TATA box-binding protein gene. Typical manifestations are ataxia and psychiatric abnormalities, followed by involuntary movement, parkinsonism, dementia, and pyramidal signs. The clinical features correlate with the length of the polyglutamine expansion.

Case Report: We describe the case of a 42-year-old patient who has been complaining progressively worsening gait disorders and cognitive impairment for about 2 years. These symptoms have been accompanied by social isolation, irritability, verbal aggression, and mild dysphagia. The patient's family history was positive for genetically confirmed SCA17 on the maternal lineage. The neurological examination revealed the following alterations: gait and upper limb ataxia mildly prevailing on the right side, cerebellar dysarthria, difficulties in fine movements of the hands, reduced lower limb proprioception, widely increased deep tendon reflexes. Involuntary movements were not observed. Remote pathological history and routine blood tests showed no major findings.

Results: Hippocampal, cerebellar and brainstem atrophy and bilateral pale nuclei hypointensity were noted on T1-weighted sequences on Magnetic Resonance Imaging. A lumbar puncture was therefore performed, and the cerebrospinal fluid analysis revealed normal protein concentration and cell count. Levels of amyloid-beta, phosphorylated-tau and total tau resulted within normal range. The genetic analysis confirmed the clinical diagnosis. Brain positron emission tomography with fluorodeoxyglucose (FDG-PET) showed bilateral hypometabolism of the sensorimotor cortex, with a slight predominance on the right, and of striatal nuclei; thalamic hypermetabolism was also demonstrated. No significant hypometabolism or distribution asymmetries were evident in the cerebellum. Neuropsychological evaluation detected a mild to moderate cognitive impairment regarding executive and visuospatial functions, attention, linguistic and praxis abilities. The "Faux Pas" test and the "Reading the Mind in the Eyes" test were performed revealing a clear deficit regarding mentalization and empathy.

Discussion: Our report provided a detailed clinical and neuroimaging finding of a SCA17 case. In addition, an in-depth description of the patient's neuropsychological picture was given and, for the first time in a SCA17 patients, tests were performed to measure levels of Theory of Mind reasoning. Our study highlights the importance of cognitive and psychological aspects in this rare disorder, emphasizing its complexity and phenotypic pleiotropism.

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LONG-TERM SAFETY OF OFATUMUMAB IN PATIENT WITH RELAPSING MULTIPLE SCLEROSIS

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Objective: To assess the long-term safety and tolerability of ofatumumab treatment in patients with relapsing multiple sclerosis (RMS).
Background: Ofatumumab, a fully-human anti-CD20 monoclonal antibody with a 20 mg subcutaneous monthly dosing regimen, is approved for treating RMS in adults. Previously published data demonstrated that ofatumumab treatment up to 30months had a favorable safety profile and was generally well-tolerated. Longer-term safety of ofatumumab in RMS patients continues to be monitored.

Design/Methods: Patients completing the core ASCLEPIOS I/II, APOLITOS and APLIOS clinical trials could enter ALITHIOS, an ongoing, open-label, umbrella extension trial. Here, we analyze the cumulative data for up to 4 years of ofatumumab treatment (data cutoff: 25-Sep-2021) in the overall (N=1969), continuous (ofatumumab in core + extension; N=1292) and newly-switched (teriflunomide core and ofatumumab extension; N=677) groups. The proportion of patients with treatment-emergent adverse events (AEs), serious AEs, serious infections including opportunistic infections, and malignancies will be assessed. Laboratory parameters including neutrophils, lymphocytes, and serum immunoglobulin (Ig) G and IgM levels will be analyzed.

Results: In data reported from ALITHIOS with a cut-off of 29-Jan-2021, representing ofatumumab treatment for up to ~3.5years, 83.8% of patients had ≥1 AEs (exposure-adjusted incidence rate [EAIR], 148.7) and 9.7% had ≥1 serious AEs (EAIR, 4.8) with a low incidence of serious infections (2.9%; EAIR, 1.4) and malignancies (0.6%; EAIR, 0.3). Across 4 years of Treatment in the Overall Safety Population, the overall rate of AEs and SAEs remained consistent with the rates observed during the core trials. The most common AEs were infections; the most frequent infections in the overall safety population were nasopharyngitis (17.5%), upper respiratory tract infections (11.1%), urinary tract infections (10.9%), and COVID-19 (10.6%). No new safety signals were identified. The overall rate of serious infections was consistent with Phase 3 ASCLEPIOS I/II trials (2.5%, EAIR: 1.44) and did not increase with treatment up to 4 years despite COVID-19 pandemic. Most COVID-19 cases were non-serious, mild-to-moderate in severity and the majority of patients recovered. IgG levels remained stable up to 4 years of treatment, while IgM levels decreased but remained above the LLN. Lymphocyte and neutrophils level remained stable throughout 4 years of treatment. Incidence rates of malignancy did not increase over time in the overall patient population.

Conclusions: Safety findings for up to 3.5 years showed ofatumumab treatment to be well-tolerated with no new safety risks identified. This additional safety data will help confirm ofatumumab's longer-term safety profile and provide further confidence to the MS community.

A CASE OF TERTIARY SYPHILIS PRESENTING WITH NEUROLUE AND LUETIC VASCULITIS

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Background: Neurosyphilis is a rare late-stage manifestation of Syphilis, a sexually transmitted disease caused by Treponema Pallidum, a spirochete that is also known as the "great imitator" because it can mimic different disease clinically and on imaging, that leads to major misleading diagnosis.

Case presentation: We report a case of a 76-year-old man with progressive cognitive disorders for over a year, decline in mood and, moreover, difficulty in walking. At the neurological examination the patient has hypopallesthesia in the lower limbs, non-responsive pupil to light on the left eye and a wide-base gait with mild plantar disconfort. Neuropsychological tests revealed a deficit in executive functions and working memory. MRI- and MRA-brain reveals chronic vascular leukoencephalopathy, widespread hemosiderin deposits and a beading pattern in the more distal Sylvian vessels, that is compatible with the presence of signs of inflammatory arteritic vascular disease, probably due to syphilitic infection. Abdominal angio-CT was also performed: it showed a focal flap of chronic dissection of the pre-carrefour abdominal aorta, which is probably due to the infection itself. Finally somatosensory evoked potentials, performed in the lower limbs, resulted bilaterally reduced as amplitude. Among serum serological tests Treponema Pallidum hemagglutination assay (TPHA) and Rapid Plasma Reagin (RPR) test was positive. CSF analysis revealed blood-brain barrier (BBB) damage with intrathecal synthesis of immunoglobulins (one oligoclonal band was detected). The cytofluorimetric examination of the CSF shows an increase in total lymphocytes, with an inversion of the ratio CD8+/ CD4+ lymphocytes and a raising number of B lymphocytes and it can be attributed to the inflammatory state due to syphilitic infection. In serologic examination of CSF, Fluorescent Treponemal Antibody Absorption (FTA- ABS), IgG to treponema pallidum and TPHA was also positive. The patient was diagnosed as neurosyphilis, and intravenous crystalized penicillin G was administered for 14 days. After one month the patient had an improvement in cognitive deficits and in walking but still an abnormal wide-base gait.

Conclusion: Syphilis can affect the nervous system in many ways. In our case clinical findings and positive serologic results were compatible with general paresis, one of the forms of neurosyphilis caused by chronic meningoencephalitis that result in cerebral atrophy. Neurosyphilis is a treatable cause of dementia, and it must be considered as a possible diagnosis in the routine workup of patients with cognitive decline.
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BEHAVIORAL DISORDERS, PTOSIS AND OPHTALMOPARESIS: INITIAL SYMPTOMS OF A RARE PARANEOPLASTIC NEUROLOGICAL SYNDROME

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Introduction: Paraneoplastic neurological syndromes (PNS) are associated with antibodies directed against antigens expressed by both the tumor and the nervous system (onconeural antibodies) [1,2]. Anti-Ma2 antibodies are a subpopulation of onconeural antibodies, associated with PNS characterized by limbic and brainstem encephalitis, often related to testicular tumors. The main clinical manifestations are hypersomnia and lethargy, states of anxiety and irritability, depression, memory loss, balance disorders and ataxia, ophthalmoplegia, epileptic seizures [3].

Case report: A 32-years-old man was seen at our hospital with a 6-months history of eyelid ptosis and ophthalmoparesis, fatigue and behavioral disorders with irritability and dysphoria. Following, laboratory and radiological findings: mild albumin-cytological dissociation at CSF analysis; anti-AChR antibodies negative on serum analysis, virological test on serum positive with IgG and IgM for Borrelia; normal results at both standard and single-fiber EMG; gadolinium enhancement of the both III

cranial nerves, fronto-parietal iuxtacortical white matter and on the left posterolateral region of the bulb at brain MRI. The conclusion was Miller-Fisher Syndrome in a patient with recent Borrelia infection and therapy with high dose intravenous immunoglobulins (IVIG) was started (0.4mg / kg / day for 5 days). After one month he did not show any improvement. On neurological examination the patient was bedridden due to severe axial ataxia, lethargic, ophthalmoplegia, bilateral ptosis, severe bradylalia and dysphonia and deep tendon areflexia. On CSF analysis we found persistence of mild albumin-cytological dissociation and a positivity of antiMa2 onconeural antibodies (Ab antiMa2). The brain MRI showed extension of gadolinium enhancement to the upper cerebellar peduncles. A PET scan was performed, showing metabolic and dimensional asymmetry of the right testicle. Testicular ultrasound showed a suspected heteroplastic lesion on the right testicle. He underwent right orchifunilectomy and, subsequently, plasmapheresis and oncologic follow-up. After one month the patient was still non recovering, he referred worsening of dysarthria and dysphagia, with episodes of inhaling food and cough. For this reason, we performed two intravenous immunotherapies with a second trial of IVIG and rituximab (375mg/m2 /week for 4 weeks), respectively. After IVIG trial and two doses of rituximab he is starting to experience benefit (improving of dysphagia).

Conclusion: This case highlights the rare onset of a brain paraneoplastic syndrome with Ab antiMa2 positivity, with ptosis, ophthalmoplegia and ataxia, preceded by nonspecific behavioral disturbances, due to testicular neoplastic lesion. The presence of antiMa2 antibodies, specific for testicular tumor lesions, allowed to a rapid reach of etiological diagnosis and, consequently, specific therapy.

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SARS-COV2 INFECTION PRECEDING CREUTZFELDT-JAKOB DISEASE: A DIAGNOSTIC MISLEADER OR HASTENER OF NEURODEGENERATION? A CASE REPORT

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Background: Creutzfeldt-Jakob disease (CJD) is a rare disorder with known phenotypic variability. A small number of cases presents without cognitive decline in the early stages, and approximately 5% with isolated ataxia, leading to a major risk of postponed or mistaken diagnosis.

Case report: Two weeks after a symptomatic SARS-CoV-2 infection, a 60-year-old man developed left arm ataxia and distal paresthesias, followed by mild postural instability, dysarthria and diplopia. He was admitted to the local hospital where he underwent CSF analysis (albuminocytological dissociation), neurophysiological study (mild polyneuropathy) and an autoimmune/paraneoplastic encephalitides antibodies panel (negative). The patient was diagnosed with post-infective Miller-Fisher syndrome and treated with intravenous immunoglobulin (IVIg). The symptoms progressively worsened, and, when, one month later, the patient presented to our clinic neurological examination revealed a severe cerebellar syndrome: dysmetric ocular saccades, scanning speech, asymmetrical limb ataxia and markedly unsteady gait. A total-body CT-scan excluded neoplasms. A 3-tesla MRI revealed cortical ribbon hyperintensities in T2/FLAIR and diffusion restriction in insular and frontal cortices, cingulate gyri and right parieto-occipital lobe, FLAIR/DWI abnormalities of the right caudate nucleus and vermian atrophy. EEG showed biphasic PSIDDs. CSF examination detected the presence of 14-3-3 protein, a very high level of tau protein with normal phospho-tau and a slightly reduced Aβ1-42 with normal Aβ42/40 ratio. Based on proposed CDC criteria, a diagnosis of probable sporadic CJD was performed. Over two weeks, the patient deteriorated to akinetic mutism, ophthalmoplegia, dysphagia, severe generalized hypertonia and myoclonic jerks. He died within two months of disease onset.

Discussion: Our case report describes an atypical presentation of CJD preceded by SARS-CoV2 infection. A pandemic, such as the COVID-19, can complicate the CJD differential diagnosis, suggesting in first place a post-infectious inflammatory disorder. In our case, the dramatic rapid worsening of the ataxic syndrome and unresponsiveness to IVIg suggested an alternative paraneoplastic or neurodegenerative hypothesis. In the subsequent diagnostic work-up, cerebral MRI was of paramount importance and led to the assessment of specific CJD biomarkers in CSF. Furthermore, the redirection towards CJD diagnosis raised a question about SARS-COV-2 infection: is its temporal correlation with disease onset coincidental, constituting only a potential misleading factor during the diagnostic process, or could systemic inflammatory responses to SARS-Cov-2 hasten the neurodegeneration process? To our knowledge, other 3 cases have been reported describing CJD temporally related to Covid-19. Further studies are needed to elucidate this problem.

*The first two authors contributed in equal measure to this abstract.

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A CASE OF INTRACRANIAL HYPOTENSION TREATING PSEUDOTUMOR CEREBRI

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Objective: We described a case of idiopathic intracranial hypertension that after lumbar puncture developed sign and symptoms of hypoliquorrhea.

Materials e methods: A 21 years old female, with BMI<25 referred us the onset, since two months ago, of throbbing headache associated to visus disturbances, caracterized by transient visual obscuration lasting few seconds at a time and occuring twenty times a day. She underwent for funduscopic examination that shown bilateral and symmetric papilledema and visual field testing that highlighted an enlarged blind spot, mostly in the right eye. We checked sierology for treponema and borrelia, and TSH values, both average. During the degency we performed firstly CT of the brain that excluded secondary causes of intracranial hypertension such a mass lesion, obstructive hydrocephalus and increased CSF production. With the MRI + angio-MRI we excluded also obstruction of venous outflow and meningitis. However we noted MRI abnormalities that suggested IIH like the flattening of the posterior sclera, distension of perioptic subarachnoid space, enhancement of the

prelaminar optic nerve, empty sella, intraocular protrusion of the prelaminar optic nerve, the vertical tortuosity of the orbital optic nerve and the most characteristic narrowing of the transverse venous sinus. According to the modified Dandy criteria, for the diagnosis of IIH, we performed a lumbar puncture in the lateral decubitus position, that shown an opening pressure of 380 mmH2O (reached 500 mmH2O after Valsalva). After removing 20 cc of CSF the pressure was 180 mmH2O, in the following days the visual disturbances disappeared and the patient started therapy with acetazolamyde. After two days, the patient had headache, worsened by upright position, nausea, neck stiffness and Kernig's sign positive.

Results: At the MRI of the spinal cord we observed a subdural fluid collection with a leaks in the dural sack and the MRI of the brain confirmed the diagnosis of intracranial hypotension by showing diffuse pachimeningeal enhancement, pituitary enlargement, and engorgement of cerebral venous sinuses. The treatment we prescribed was bed resting and analgesic therapy with caffeine combined paracetamol.

Discussion: Since this complication occurred we could compare neuroimaging indirect sign of both intracranial hypotension and hypertension and see how they changed in the same background.

Conclusion: To prevent complication after lumbar puncture, strictly bed rest and hydratation is strongly recommended even if the patient is young and the procedure was easily performed.

ACUTE DISSEMINATED ENCEPHALOMYELITIS AFTER mRNA-1273 COVID-19 VACCINE: A CASE REPORT AND REVIEW FROM LITERATURE

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Objectives: Acute disseminated encephalomyelitis (ADEM) is a rare immune-mediated demyelinating disorder of the Central Nervous System (CNS), often occurring post-infections and post-immunization, although a causal relationship has never been established. The most common vaccinations associated with ADEM are the non-neural measles, mumps and rubella vaccines, yet a few cases have been reported after SARS-CoV2 vaccination.

Materials and methods: Here we describe a case of ADEM presenting 4 weeks after receiving the first dose of SARS-CoV2 mRNA-1273 vaccine.

Results: A 61 years-old woman, with a history of rheumatoid arthritis and cryoglobulinemia requiring immunosuppressive treatment, developed headache and fever two weeks after vaccination. Symptoms persisted for 1 week, but then spontaneously improved. At 4 weeks from the vaccine dose, she was admitted to the ER for acute onset of speech impairment, diplopia, hearing loss and dizziness. On admission, neurological examination showed mild aphasia, sensorineural hear impairment, abducens nerve palsy in the right eye and ataxic gait. Bloodwork excluded inflammatory abnormalities and infectious disorders; extensive immunological screening, including anti-myelin oligodendrocyte glycoprotein (MOG) antibodies, anti-acquaporine4 (AQP4) antibodies, anti-gangliosides antibodies and HLA-B51 typing, was unremarkable, except for the presence of cryoglobulins. Cerebrospinal fluid (CSF) analysis revealed increased protein count, mild pleiocytosis with a high percentage of lymphocytes and positive oligoclonal bands. CSF-screening for infectious agents, namely herpes simplex virus, enterovirus, Epstein-Barr virus, and mycoplasma, was negative. Brain and spinal cord Magnetic Resonance Imaging (MRI) demonstrated T2-weighted and fluid-attenuated inversion recovery (FLAIR) hyperintense multiple lesions, involving the basal ganglia, cortical-subcortical temporal lobe and cerebellar hemispheres, characterized by partial gadolinium-enhancement. The absence of cerebral vascular abnormalities at MRI excluded the diagnosis of vasculitis and ophthalmologic evaluation was negative for other rare immunological disorders, namely Susac and Cogan Syndrome. As first line therapy, high-dose IV methylprednisolone was administrated, followed by IV immunoglobulin treatment, both showing a poor response. The patient was finally treated with seven plasma exchanges every other day, with significant progressive clinical improvement.

Discussion: The typical clinical presentation, the temporal association with SARS-CoV2 vaccination and the neurological improvement with plasma exchange are suggestive for diagnosis of post-vaccination ADEM. At one-year follow-up evaluation, the patient referred a complete resolution from symptoms, as confirmed by neurological examination and MRI improvement.

Conclusions: To note, demyelinating syndromes with heterogeneous clinical presentation have been described after mRNA-based vaccine, often occurring in patients with history of immune-mediated disease. Prompt diagnosis and treatment are warranted to improve neurological outcome and prognosis.

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ADULT LATE-ONSET KBTBD13-RELATED CONGENITAL MYOPATHY

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Objectives: Nemaline myopathy (NM) is a rare neuromuscular disorder ranging from severe childhood onset to milder forms. Mutations in at least 12 different genes are described, all encoding proteins associated with the structure or regulation of the thin filament of the skeletal muscle sarcomere. We describe the case of NM diagnosed in late-adult age to underline clinical heterogeneity of disease.

Patient and Methods: We describe the case of a 75-year-old woman complaining of a long-standing history of exercise intolerance from adolescence. She reported progressive worsening of symptoms and inability in rising from the crouched position without support. She had difficulty in running and climbing stairs. No family history of neurological diseases was reported. Past medical history included clinical-follow up in Kaposi Sarcoma, hypertension, and dyslipidemia. Neurological examination disclosed positive Gowers' test, mild weakness in legs' extension and hyporeflexia in lower limbs. Blood test, neurophysiological studies, muscle biopsy and genetic analysis were performed.

Results: Blood tests revealed mild iperCkemia and electromiography showed a diffuse moderate myopathic pattern. Vastus Lateralis muscle biopsy showed marked myopathic changes characterized by the presence of cytoplasmic anomalies such as "rods" and "core like" structures. A next-generation sequencing (NGS) panel including genes involved in congenital myopathies revealed the presence of the heterozygote variant (c.1170G>C) resulting in p.Lys390Asn in the KBTBD13 gene, predicted to damage the strands of the beta-propeller blades and reported as pathogenetic for NEM type 6.

Discussion: KBTBD13 gene encodes a protein involved in functional complex formation Cul3 RING ubiquitin ligase. KBTBD13 mutations identified in NEM6 patients are located within the highly conserved second and fifth Kelch repeats. Missense variant (c.1170G>C) p.Lys390Asn in KBTBD13 gene is only described in four patients of a Spanish family with autosomal-dominant inheritance and childhood onset. Our case differs in clinical presentation for later onset of disabling symptoms, no signs of muscle atrophy and absence of muscle weakness in upper limbs.

Conclusions: Symptoms in NM type 6 may be underestimated and therefore patients may present at neurological evaluation even in late-adult age. A proper clinical history collection can drive the suspicion of a genetic disorder. Congenital myopathies with mild phenotype as NM type 6, although rare conditions, should be considered in the differential diagnosis of a slow progressive muscle weakness also in late adult age.

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A CAUSE OF A DOUBLE TARGETING IN PD-DBS: RIGHT STN AND LEFT ZONA INCERTA

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Objective: This case report describes a novel approach that utilizes a double targeting (subthalamic nucleus and zona incerta) for Deep Brain Stimulation (DBS) to effectively control a highly lateralized tremor in Parkinson's Disease (PD), as well as a generalized akinesia ad rigidity. In DBS treatment, the subthalamic nucleus (STN) is currently the most established target. Deep brain stimulation of caudal zona incerta (cZI-DBS) shows similar or better results than STN DBS, in terms of motor improvement. Furthermore, DBS of this region induces a profound effect on tremor and it is free of negative influence on speech (Blomstedt et al., 2018).

Materials: This is a case study of a 55-year-old, right-handed man who developed right lateralizing symptoms indicative of PD in 2010 characterized by a lower limb resting tremor, involving soon after the upper limb. After nine years, optimal medical management did not confer sufficient control on his right side tremor.

Methods: On December 2019 he underwent bilateral DBS targeting the right STN and the left caudal zona incerta.

Results: Both intraoperatively and post-operatively electrode stimulation resulted in a significant improvement of akinesia, rigidity as well as resting tremor. At 1 and 3 and 12 months post initial programming, no montage changes have been made, and the patient has experienced a reduction in Motor MDS-UPDRS scores from 59 to 9 (evaluation in on stimulation and off medication condition), a full resolution (right hand resting tremor from 4 to 0) of resting tremor and a normalization of handwriting, as well as a significant reduction in his medication requirements.

Conclusion: Symptoms control was achieved implanting the adjacent Zona Incerta (ZI) on the left side and the Subthalamic Nucleus (STN) on the right side. This approach could be considered a therapeutic strategy in young patients, poorly responsive to medical treatment, with a predominant tremor phenomenology, highly lateralized. Moreover it supports a personalized DBS-targeted therapy in patients with Parkinson disease.

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ATYPICAL PRESENTATION OF NMDA-R ENCEPHALITIS OVERLAPPING CENTRAL NERVOUS SYSTEM DEMYELINATING SYNDROME: A CASE REPORT

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Background: Anti-N-methyl-D-aspartate receptor (Anti-NMDAR) encephalitis represents the most frequent encephalitis associated with surface antigens antibodies. The disorder predominantly affects female children and young adults. The most common clinical presentation is characterized by psychiatric symptoms, seizures, and movement disorders. A large proportion of cases is associated with identifiable tumours, usually ovarian teratoma. At symptoms onset, about half of patients, presents magnetic resonance imaging (MRI) hyperintensities in long-TR sequences in the cerebral, cerebellar cortex or in the mesial-temporal region. Herein we present a case of a patient with suspected central nervous system (CNS) demyelinating disease and subsequently found to be positive for anti-NMDAR antibodies.

Discussion: A Caucasian 68-years-old man was admitted to Neurology Department with a history of three-months ataxic syndrome and urinary disturbances, preceded by fatigue, behavioural disorders including major irritability, apathy and depression. Brain MRI showed multiple T2 hyperintensities with no gadolinium enhancement, suggestive for CNS demyelinating disorders. Spinal cord MRI was negative. The electroencephalogram was unremarkable. Cerebrospinal fluid (CSF) analysis revealed slight increased protein level, presence of 13 oligoclonal bands. Whole-body 18F-fluorodeoxyglucose-PET revealed a neoformation in right parotid gland, suggestive of benign Warthin's tumour and in right renal pelvis (not susceptible of surgical removal). In the suspicion of CNS demyelinating disease, the patient was initially treated with 5-grams-intravenous methylprednisolone, with a partial recovery of ataxic symptoms. Although the diagnosis of suspected CNS demyelinating disorders could not be ruled-out, a diagnosis of anti-NMDA-r encephalitis was advanced since serum and CSF were positive for anti-NMDAR antibodies. Therefore, Rituximab was started. After six months, the patient was clinically and radiologically stable. Serum and CSF NMDAR antibodies were still positive after six months.

Conclusion: CNS demyelinating diseases are associated with other autoimmune disorders. Recent literature has described a very little number of anti-NMDAr encephalitis overlapping with multiple sclerosis (MS). The diagnosis and management of our patient was challenging due to atypical epidemiological features for both MS and anti-NMDAr encephalitis. Clinical and radiological presentation suggested the first hypothesis, while the serum and CSF findings of anti-NMDAr antibodies

addressed the diagnosis to the second suspicion. In this case-report CSF oligoclonal bands were not helpful, since they could be found in both diseases. However, although it could be not excluded that NMDAR antibodies played an independent pathogenic role or were an epiphenomenon of a demyelinating syndrome, we decided to treat our patient with an anti-CD20 monoclonal therapy, obtaining clinically and radiologically stability after six months.

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A CASE OF THYMOMA-ASSOCIATED ENCEPHALITIS AND MYASTHENIA GRAVIS WITH ANTI-MUSK ANTIBODIES: RARETY AMONG THE RARE

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Introduction: Up to 50% of thymomas are associated with paraneoplastic neurologic syndromes (PNS), the most common being myasthenia gravis (MG) with anti-AChR antibodies (Ab). In less than 6% of cases, thymomas may be associated with limbic encephalitis or, even more rarely, with extralimbic encephalitis, with lesions extending beyond the mesial temporal lobe structures. Here we present a rare case of a patient with a thymoma-associated MG with positive anti-MuSK Ab and a paraneoplastic encephalitis (TAPE) with CASPR2 and Hu Ab.

Case report: In June 2020, a 34-year-old man started to develop diplopia, generalized weakness with inferior limb fasciculations and a progressive unexplained weight loss. The first diagnostic workup was negative. Two months after, he developed a confusional state associated with visual hallucinations and was hospitalized. Contrast-enhanced brain MRI showed multiple foci of cortical-subcortical hyperintensity involving both hemispheres, with greater extension in the left temporal and frontoopercular cortex, CSF and serum search for onconeural antibodies revealed positivity of anti-Hu and anti-CASPR2 Ab. A PNS was suspected and full body imaging showed a large mediastinic mass, later confirmed via biopsy to be a metastatic type B2, stage IVA, thymoma. Assays for AChR- and MuSK-Ab were repeated several times during hospitalization and follow-up, in three different hospitals laboratories, with negative results for AChRAb and surprisingly positive results for anti-MuSk Ab. He was treated with intravenous methylprednisolone followed by 0.4 g/kg daily immunoglobulin (IVIG) for a total of 4 days and discharged with oral prednisone. Meanwhile he underwent 6 cycles of neoadjuvant chemotherapy (cisplatin, doxorubicin and cyclophosphamide) before radical surgery, performed in March 2021. After that he experienced a progressive improvement of neurological symptoms with negative conversion of CASPR2 and Hu Ab but not of anti-MuSK Ab and at the last follow-up visit he could begin to taper steroid therapy.

Conclusion: Based on literature review, our patient is one of the few reported cases of TAPE in which aggressive and radical treatment of the tumor along with immunotherapy provided good recovery. To date, neoplastic or inflammatory thymus changes have not been shown to be involved in the pathogenesis of MuSK MG and in addition to our case there are only two other descriptions of thymoma associated MuSK MG. Although unusual, this emerging evidence suggests that MuSK MG could have a wider spectrum of immunological and clinical presentation than previously recognized and that MuSK positivity itself does not rule out the need of a screening chest CT scan.

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CEREBRAL NOCARDIOSIS MIMICKING DISSEMINATED TUMOR LESIONS IN A PATIENT WITH RECURRENT GLIOBLASTOMA

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Introduction: Disseminated nocardiosis is a rare opportunistic infection caused by Gram-positive bacteria, strongly associated with immunosuppression [1]. It typically causes soft tissue and pulmonary lesions, but virtually any organ system may be involved [2]. The central nervous system involvement may mimic brain metastases.

Objectives: Here we describe the case of a patient with a recurrent glioblastoma, on treatment with regorafenib and corticosteroids, with a brain imaging initially strongly suspicious for cerebral disseminated metastasis.

Case Presentation (Materials, Methods, Results): Our patient was a 64-year-old Italian male, with a three-year history of carpus callosum glioblastoma (according to WHO classification [3]), initially treated with temozolomide (TMZ) plus concomitant radiation therapy, then with adjuvant TMZ (23 total courses). After the first two years of clinical and radiological stability, he had a radiological relapse, so a second line chemotherapy (CHT) with regorafenib was started, obtaining an initial response. To control cerebral edema, he was also on chronic intermediate-dose dexamethasone (2-4 mg/daily). Then, after other 12 months on CHT and steroids, he presented a neurological worsening, with a remarkable generalized asthenia and malaise, and a progressive lower limbs weakness, leading to paraparesis. He was admitted to our neurological clinic. A brain Magnetic Resonance Imaging (MRI) showed several diffused T2-hyperintense lesions, with a subtle contrast-enhancement, initially thought to be disseminated metastatic lesions. A neutrophilic leukocytosis with high C-reactive protein level were found on his blood tests and a chest X-ray revealed bilateral lung consolidations. Thus, blood, urine and bronchoscopic cultures were performed. His transthoracic echocardiogram was negative for endocarditis. In the meantime, an empiric antibiotic therapy was started. Finally, Nocardia nova grew on his cultures. A total-body computed tomography scan confirmed a bilateral lung involvement. Specific antibiotic and antifungal therapies were started and continued for over three weeks. A months-control brain MRI showed a more extensive dissemination of the brain lesions, with a typical ring-

enhancement. Meanwhile, the patient continued to worsen. Chemotherapy was definitively suspended, and he died after few months.

Discussion and Conclusions: In this case a cerebral nocardiosis was initially mistaken for metastatic brain cancer in patient on chronic corticosteroids. Neurologists should be aware of the potential for opportunistic infections with steroid use. When an immunosuppressed patient presents with multiple brain lesions, even though a fair oncological history, a disseminated opportunistic infection should be considered.

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CAROTID FREE-FLOATING THROMBUS MASQUERADING A CAROTID WEB: CO-OCCURRENCE OF TWO RARE CAUSES OF STROKE

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Objectives: Juvenile stoke is a heterogeneous entity, both in terms of etiology and presentation, making accurate and timely diagnosis challenging. There are several causes of Juvenile Stoke including carotid free-floating thrombus (CFFT) and carotid web (CW). CFFT is an uncommon condition, in which thrombus formation is often triggered by an underlying arterial lesion, most commonly atherosclerosis, rarely trauma or arterial dissection [1]. CW is a shelf-like lesion along the posterior wall of the internal carotid artery bulb and is considered to be a rare variant of fibromuscular dysplasia (FMD) [2,3]. To the best of our knowledge, our case represents the first report in literature about the co-occurrence of these two rare conditions as a cause of cerebral ischemia.

Case report: An otherwise healthy 45-year-old female patient presented to our Emergency Department (ED) after subacute onset of left motor-sensory facio-brachial syndrome. The CT scan performed in ED was negative for cerebral ischemia. Brain MRI revealed multiple ischemic embolic lesions in the right internal carotid artery (ICA) distribution. Angio-CT showed a stenosis of 45% of the right ICA with a superimposed CFTT, the other ICA was unremarkable. Considering the high embolic risk, an endovascular approach was preferred over traditional surgery. Angiography revealed that CFTT underlies a carotid web: a stent placement was performed. No intraoperative complication or distal clot migration was reported. The patient was discharged on double antiplatelet therapy without further events.

Discussion: In literature CW and CFFT have been described as two uncommon and distinct causes of cryptogenic strokes. The discovery of CFTT underlying a CW proved that these two rare conditions may coexist. The presence of a CW should be taken into consideration in patients with CFTT without vascular risk factors. In these patients a stent placement may represent a valid treatment option with good safety profile.

Conclusion: Set the correct diagnostic and therapeutic pathway is fundamental to avoid the significant morbidity and mortality and the potential for lifelong disability which is associated with juvenile stroke.

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BRAIN STRUCTURAL ABNORMALITIES AND COGNITIVE CHANGES IN A PATIENT WITH 17Q21.31 MICRO-DUPLICATION AND EARLY ONSET DEMENTIA: A CASE REPORT

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Objectives: 17q21.31 microduplication is a rare, recently described condition frequently associated with psychomotor delay, behavioural disorders and poor social interaction. Here we described the pattern of brain structural damage and cognitive profile evolution of an adult patient with a normal intellectual development and a 17q21.31 microduplication.

Materials: A.B., 57 years old, male, was admitted to the Neurology Unit of San Raffaele Hospital (Milan). His wife reported obsessive and repetitive behaviours, irritability, scarce hygiene and memory loss occurring one year prior to hospitalization. His father died at 68 years with similar behavioural symptoms, his living sister has behavioural disturbances, and his son was diagnosed with Lennox-Gastaut and Asperger syndromes. Blood and cerebrospinal fluid (CSF) samples, previously analysed, have revealed a 17q21.31 microduplication, the same held by the patient's sister and son, and pathological total and phosphorylated tau levels. During hospitalization, A.B. underwent an MRI scan, an FDG-PET, and a neuropsychological assessment. Cognitive evaluation was repeated seven months after hospital discharge.

Method: For MRI examination, 16 age- and education-matched male healthy subjects were selected. Voxel-based morphometry (VBM) analysis to investigate gray matter (GM) volume differences between patient and healthy controls was performed adjusting for age, education, and total intracranial volume. VBM results were tested at $p<0.001$ uncorrected for multiple comparisons.

Results: Compared to controls, A.B. had greater selective GM atrophy in the right hemisphere, involving amygdala, hippocampus, inferior and superior temporal gyri. He also showed smaller clusters of left parahippocampal and temporal atrophy. FDG-PET reported bilateral hypometabolism of parahippocampal, middle frontal and posterior cingulate cortices. During hospitalization, his behavioural profile was characterized by anosognosia, impulsivity, stereotypies, apathy, emotional indifference, irritability, and aggressiveness. His cognitive testing revealed main attentive-executive disturbances, and difficulties in understanding non-literal and pragmatic language. He received a diagnosis of early onset dementia. After 7 months, he developed empathy loss, perseverative behaviour, changes in his eating habits, and he significantly worsened in executive-attentive abilities.

Discussion: In our patient, 17q21.31 microduplication was associated with a neurodegenerative condition characterized by prevalent right temporal damage, pathological CSF tau, behavioural disturbances, memory

impairment, attentive-executive and abstract language dysfunctions, and fast disease progression. Patient's father and sister likely were affected by the same neurodegenerative condition, while the son displayed a mixed of neurological and psychiatric syndromes.

Conclusions: 17q21.31 microduplication caused heterogeneous syndromes, reflecting the complex interaction between genetic substrate and clinical phenotypes.

Supported by: European Research Council (StG2016_714388_NeuroTRACK) and the Foundation Research on Alzheimer Disease.

BILATERAL ABDUCENS NERVE PALSY DUE TO CAROTID-CAVERNOUS FISTULA: A CASE REPORT

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Palsies of the sixth cranial nerve are among the most frequent cranial nerve disorders, mainly because of the long intracranial path of the abducens nerve. Common causes include microvascular ischemia, diabetes, and arterial hypertension, although some life-threatening conditions may also occur, such as disorders causing intracranial hypertension. Sixth nerve palsy is mostly unilateral, although few cases of bilateral involvement has been also described in the literature. In this report, we present a rare case of a 78-year-old female with bilateral abducens nerve palsy due to a right high-flow carotid-cavernous fistula. At the neurological examination, she presented with convergent strabismus in the right eye and bilateral abduction deficit. Supra-aortic vessel ultrasound detected increased speed and "arterialization" of the right jugular vein and in the ophthalmic vein, as well as a markedly increased diastolic velocity in the right internal carotid artery. Brain MRI scan showed a marked enlargement of both cavernous sinus, especially from the right side, and both ectasia and tortuosity of several extracranial veins, particularly of the right upper ophthalmic vein. Endovascular treatment was than performed, leading to a complete occlusion of the fistulous tract. At a two-month clinical follow-up, a complete resolution of the abduction deficit was noted. This case shows as a bilateral abducens nerve palsy, though rare, can reveal a severe and possibly life-threatening condition; as such, prompt diagnosis and adequate intervention are crucial to obtain clinical recovery and functional independence.

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ENCEPHALOPATHY IN A PATIENT WITH IDIOPATHIC GENERALIZED EPILEPSY BEING TREATED WITH VALPROIC ACID AND LACOSAMIDE, A CASE REPORT

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Valproic acid (VPA) is a widely-used first generation antiepileptic drug. However, toxicity, induced by other antiepileptic agents, when used as combination therapy, has been commonly reported. The most common manifestation is a hyperammonemic encephalopathy which symptoms can range from mild drowsiness to coma. In this report we present the case of a 17-year-old female patient complaining toxicity due to VPA and lacosamide (LCM) in combination, with normal serum ammonia levels. The patient, suffering Childhood Absence Epilepsy from the age of 8 and treated with VPA 1000 mg daily, after an unplanned pregnancy, presented episodes of loss of consciousness associated with "four limbs tremors" and VPA was reintroduced, in association with LCM 400 mg daily. She came to our department for the presence of marked drowsiness and the aforementioned episodes occurring more than once a day. The neurologic examination was normal except for the presence of severe drowsiness. The blood chemistry showed a slightly high valproic acid level (109 mg/dl, n.v. 50-100), while serum ammonia level was within normal range (41 mmol/L, n.v. 18-72). The long-term EEG monitoring revealed a high-voltage monomorphic delta activity occurring both during sleep and wakefulness. Brain MRI and cerebrospinal fluid analysis were performed, showing no significant pathological findings. For this reason, lacosamide was slowly reduced until withdrawal. After two days, the patient showed a rapid clinical improvement and a complete EEG normalization. In conclusion we would like to underline how the possible negative effect of the drug association between VPA and lacosamide, still poorly described in literature, should always be considered in any patient under multiple antiepileptic drug therapy, complaining altered mental status.

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INCREASED CREATIVITY AS A SIDE EFFECT OF DOPAMINE AGONISTS TREATMENT IN PARKINSON'S DISEASE: A CASE REPORT

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Introduction: Impulsive control disorders (ICDs), as pathological gambling, compulsive shopping, binge eating and hypersexuality, are common side effects of dopamine agonists (DA) treatment in Parkinson's disease (PD). But in this spectrum of side effects other symptoms are sometimes included. Upon these, enhanced creativity has been described, but it is usually not common and not claimed as negative side effect. Here we report a case of a PD patient, who developed a new compulsive painting activity, which he had never experienced before, after starting treatment with DA.

Case presentation: A 65-year-old man with a history of bipolar disorder, was firstly referred to our movement disorders unit for the development of a parkinsonian syndrome characterized by: mild global and right-side bradykinesia, resting and postural tremor of upper limbs (mainly on the right side), and Rabbit syndrome-like lip tremor. The patient also complained hyposmia, sleep REM behavior disorders, apathy, and low mood. 123I-Iofuplane SPECT imaging displayed impaired bilateral striatal uptake of the tracer, more pronounced on the left side. Thus, a diagnosis of idiopathic PD was performed, and a levodopa/carbidopa treatment was started with an improvement of motor symptoms. After

three years of treatment, the patient experienced a worsening of the disease with increased tremor, postural instability, and upper limbs rigidity. Thus 2,1 mg a day of Pramipexole was prescribed with a four-week titration period. At the 10 months follow-up, motor symptoms had significantly improved, but ICDs related to dopaminergic treatments developed, particularly an increasingly and compulsive-like interest in painting was observed. The patient used to spend a consistent amount of time in this new activity and produced more than 60 paintings in the first months following the Pramipexole introduction. Notably he had never painted before, nor anybody has ever noticed his painting abilities. Unfortunately, the patient also experienced compulsive shopping, obsessive behavior, visual hallucinations, and color perception disturbances. For this reason, Pramipexole dosage was reduced to 0.52 mg /day. As a result, DA side effects disappeared but the patient completely stopped his artistic production and his mood also worsened.

Discussion: Enhanced creativity in artists has been previously described as an effect of DA treatment in PD, but this case represents one of the rare reports of a new onset drug-induced art activity in a PD patient.

INCIDENT ANTI-LGI1 AUTOIMMUNE ENCEPHALITIS DURING DEMENTIA WITH LEWY BODIES: WHEN OCCAM RAZOR IS A DOUBLE-EDGED SWORD

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Background: Quick cognitive deterioration and seizures seldom occur in Dementia with Lewy bodies (DLB) [1] but other concomitant conditions disrupting the typical course may be neglected by following the Occam razor rule uncritically.

Case report: We describe a 74-year-old male with a slowly progressive cognitive impairment with probable RBD and visual hallucinations, reduced basal ganglia dopamine transporter uptake on SPECT, grossly impaired myocardial I-123 MIBG scintigraphy, bilateral parieto-occipital hypometabolism on [18F]-fluorodeoxyglucose-PET, and slowing-down of EEG background activity, consistent with probable DLB. The MMSE score was 19/30 and the CDR score was 2. Treatment with rivastigmine resulted in cognitive and behavioral improvement (MMSE score 24/30). Two months later, he experienced several episodes of sudden and short paroxysmal myoclonus-like movements with psychomotor arrest, suspected of complex partial seizures and paralleling cognitive worsening. Despite incremental dosing of antiepileptics drugs, a generalized convulsive seizure, and multiple daily episodes of faciobrachial dystonic seizure (FBDS) occurred while EEG showed impressive worsening with sub-continuous delta activity but no epileptiform abnormalities even during the FBDS episodes, leading to hospitalization. Moderate hyponatremia (128 mEq/l) was found, while brain MRI was unchanged and RT-quic on nasal brushing was negative for prion protein. Detection of serum anti-leucine-rich glioma-inactivated 1 (LGI1) antibodies supported the diagnosis of anti-LGI-1 autoimmune encephalitis. Treatment with intravenous methylprednisolone (500 mg for 5 days), followed by two monthly cycles of IV immunoglobulins (2 g/kg in five consecutive days) resulted in cognitive improvement, significant reduction of FBDS and antiepileptics dosing decrease.

Discussion: Seizures are reported in around 2.5% of DLB patients and relate to cortical network hyperexcitability due to deposition of aggregated proteins (e.g., alpha-synuclein, tau) or concurrent amyloid plaques [2]. In this case, the co-occurrence of anti-LGI1 autoimmune encephalitis was responsible for epilepsy and rapid cognitive with EEG worsening, both significantly improving with immunotherapy. Although AEs may be insidious mimics of neurodegenerative dementias [3], two core clinical features, two indicative and two supportive biomarkers for DLB strongly suggest co-pathology. We speculate that during DLB-related neuronal degeneration the presentation of neo-autoantigens might have triggered an immune response with autoantibodies against the neuronal cell-surface (e.g., LGI1), facilitated in entering the brain by a less intact blood-brain barrier, common in the elderly.

Conclusions: Occurrence of epilepsy and abrupt cognitive worsening in DLB may be challenging for clinicians and need a thorough investigation to exclude concomitant, treatable conditions.

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MAGNETIC RESONANCE INTRACRANIAL VESSEL WALL IMAGING (VWI) IN SUSAC SYNDROME: POTENTIAL RELEVANCE FOR DIAGNOSIS AND THERAPEUTIC MANAGEMENT

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Aims: To evaluate the role of high resolution Intracranial Vessel Wall Imaging (VWI) to detect disease activity in a case of Susac Syndrome (SS).

Material and Methods: A 40-year-old woman with a confirmed diagnosis of SS under specific therapy for this disease, received two brain 3T magnetic resonance imaging (MRI) scan 6 months apart. In the second one the sequence Proton Density Weighted Image (PDWI), before and after gadolinium, was included in order to explore the presence of inflammation of vessel walls.

Results: Despite conventional MRI did not show new lesions, PDWI revealed enhancement of an arteriola with the "tram track" sign, a doble linear enhancement attributable to inflamed arteriolar walls; as a collateral finding, an enhancement of right inner ear structures was observed. In addition, retinal fluorescein angiogram (FA) performed a few days later showed new arterial wall hyperfluorescence (AWH) of retinal arterioles, confirming persisting inflammatory activity despite treatment.

Discussion: SS is a rare immunological disorder, that at pathological level appears based on immune-mediated inflammation occlusion affecting small vessels of retinal, inner ear and brain small vessels. Lesions of the corpus callosum, the so-called "snow ball lesions" considered highly suggestive of SS, are usually interpreted as microinfarcts due to occlusion of tiny arterioles. One additional supportive finding of small vessel occlusion, i.e. evidence of wall's inflammation of small brain arterioles, was highlighted in this case by high resolution VWI sequences. Although not specific of SS, this sign could support SS diagnosis in the early phase when clinical and/or neuroimaging triad are incomplete, allowing anticipation of treatment. Furthermore, in the present case, an abnormal enhancement of the inner ear observed by this MRI sequence, anticipated an additional cardinal diagnostic element. Current available markers of suboptimal therapeutic response are: presence of new lesions or persistent active enhanced lesions on standard MRI, new visual field defect and evidence of AWH on FA. In addition, these data suggests that evaluation

of small vessels inflammation through High resolution VWI might add valuable information, particularly in central nervous system predominant SS and that stability of brain lesion load is not sufficient to establish an absent disease activity. Concordant results with FA, the most accurate test to evaluate disease activity in SS, validate also accuracy of this MRI marker.

Conclusions: The proper use of VWI could represent a supportive tool in diagnostic and mainly therapeutic management of SS.

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PARAINFECTIOUS ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM) ASSOCIATED WITH PNEUMOCOCCAL PNEUMONIA: A CASE REPORT

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Objective: To describe a case of parainfectious acute disseminated encephalomyelitis (ADEM) [1] associated with pneumococcal pneumonia.

Case report: A 48-year-old man presented with cough, dyspnea, and fever. His past medical history was unremarkable. A chest x-ray revealed severe pneumonia with positive urine antigen. Intravenous antibiotic therapy was started, with improvement. Six days later, he complained urinary retention and lower limbs weakness; neurological examination revealed confusion, paraplegia with brisk tendon reflexes and bilateral ankle clonus. Spinal MRI scan showed elongated signal changes from the lower cervical spine to the conus medullaris throughout the whole central area of the spinal cord. Brain MRI scan revealed abnormal signal of the right cerebral peduncle, extending cranially to the internal capsule and caudally to the anterolateral region of the upper brainstem, and a smaller lesion within the left superior cerebellar peduncle. CSF analysis showed increased proteins (116 mg/dL), 26/uL white blood cell count (mainly mononuclear cells), and a concentration of glucose of 51 mg/dL. Blood and CSF culture showed no bacteria and viral screening via Multiplex-PCR tested negative. Oligoclonal bands on serum and CSF were positive with a mirror pattern. Anti-AQ4 antibodies on serum were negative, while anti-MOG antibodies were positive. A nine-day course of intravenous methylprednisolone was administered, followed by oral prednisone. The patient was admitted to a rehabilitation unit for three months and showed a gradual improvement of the mental status and lower limb strength. At one month follow-up visit, he was able to walk without aids, but the bladder function remained impaired with self-catheterization needs. After three months the MRI scan showed a marked reduction of the lesions.

Discussion: In the present case, the clinical course, laboratory data and neuroimaging were consistent with parainfectious ADEM [2]. As far as we know, ADEM has never been reported following pneumococcal pneumonia [3].

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A REVERSIBLE SPLENIAL LESION IN A PATIENT WITH ANTI-NMDAR ENCEPHALITIS

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Objective: Here we describe the case of a 30-year-old woman affected with a N-methyl-D-aspartate receptor (NMDAR) encephalitis who also developed a reversible splenial lesion.

Case presentation: In December 2021 she presented with acute psychosis characterized by religious delusions, hallucinations and disorganized behavior. She was first admitted to a psychiatric ward after performing a brain CT-scan and electroencephalogram (EEG), both normal. She was initially treated with haloperidol and then discharged. After discharge, the patient developed severe muscular rigidity. Haloperidol was gradually withdrawn and switched to lurasidone. After few days, she presented catatonic and the psychiatric consultant decided to withdraw lurasidone. Because of catatonia and fever onset, she was admitted in the Psychiatric Unit of our hospital in January 2022. Neuroleptic malignant syndrome was ruled out because of normal creatine kinase concentration and antibiotic treatment was started for right basal pneumonia. A brain MRI showed a centimetric signal hyperintensity in DWI and T2-sequences in the splenium of corpus callosum, without contrast enhancement and slightly enhanced signal in FLAIR in right cingulate cortex. She was then admitted to our Neurology Unit where a lumbar puncture was performed. Abdomen CT scan showed a small tumor close to the right ovary serum. The patient was treated with intravenous high dose methylprednisolone (1000 mg per 5 days) and intravenous immunoglobulins (20 g per 5 days) and markedly improved within one month. A brain MRI performed in February 2022 showed that the callosal lesion disappeared. Further serum analyses revealed high-titers of NMDAR antibodies (1:100) and during a laparoscopic surgery performed in April 2022, two small teratomas were resected.

Discussion: Transient localized lesions of the splenium of the corpus callosum are often associated with antiepileptic or neuroleptic withdrawal, metabolic disturbances, high altitude and thyroid autoimmune diseases. These lesions probably reflect cytotoxic edema and reversible demyelination, resulting from a cytokine cascade and glutamate excitotoxicity. Clinical manifestations are those of mild encephalopathy/encephalitis and brain MRI shows transient DWI alteration of the splenium. Anti-NMDAR encephalitis is associated with an increased concentration of inflammatory cytokines.

Conclusions: In our patient, the co-occurrence of discontinuation of neuroleptic drugs and antibodies anti-NMDA could have provided a basis for the cytokine cascade leading to cytotoxic edema in splenium. To the best of our knowledge, only one another case of reversible splenial lesion has been already described in a young patient with anti-NMDAR encephalitis, suggesting that autoimmune encephalitis should be considered as a contributing factor in the genesis of callosal reversible lesions.

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ATYPICAL RARE PRESENTATION OF IDIOPATHIC INTRACRANIAL HYPERTENSION WITHOUT HEADACHE AND WITH THE VITH AND VIITH NERVE PALSIES

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Background: Idiopathic intracranial hypertension (IIH) is a clinical syndrome of unknown aetiology, characterized by an isolated increase in intracranial pressure without hydrocephalus or intracranial masses and normal CSF composition [1]. IIH affects predominantly overweight/obese women (Man-to-Woman ratios range from 1:6 to 1:15; incidence is 1-2/100000 in the USA). IIH is clinically associated with headache, papilledema, blurred vision, vomiting, dizziness and pulsatile tinnitus. Less common symptoms are dysfunction of one or more cranial nerves (CN), internuclear ophthalmoplegia, hearing loss, and olfactory dysfunction [2]. Far from being benign, IIH causes permanent vision loss in up to 10% of affected patients.1 Prompt syndrome recognition is therefore critical. Here, we describe the case of a 45-year-old obese woman with an unusual IIH presentation, without a headache and with sequential CN VI and CN VII palsies as the primary clinical manifestations.

Case Report: A 45-years-old obese woman (BMI=31) presented to the Emergency Room of this Hospital with a few days' history of diplopia. Past medical history was negative, except for unsuccessful bariatric treatment in the past two years. The neurological examination documented a right CN VI palsy; visual acuity was normal, but the fundus oculi revealed bilateral papilledema with peripapillary flame-shaped haemorrhages. She did not complain of headaches. An MRI with venography was negative for intracranial masses but documented an enlarged right optic nerve sheath and an empty sella. A diagnosis of possible IIH was made, and the patient started acetazolamide (250 mg twice a day) with an improvement of diplopia. However, three weeks after the presentation, a right CN VII palsy ensued, and this time she was admitted to our Neurology Unit. A repeat MRI venography showed the same abnormalities seen in the previous MRI. A lumbar puncture revealed slight increased intracranial pressure with normal CSF composition. Biochemical and immunological workups were negative. Prednisone was added to acetazolamide. Cranial nerve deficits improved, but papilledema persisted. Visual acuity continues to be normal, and no headache is reported. She continues her therapeutic regimen.

Discussion: Unusual IIH presentations are now better known [2]. Our case was rare and uncommon because of the absence of headache, bilateral papilledema, a serendipitous discovery, with normal visual acuity and sequential VI and VII cranial nerve palsies. Palsies of these cranial nerves in the absence of headache should prompt a diagnostic workup also for IIH [3]. The mechanisms underlying the proteiform symptoms that characterize IIH are poorly understood and should stimulate further research.

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A CASE OF FOODBORNE BOTULISM AS A STROKE MIMIC. A CHALLENGING NEUROPHYSIOLOGICAL DIAGNOSIS IN EMERGENCY SETTING

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Introduction: Foodborne botulism is an acute potentially life- threatening paralytic syndrome caused by the ingestion of food contaminated with toxins produced by Clostridium botulinum. Classically, clinical manifestations of botulism are described as symmetrical cranial nerves palsy with secondary symmetrical ascending flaccid paralysis, preceded by gastrointestinal manifestation. However, neurological symptoms onset may be confusing in the earliest clinical presentation and may therefore be confused as ischemic stroke. This may delay antitoxin treatment and worsen the patient's prognostic outcome.

Case Description: A 49-year-old male with a history of hypercholesterolemia was admitted to the emergency room due to an onset of dizziness, diplopia, dysarthria and dysphagia. The neurological disturbance begun acutely the night before and was preceded by a nausea. Stroke physician was alerted to evaluate the case for suspected posterior circulation ischemia. Neurological examination revealed mild divergent strabismus in the right eye, right facial nerve weakness and dysarthria, unreactive bilateral mydriasis. CT and CT angiography scan showed no abnormalities. Few hours later patient's clinical condition progressively deteriorated when difficulty in swallowing, severe bilateral ptosis, and shortness of breath appeared. There was no need for mechanical ventilation. The patient revealed afterwards the ingestion of a poorly preserved food. Botulism intoxication suspicion was made, and botulinum antitoxin was administered within the first three hours of hospital admission. Botulinum toxin was found in stool sample only. Electrophysiological tests, performed during hospitalization, showed reduced compound muscle action potentials (CMAPs), low amplitudes and short durations of motor unit potentials (MUPs), and non-incremental response in repetitive high-frequency stimulations (RNS). The Single Fiber EMG (SFEMG) on the right "orbicularis oculis" showed instable MUPs with prolonged abnormal jitter. Neurological improvements were progressively observed in the following days. The patient was discharged after 20 days of hospitalization in good general conditions.

Discussion: In our case, although stroke alert was given in the first place, amnestic data together with clinical findings let to prompt recognition. Antitoxin treatment was administrated, and clinical benefit was seen in the following days. EMG/ENG findings of a presynaptic neuromuscular dysfunction were helpful in supporting the hypothesis of botulinum intoxication. Moreover, a complete neurophysiological evaluation could provide a useful tool in differentiating from other neuromuscular junction diseases. Identifying botulism in the earliest hours of hospital admission represent a challenge for the clinician and can potentially change prognostic outcome.

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ADULT-ONSET CEREBRAL FOLATE DEFICIENCY WITH STABLE BRAIN MRI AND CLINICAL FINDINGS UP TO 5 YEARS. A CASE REPORT

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Background: Cerebral folate deficiency (CFD) is a rare neurological syndrome characterized by low cerebrospinal fluid concentration of 5-methyltetrahydrofolate in the presence of normal peripheral folate metabolism, associated with FOLR1 gene mutations [1]. CFD may have a wide range of symptoms, which started at few months of age with irritability and sleep disturbance and usually proceed with severe epilepsy, cerebellar ataxia, and psychomotor retardation [1]. We describe an adult case of CFD showing stable disease course and MRI appearance.

Case description: We describe a 47 years-old man with a history of drug abuse and psoriasis (previously treated with adalimumab), who came to our Unit with vertigo and vertical double vision in left/upper-left gaze position. Brain MRI, performed at presentation, showed diffuse bilateral white matter hyperintensity, with gadolinium enhancement on the left cerebellar peduncle. Blood routine and autoimmunity tests, lysosomal enzymes, lactate and pyruvate; and serum heavy metal evaluation were all within normal range. Electroneuromyography was unremarkable. Cerebrospinal fluid analysis showed increased proteins and the presence of numerous unmatched oligoclonal bands; virus assays were negative. Genetic analysis for CADASIL and CARASIL was negative. Cognitive functions were preserved except for mild alterations in executive and attentional functions. Brain-MR spectroscopy revealed a decrease of N-acetyl-aspartate/Creatine ratio and mild increase of Choline/Creatine ratio, compatible with axonal and myelin damage. The genetic test (performed with Next Generation Sequencing) revealed FOLR1 double gene heterozygous mutation (c.45G>T and c.493+2T>C), which is indicative for CFD. A follow-up of 5 years shows stable neurological and MRI findings.

Conclusion: Although rare, FOLR1 gene mutations can happen in adults with poor clinical findings. Folinic acid therapy can reverse the clinical symptoms and improve brain abnormalities and function. Therefore, CFD should be considered in adult patients with neurological symptoms and a severe leukodystrophy-like MRI patterns, in the presence of a stable disease course. As only a limited number of cases are reported yet, more cases in the future will help us study the phenotype and better characterization of this new clinical entity.

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AN UNUSUAL CAUSE OF COMA

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Objective: The artery of Percheron (AOP) is a rare variant of the paramedian thalamic artery that supplies the medial nuclei of the thalamus and the rostral midbrain. The presentation of an infarct in this territory varies widely and is often characterized by nonspecific neurological deficits, with altered mental status, behavior and memory impairment, ocular movement abnormalities and motor deficits. Lacking the classic signs of stroke, many of these patients experience a delay in recognition and treatment. We describe the case of a patient who presented with coma and motor deficits due to an AOP infarct.

Materials, methods and results: A 63-year-old Caucasian men developed a sudden loss of consciousness. At the admission to the emergency department, the patient had a Glasgow Coma Scale (GCS) of 6 points (O: one point, V: one point, M: four points). A computed tomography (CT) scan of the head ruled out acute intracranial pathology. A CT angiography was performed but no occlusion was seen. Though an EEG in acute phase could not have been performed, in the hypothesis of a non convulsive status epilepticus, he was treated with Levetiracetam with no benefit. A brain MRI was performed, diffusion-weighted MRI revealed acute infarcts in the bilateral thalami extending toward the rostral midbrain. The diagnosis of acute ischaemic stroke of the AOP was made and antiplatelet therapy was started.

Discussion: The acute occlusion of the AOP is a rare event. Worldwide, it is responsible for 0.1 to 2% of ischemic strokes. This anatomical variant is estimated to exist in 4-11.7% of the general population. The CT imaging typically shows no abnormalities in acute AOP infarction. The CT angiography also tends to be normal, as occlusions in such small arteries are usually not distinguishable. Given the inability of many imaging modalities to resolve an AOP infarct, many patients with this type of stroke go undiagnosed for the first several hours until MRI is performed, with consequent delaying of proper treatment.

Conclusions: Bilateral thalamic stroke with or without midbrain involvement due to occlusion of the anatomical variant of Percheron artery is a rare entity, which can be difficult to identify because of its broad spectrum of clinical signs. This case highlights the importance to consider AOP infarct in the differential diagnosis of coma when assessing patients with uncommon neurological deficits of unclear origin, since early recognition of AOP occlusion may lead to rapid treatment and more favorable outcomes.

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GIANT PERIVASCULAR VIRCHOW-ROBIN SPACES: A RARE CAUSE OF ADULT ONSET PROGRESSIVE SPASTIC PARAPARESIS

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Background and Aims: Adult-onset, chronic progressive spastic paraparesis may be due to a large number of causes and poses a diagnostic challenge. The differential diagnosis is broad and includes genetic diseases, rare neuro-metabolic diseases and hypovitaminosis. Here we report

a case of a 47-year-old woman, with a family history of gait abnormalities, admitted to our Neurology Unit for the onset, 6 months earlier, of progressive lower limbs weakness and spasticity. Her medical history was remarkable for ventricular shunt surgery for an idiopathic triventricular obstructive hydrocephalon at the age of 20 years. The surgery was followed by complete remission and subsequent shunt closure after few years. On admission, neurological examination showed spastic gait, right exotropia with pupillary anisocoria, mild dysathria and lower limbs weakness with hyperreflexia.

Methods: We performed blood tests, including deficiency screening, a brain and spinal cord MRI and a motor evoked potential (MEP) study.
Results: Blood tests were unremarkable. Brain MRI showed a diffuse presence of intraparechymal perivascular cysts, mainly in the midbrain and diencephalon, with the largest one in the right midbrain. On diffusion tensor imaging the right corticospinal tract in the cerebral peduncle appeared significantly compressed in its antero-lateral portion. The MEP study confirmed impaired motor function of the lower limbs.

Conclusions: Patient was diagnosed with 'Paraparesis due to giant Virchow-Robin spaces (GVRS)', a rare cause of adult-onset paraparesis. GVRS is a medical condition of unknown origin, without a clear genetic background. The patient underwent ventricular shunt re-placement with progressive neurological recovery over months, as demonstrated both by clinical and MRI follow-up.

MILD CLINICAL PRESENTATION OF ISOLATED NEUROSARCOIDOSIS WITH LEPTOMENINGITIS

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Introduction: Sarcoidosis is a multisystemic chronic granulomatous disorder involving lungs, skin and kidneys, characterized by a wide range of neurological presentations, including cranial neuropathy, myelopathy, meningitis and peripheral neuropathy. Isolated neurosarcoidosis (NS) occurs in about 10-20% of patients affected by sarcoidosis [1].

Case: A 46-year-old male presented with a one-week history of blurring in the left eye and hypoesthesia of the left leg. Three months before our observation, he had developed asymptomatic COVID-19 infection. At age 13, he had suffered from the rupture of a lumbosacral spinal arteriovenous malformation, surgically treated with complete recovery. Neurological examination showed left-eye mild visual-acuity reduction, hypo-elicitable lower-limb deep-tendon reflexes and left thigh numbness. Results: blood laboratory work-up was unremarkable. CSF showed massively raised proteins (about 17.000 mg/L, normal range: 150 – 450mg/L), leukocytic pleocytosis (7 cells/mm), hyperglycorrhachia and xanthochromia. Microscopic exam was negative for neoplastic cells. No oligoclonal-band synthesis was found. CSF microbiological exams were negative. Ophthalmological evaluation and optical coherence tomography revealed papilledema and defect in the inferior nasal paracentral quadrant of the left eye. Brain MRI showed diffuse T2-hyperintense meningeal lesions with homogeneous contrast enhancement (CE) in T1-weighted images in optic nerves bilaterally, with left prevalence, left cavernous sinus, temporal pole, cerebellum, left temporal and right frontal cortical surfaces. Spinal MRI revealed extensive cervical myelitis with intramedullary and leptomeningeal nodular, lumbar spine and cauda equina CE. No area of systemic hypermetabolism on Fluor-18-deoxyglucose positron-emission tomography (18FDG-PET)/CT total body was found. A diagnosis of possible NS according to NS Consortium Consensus Group diagnostic criteria was made, after careful exclusion of alternative diagnoses [2]. A brain biopsy was not considered because of the unfavorable ratio between high surgical risk and low clinical severity. A 5-gram intravenous methylprednisolone course was performed, with benefit on blurred vision and leg sensory symptoms.

Conclusion: Meningeal and spinal involvement are frequently described in NS, leading to possible misdiagnosis with other clinical entities such as meningeal carcinomatosis and CNS infection [1]. To our best knowledge, xanthochromia due to extreme increase in CSF proteins has never been reported in NS. NS diagnosis is especially challenging because of the lack on sensitive and specific biomarkers, the wide range of clinical presentations and the possible high degrees of clinical-radiological dissociation, as our case further highlights [3]. Careful imaging and CSF evaluation aiming to exclude all the other infectious, inflammatory and neoplastic causes of CNS parenchymal involvement is the key for a correct assessment.
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BILATERAL PREFRONTAL HYPERMETABOLISM AT BRAIN 18FDG-PET IN A CASE OF BEHAVIORAL VARIANT OF FRONTOTEMPORAL DEMENTIA

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Introduction: Frontotemporal dementia (FTD) represents a spectrum of clinical syndromes characterized by neuronal degeneration involving the frontal lobes and the anterior portion of the temporal lobes. Behavioral variant of frontotemporal dementia (bvFTD) is characterized by the progressive deterioration of personality, social behavior and cognition. The aim of the present study is to describe a case of bvFTD, with negative genetic analysis for known mutations involved in the pathogenesis of the disease, which showed a hypermetabolism at brain 18FDG-PET in bilateral prefrontal cortex.

Materials: Neurological, neuroradiological and neurogenetic reports.

Method: Review of the patient's clinical history.

Results: A 61-year-old patient reported an 8-month history of asthenia and dizziness, followed by rapidly progressive psychomotor agitation. Subsequently she developed a decrease in interests, moriatic attitude, hyperphagia and phenomena of perseveration and obsessions. She underwent Mini Mental State Examination (18/30), blood tests (including antibodies related to paraneoplastic and autoimmune encephalitis), lumbar puncture (tau, p-tau, β-amyloid were normal, and antibodies related to paraneoplastic and autoimmune encephalitis resulted negative), and neuropsychological evaluation (showing deficits of executive, memory and visuo-constructive functions, and significant behavioral alterations, in an apathetic sense, but with disinhibited and dysexecutive components). A

psychiatric evaluation did not conclude for a mental disorder. A genetic screening was carried out to analyze the main genes involved in the pathogenesis of FTD (including C9ORF72, MAPT, GRN, TARDBP, SQTSM1, UBQLN2, VCP, CHCHD10, and FUS), which resulted negative. Finally, the patient underwent brain MRI, showing frontal lobe atrophy, and brain 18FDG-PET, showing bilateral prefrontal hypermetabolism. The diagnostic criteria for bvFTD resulted to be fulfilled.

Discussion: The interpretation of frontal hypermetabolism was challenging. Such finding can be detected in psychiatric disorders (e.g. borderline personality disorder), whose differential diagnosis with bvFTD is often difficult to disentangle. Nevertheless, the clinical picture and the presence of frontal atrophy were consistent with bvFTD. The observation of cortical hypermetabolism has been reported in different neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis, and may reflect the activation of microglia. Notably, a picture characterized by bvFTD associated with bilateral frontal hypermetabolism at 18FDG PET has been described in a patient carrying C9ORF72 hexanucleotide repeat expansion.

Conclusions: To the best of knowledge, this is the first case of bvFTD associated with bilateral frontal hypermetabolism at 18FDG PET, in the absence of genetic mutations.

A DISTAL MOTOR NEUROPATHY IN A YOUNG MALE WITH A NOVEL SIGMAR1 SUBSTITUTION MUTATION

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Introduction: Distal hereditary motor neuropathies (dHMN) are a group of inherited diseases associated with symmetric distal weakness and muscular atrophy. Mutations in about 30 genes have been linked to dHMN. Here we describe a case associated with a novel mutation in the sigma non-opioid intracellular receptor 1 gene (SIGMAR1).

Case Report: An 18-year-old was referred to our Neurological Department for the bilateral symmetrical distal weakness of the upper and lower limbs. Symptoms started in the upper limbs three years before and progressively involved the lower limbs, with a significant worsening in the last months. At that time he stopped playing sports and lost his job. The patient had Senegalese origins and distant consanguineous parents. At the neurological evaluation we noted bilateral pes cavus with internally rotated feet and inability to walk on tiptoes and heels. Severe diffuse distal muscle atrophy was present bilaterally, with reduced muscle strength (MRC 2-3/5 diffusely). Deep tendon reflexes were widely decreased; plantar reflexes resulted in flexion. Cranial nerves and sensory examinations were normal. The electromyographic study showed distal symmetrical demyelinating motor polyneuropathy involving upper and lower limbs. The sensory nerve conductions were normal. In addition, giant motor unit potentials were present bilaterally at the vastus medialis. Cerebrospinal fluid examination (cells, proteins number, isoelectric focusing) was unremarkable. Serological exams for HIV, HBV, and HCV were negative. Blood dyscrasias and monoclonal gammopathies were excluded and research for antibodies against GM-1 was negative. Thus, a genetic analysis was performed, assuming a hereditary cause of the disorder, looking firstly for gene mutations most frequently associated with demyelinating neuropathy (PMP22, MPZ, GJB1, GDAP1). With next-generation sequences, a homozygous substitution mutation was found on exon 4 of the SIGMAR1 gene (reference sequence: NM_005866; variant c.653T>G), which predicts a missense substitution: p.L218R (hg19: chr9:34635648 T>G). This is a new mutation, never described before, even if in the SIGMAR1 gene other pathogenic mutations have already been identified in patients with similar phenotype [1] but with predominantly axonal features at the conduction studies [2].

Discussion: There is some evidence supporting the hypothesis that this mutation may be pathogenic: 1. it is absent in control groups; 2. there is computational evidence "in silico" predicting its pathogenicity; 3. other missense homozygous and hemizygous mutations in the same gene and domain have already been identified in patients with distal motor neuropathy. This genetic variant is then classified by ACMG 2015 guidelines [3] as probably pathogenic.

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POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES) AFTER BLOOD TRANSFUSION: A CASE REPORT

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Introduction: Posterior reversible encephalopathy syndrome (PRES) is a transitory clinico-radiological syndrome characterized by variable signs and symptoms (e.g., headache, seizures) accompanying vasogenic edema in the occipital and parietal lobe on brain imaging. PRES has been associated with several medical conditions, but the pathophysiology is unclear.

Case Report: We describe a case of a 33-year-old female who was found to be severely anemic (Hb: 2.8 gr/dL) due to a bleeding, uterine myoma. She was transfused with eight units of packed cells and underwent laparotomic hysterosalpingectomy. Four days after, she went through two episodes of bilateral tonic-clonic seizures. The electroencephalogram (EEG) showed diffuse slowing with rare epileptiform waves in the occipital regions. Antiepileptic drugs (AEDs) were started (levetiracetam, benzodiazepines). The brain CT scan was unremarkable. Concomitantly, she started suffering from hypertension. After two days, she went through new episodes of tonic-clonic seizures. The patient developed tetraparesis, visual loss, and progressive consciousness deterioration. The EEG showed focal status epilepticus; AEDs were increased (brivaracetam, lacosamide). The patient was largely investigated for infectious and hematological etiologies, with unremarkable results; cerebrospinal fluid was normal. The brain MRI scan showed FLAIR hyperintensities in the white and gray matter of the occipitoparietal lobes bilaterally, with contrast enhancement, consistent with PRES. In the following three weeks, the patient's conditions improved and the brain MRI showed resolution of brain lesions.

Discussion: Blood transfusion is a rare possible cause of PRES. Brain lesions are generally reversible, but immediate recognition of suggestive clinical features and brain imaging findings is fundamental to prescribe appropriate therapy.

OPHTHALMOPATHY IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: CONSEQUENCE OR COINCIDENCE?

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Introduction and Aim: Neuro-ophthalmogical complication, although rare, is described associated with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) specially in patients with severe damage of the blood-brain barrier and a long history of disease, however not always very clear are the mechanisms underlying the process. We described the case of a man affected by CIDP which developed ophthalmopathy with evidence of anti-GQ1b and anti-GT1a IgM antibodies.

Materials and Methods: A 11 years old boy presented onset of progressive sensory-motor impairment at four limbs for which, at that time, diagnosis of CIDP was postulated. Therapy attempt with azathioprine and interferon failed and, after 4 months, therapy with intravenous immunoglobulin in association with occasional boluses of steroids, due to frequent relapsing-remitting clinical course, was started. Clinical stabilization was achieved until the age of 25 when the patient complained mild exophthalmo with progressive proptosis and lid retraction, photophobia and inconstant diplopia. At the age of 35 years old he came to our attention; neurological examination revealed, stable over the last 20 years, distal on hands and feet associated with hypoesthesia and hypopallesthesia.

Results: The visual field analysis showed a nonspecific hyposensitivity in the inferior sector in the right eye, no visus deficit or fundus oculi alterations were detected. Brain MRI showed bilaterally roots hypertrophy on optic nerves with signals alteration in T1 and T2 sequences and slight post-contrast enhancement. Searching for monoclonal gammopathy, paraneoplastic markers, investigations for gravis myasthenia, as well as thyroid function and panel for gene mutations associated to inherited neuropathies were negative. Anti-gangliosides panel showed a high positive titer of IgM-GT1a and IgM-GQ1b, not reported in childhood. Electroneurography was confirmed stable over time.

Discussion and Conclusion: Cranial nerves involvement is found, at different extent, in about 15% of CIDP cases and hypertrophic cranial nerves thickening at MRI has been observed in sporadic cases, usually in relation to long disease history and grade of cerebrospinal fluid barrier disruption. On the other hand, IgG anti-GQ1b and anti-GT1a antibodies are positive in about 90% of cranial nerves involvement and less frequently in the acute inflammatory demyelinating polyneuropathy. In our case we can hypothize in the disease course of the patient the occurring of an incidental acute cranial nerve compromise, however with a slow progression, probably attenuated but not limited by treatment ongoing. Different priming and response to immunomodulatory therapy of immune system are to know more in depth in cranial nerve involvement in nerve peripheral dysimmune disorders.

A CASE OF MEDULLA OBLONGATA INVOLVEMENT IN A SHORT-TERM RECURRENT TRANSVERSE MYELITIS ASSOCIATED WITH ANTIPHOSPHOLIPID ANTIBODIES

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Objectives: Transverse myelitis (TM) is a rare manifestation related to antiphospholipid antibodies (APLA). We present a case of longitudinal extensive transverse myelitis (LETM) associated with APLA. APLA-related TM could have peculiar clinical and radiological features that help in diagnosis.

Materials/ Method/ Results: A 60 year old male was admitted to our department because experienced altered taste sense in right portion of tongue and subsequently dysaesthetic disorders in right upper hemisome. His brain and medullary magnetic resonance (MRI) showed T2 hyperintensity in right medulla oblongata, extended up to C3. All microbiological and citologic cerebrospinal fluid (CSF), oligoclonal bands and CSF and serum aquaporin4- IgG, serum neural antigens antibody exams were negative. Visual evoked potentials were normal. As pathogenesis of myelitis was uncertain, he underwent antiviral and corticosteroid therapy. Single significant result was IgM anti-β2-glycoprotein I (anti-β2GPI) antibodies. One month later MRI showed disappearance of previous findings, however documented T2 hyperintensity from C7 to D6, with medullary enhancement, without symptomatology. Six months later MRI documented findings disappearance. IgM anti-cardiolipin (aCL) and IgM anti-β2GPI antibodies were confirmed after corticosteroids withdrawal.

Discussion: anti-phospholipid syndrome (APS) is characterized by recurrent thrombosis and obstetrical morbidity. However extra-criteria clinical features have been related to APLA. APLA associated TM mainly affects thoracic segment. Some patients experience LETM. Bulb involvement has never been described. Recurrent TMs are uncommon, raise possibility of vascular or autoimmune diseases and are described with APLA. Our patient presented recurrence about one month later, shortest time of relapse described. Some APLA associated TMs, like our patient, show normal findings on follow-up MRI, another not clarified peculiarity. Pathophysiology is unknown. Some observations prompts the question of whether other than vascular injuries are involved. Firstly, some patients had therapeutic INR levels at time of TM. Secondarily, in cases of LETM, it is difficult to explain how a thrombotic process could involve different levels of spinal vessels. Some support an immune-mediated pathogenesis with proof of binding of APLA to brain cells.

Conclusion: This case allows to consider diagnosis of LETM in patients with bulbar clinical onset. Moreover in presence of LETM, in addition to neuromyelitis optica spectrum disorder, alternative diagnosis of APLA associated TM should be considered. Follow-up resolution of MRI findings and recurrence could represent peculiar features of APLA associated TM. Consideration of this extra-criteria manifestation would lead to earlier diagnosis of APS, to study different pathogenetic mechanisms and to more adequate treatment.

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TWO SUBSEQUENT DIAGNOSIS OF IDIOPATHIC INTRACRANIAL HYPERTENSION AND MULTIPLE SCLEROSIS: A CASUAL ASSOCIATION OR A COMMON PATHOGENETIC SUBSTRATE?

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Objectives: We present the case of a patient with two subsequent diagnosis of idiopathic intracranial hypertension (IIH) and Multiple Sclerosis (MS). It underlines the importance of suspecting increased intracranial pressure in patients with MS, which if not treated it may result in permanent visual failure. Secondly, the two pathologies association could suggest a common immunological substrate.

Materials/Method/Results: A 18 year old female patient was referred to our department because of intractable olocranic headache and diplopia. She reported polycystic ovary syndrome and had a severe obesity. Her

brain magnetic resonance (MRI) was normal. The lumbar puncture revealed an opening pressure of 88 cmH2O. Microbiological cerebrospinal fluid (CSF) studies were negative. At ophthalmic examination, right papilla was relieved and the left was hyperemic, accompanied by peripapillary venous congestion and bleeding in left superior sector. She fulfilled the modified Dandy diagnostic criteria for IIH. In the subsequent five months she took acetazolomide and losted weight, with recovery from headache and improvement of ophthalmological findings. At sixth month of follow-up, she developed blurred vision in left eye. Her new brain MRI showed multiple periventicular, subcortical and infratentorial T2 hyperintense white matter lesions, one of which, in the right corona radiate, was enhancing. This MRI revealed spatial and temporal dissemination of white matter lesions, that allowed to make diagnosis of MS. She assumed parenteral corticosteroid therapy for five days, with symptoms resolution.

Discussion: Both MS and IIH are neurological diseases mostly affecting young adults, mainly women. IIH, resembling many MS patients, may show a course with "remission and relapses". Symptoms and signs in both conditions can overlap. MS has a complex immune-mediated pathogenesis, IIH etiology is instead unclear. IIH has been descripted in association with several other autoimmune conditions. Some authors show a proinflammatory cytokine profile in serum and CSF of IIH patients. B mediated mechanisms are involved in MS pathogenesis. Even in IIH patients, some authors show polyclonal B-cell expansion in the CSF and others demonstrate various patterns of oligoclonal bands.

Conclusion: The two pathologies association could not be coincidental, but underlies a common immunological substrate. So in the work-up of IIH it could be useful to include immunological studies that could clarify the pathophysiology of this enigmatic disease or allow to find biomarker of clinical fenotipes, leading to a more specific treatment.
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SYNCOPE IN IDIOPATHIC INTRACRANIAL HYPERTENSION. AN "INTRACRANIC" MECHANISM

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We describe a case report on a 57-year-old woman with recurrent reflex syncope and idiopathic intracranial hypertension-related headaches resolved after lumbar puncture with cerebrospinal fluid subtraction. During follow-up, both syncopal episodes and headache over the first year disappeared. Successively, progressive recurrence of migraine-like headaches and pre-syncopal or syncopal events reappeared but, after a secondlumbar puncture, the patient reported the resolution of the headache and syncopal episodes at a 6-months follow-up. A novel mechanism enhancing reflex syncope in the presence of intracranial hypertension and reduced intracranial compliance is discussed. Idiopathic intracranial hypertension (IIH) is an uncommon disease mainly affecting obese woman of childbearing age characterized by a raised intracranial pressure (ICP) without evidence of other intracranial pathology. Intrinsic and/or extrinsic stenoses of dural sinus tree can be found in almost all cases and represent a sensitive (93%) and specific (93%) IIH neuroradiologic marker. [1] Papilledema and chronic headache are considered IIH diagnostic landmarks although headache may lack in up to 15% of the cases and the condition may present without papilledema (IIHWOP). [2] The true prevalence of IIHWOP is unknown but might be much higher than currently believed (2-22/100.000) due to underrating, misdiagnosis and asymptomatic cases. [3] Actually, a raised intracranial pressure associated to significant sinus stenosis can be found in about 11,1% of individuals without signs or symptoms of IIH, namely about 3 orders of magnitude greater than the estimated prevalence of forms with papilledema. Syncope is defined as a transient loss of consciousness (TLOC) due to a transient cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery. Global cerebral hypoperfusion, determined by cardiac output and/or total peripheral resistance decrease, represents the final mechanism of all forms of syncope (cardiac, reflex and due to orthostatic hypotension). Syncopal-TLOC has been always referred to an "extra-cranic" mechanism triggering by a decrease in cardiac output and/or total peripheral resistance. However, a syncope-related "intracranic" mechanism, determining an alteration of brain "perfusion pressure", has been never reported. We hereby report on a case of recurrent syncope associated with IIHWOP, showing the abrupt and sustained remission of syncope and headache after lumbar puncture with cerebrospinal fluid (CSF) subtraction.
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EARLY-ONSET CEREBRAL AMYLOID ANGIOPATHY FIVE DECADES AFTER A CADAVERIC DURA MATER GRAFT: A CASE REPORT

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Cerebral amyloid angiopathy (CAA) is characterized by misfolded amyloid β-peptide deposits within small-sized blood vessels of the brain and leptomeninges. CAA is an important cause of lobar intracerebral haemorrhage in the elderly. Moreover, CAA is associated with ischemic cerebrovascular events, inflammatory leukoencephalopathy and cognitive impairment. Early-onset CAA has been rarely described in patients with a history of human cadaveric pituitary hormone's treatment and neurosurgical procedures in early life, several years before the neurological symptoms' onset. In those patients, a human-to-human amyloid transmission was postulated. We report a case of lobar haemorrhagic stroke in a 51-year-old woman with unremarkable previous medical and family history, except for a neurosurgical procedure with cadaveric dura mater graft at the age of two years. A complete clinical and neuro-radiological assessment didn't allow to find a clear causative process; therefore, a cerebral biopsy was obtained. The neuropathological examination showed severe cerebral amyloid angiopathy in many leptomeningeal and cortical

vessels, appearing as thickening of the wall laden by amorphous material, with yellow fluorescence after thioflavines and Aβ immunoreactivity. Immunohistochemistry also revealed the presence of rare parenchymal Aβ deposits, while tau pathology was absent. Our report increases the number of patients with early-onset iatrogenic amyloid-beta-related CAA. In our opinion, a systematic monitoring of individuals who have had neurosurgical procedures in early life, especially involving cadaveric dural grafts, is mandatory.

TACROLIMUS-INDUCED NEUROTOXICITY: A CASE OF "MUTISM" WITH CONSISTENT BRAIN MRI ABNORMALITIES

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Introduction: Tacrolimus is a calcineurin inhibitor widely used as immunosuppressant to prevent rejection after solid organ transplantation. Tacrolimus-induced neurotoxicity is a heterogeneous entity encompassing a spectrum of manifestations like encephalopathies, seizures, psychiatric symptoms, visual deficits [1]. A very rare but serious adverse event of tacrolimus is "akinetic mutism", a clinical syndrome characterized by the inability to produce voluntary movements or speech without any loss of awareness [2].

Case description: We report the case of a 42-year-old woman who underwent an orthotopic liver transplantation and was treated with intravenous methylprednisolone, mycophenolate mofetil, and tacrolimus. She had an uneventful postoperative course until day 6 after surgery, when she suddenly developed difficulties speaking, leading to anarthria, and swallowing. Two CT scans, one in the acute phase and the second after 24 hours from the symptom's onset, were negative. Metabolic work-up and lumbar puncture - that included infective and autoimmune screening – were negative. Electroencephalogram only showed a global slowing, without focal or epileptiform abnormalities. A brain MRI showed a DWI and FLAIR signal hyperintensity in the bilateral precentral inferior cortex, consistent with the neurological symptom presented by the patient. Although tacrolimus blood levels were within the therapeutic range, assuming a possible drug-induced neurotoxicity, tacrolimus was substituted by everolimus. Unfortunately, the patient only partially improved: at a two-month follow-up from the discharge, she still has difficulties swallowing and speaking, and she mainly uses nonverbal tools to communicate.

Discussion: Akinetic mutism is a rare disorder characterized by a loss of speech and sometimes slowed body movements, with maintained levels of alertness. Possible etiologies include cerebrovascular events, tumours, and medications including calcineurin inhibitors. Diagnosis is clinical, and brain MRI is generally normal or – rarely – it shows diffuse and nonspecific leukoencephalopathy. According to our knowledge, this is the first described case in which brain MRI demonstrated a bilateral lesion consistent with the neurological symptom. In medication-induced akinetic mutism, treatment involves drug withdrawal; generally, an early recognition of the syndrome and a prompt drug substitution lead to a complete recovery, although it was not the case in our patient.
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THE ANTI CD-20 AND STEROID THERAPY IN CLIPPERS DISEASE

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Background and aims: Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a rare CNS inflammatory syndrome. Steroid treatment is effective in treating the inflammatory component of the disease, but long-term treatment of CLIPPERS with steroids is limited by side effects. Steroid withdrawal is associated with recrudescence of the disease, and each relapse is associated with additional disability. Moderately efficacious steroid-sparing treatments include rituximab (mouse chimeric anti-CD20 monoclonal antibody). Anti-CD20 molecules benefit several antibody-mediated CNS inflammatory diseases. Herein, we describe a case of CLIPPERS successfully treated over the course of 2 years.

Methods: A 67-year-old patient presented with subacute development with rapidly worsening course of ideo-motor slowing and difficulty in speech. Encephalic MRI showed altered periventricular white matter signal, and numerous bulbo-pontine and cerebellar punctate lesions, with modicum of contrast-enhancement in some of these. In CSF, absence of oligoclonal bands and negative screening for tumor-like lesions. The patient started dexamethasone 2 mg therapy and after 3 months was given Rituximab 1000 mg ev every 6 months for 2 cycles, followed by long steroid tapering with significant clinical improvement. After 5 months, the patient had clinical and radiological worsening with a severe increase in the number and size of areas already reported with mdc enhancement; contemporary lymphocyte count showed B cell control below 2%. Corticosteroid therapy was started again, low dosage of oral prednisone, for another 6 months continuing the administration of Rituximab 1000 mg ev; after one year from onset, the steroid therapy was stopped without new clinical improvement up to stabilization.

Results and Conclusions: Our case confirm how in the Clippers disease both there is a high sensitivity to steroid therapy and the prevalent reactive cellular share is of B lymphocytes. Considering the time of onset of biological activity by anti-CD20 drugs, the most appropriate strategy in our opinion is to start with a steroids and anti-CD20 combined inductive therapy and, after at least 6 months of therapy, a slow and gradual reduction of steroid treatment. In our case, using this therapeutic combination, the clinical picture remained stable 2 years after the onset with the last year only an anti-CD20 treatment without steroid treatment. Furthermore our case adds to other scientific evidence in which the efficacy of long-term anti-C20 treatment in Clippers emerges.
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NEUROLOGICAL INVOLVEMENT IN MAINZER-SALDINO SYNDROME

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Objective: Mainzer-Saldino syndrome (MSS) is an ultrarare autosomal recessive ciliopathy characterized by skeletal abnormalities, chronic kidney disease, and retinal dystrophy. Occasional features include hepatic fibrosis and cerebellar ataxia, but until now there are no reported cases of neurologic comorbidities. We report the case of a 24-year-old woman affected by MSS presenting with relapsing-remitting multiple sclerosis.

Materials: The patient was diagnosed with MSS at the age of 14 years and harbored the mutation in the Intraflagellar Transport 172 (IFT172) gene. Her non-consanguineous parents were wild-type, whereas her asymptomatic sister carried the same mutation. She had autoimmune duttopenic liver disease, retinal dystrophy, and polycystic ovary syndrome. At the age of 16 years, she underwent kidney transplantation due to end stage renal failure; prednisone and tacrolimus were started. Since 2019, she experienced several intermittent episodes of vision blurring of the right eye, followed by episodes on urge incontinence, numbness and tingling in the cervical region and hands.

Methods: Case Study.

Results: Neurological examination showed visual field concentric reduction, horizontal nystagmus and mild spasticity of upper and lower left limbs with hyperreflexia. No strength deficits were found, cutaneous plantar reflex was flexor. Body mass index (BMI) was 36.2. Brain MRI showed multiple juxtacortical and subcortical white matter lesions, one of which with gadolinium enhancement. Intrathecal synthesis of oligoclonal IgG were found.

Discussion: Multimeric IFT complex regulate the assembly, maintenance, and functioning of cilia, which is also involved in a range of fundamental biological processes including cerebral morphogenesis through the regulation of neural progenitor proliferation and neuron radial migration. Both neurons and glia express cilia, whose impairment results in a wide spectrum of disorders known as neurociliopathies. IFT components are also expressed in non-ciliated cells, such as lymphocytes, and can regulate immune synapse assembly.

Conclusion: Even though neurociliopathies are pleiotropic disorders, this is the first case of Mainzer-Saldino syndrome complicated with multiple sclerosis. Whether this association is causal or share common pathophysiological mechanisms remain speculative.

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PROGRESSIVE COGNITIVE DECLINE IN AN ATYPICAL NEURO-SJOGREN'S SYNDROME: A CASE REPORT

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Objectives: To describe a subacute multidomain cognitive impairment in a case of Neuro-Sjogren's Syndrome (N-SS) with a central nervous system (CNS) presentation.

Materials and Methods: A 51-year-old female was admitted to our Emergency Unit for an acute onset cerebellar syndrome (nausea, vomiting, subjective dizziness, and gait instability) and cranial nerve paralysis (ageusia, right hemifacial hypoesthesia).

Results: Vital signs were normal. Past medical and family history was unremarkable. Neurological examination showed anisocoria (right> left), horizontal and up-beating gaze evoked nystagmus, hypoesthesia in the right V territory, right central VII cranial nerve paralysis, left side limbs and gait ataxia requiring bilateral support. Brain MRI showed a left T2-hyperintense, T1-hypointense, DWI restricted ponto-cerebellar area, involving the superior and medium cerebellar peduncles, showing ring-enhancement and mass effect. Infectious, paraneoplastic, and neoplastic etiologies were excluded by blood and CSF analysis. She was treated with antibiotics without benefit, and a high-dose iv methylprednisolone course with partial remission. One month later, she complained of emotional lability and disinhibition. In the ensuing months, motor deficits improved, with a residual mild ataxic syndrome and Holmes tremor, while cognitive functions subacutely deteriorated. Neuropsychological tests showed a multidomain cognitive impairment, mainly in frontal functions. Follow-up brain MRI showed the disappearance of the ponto-cerebellar lesion but the appearance of a left hypertrophic olivary degeneration. No new or enlarged frontal lesions were detected. During follow-up serology for markers of autoimmune and paraneoplastic syndromes were repeated and high titer SSA/RoA and SSB/La were detected. Schirmer test was borderline. Salivary gland ultrasound was normal. Salivary gland biopsy and 18-FDG brain PET have been planned.

Discussion: Our patient showed a peculiar clinical and neuroradiological presentation of N-SS with acute brainstem onset followed by progressive cognitive impairment. CNS involvement is common in N-SS, usually depicted as brain fog. Brain lesions usually show a multiple sclerosis-like pattern. In our case the degree of cognitive impairment was greater than the usual mild involvement of attention, short-term or long-term memory as well as executive and visuospatial domains.

Conclusions: Cognitive impairment in patients with N-SS can result from a multifactorial process disrupting pathways rather than related to structural damage in specific brain areas. Further studies are needed to better investigate the spectrum of involved cognitive domains. Neuropsychological testing should be routinely performed in these patients, during the disease course and treatment, to objectively demonstrate treatment efficacy on progression.

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A RARE CASE OF BOW HUNTER'S SYNDROME: A DYNAMIC VERTEBRAL ARTERY OCCLUSION DURING NECK EXTENSION

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Objective: Bow Hunter's syndrome (BHS) is a rare cause of dynamic vertebrobasilar insufficiency (VBI) [1]. It is usually caused by extrinsic compression of vertebral arteries during neck rotational movements, but in a few cases it can also occurs after head extension [2], like the case we presented.

Materials and Methods: We reported the case of a 74 year-old man hospitalized because of epigastric pain, drop-attack, lipothymic symptoms, diaphoresis and dizziness triggered by head movements. After a first cardiologic evaluation, excluding critical coronary artery stenosis and acute heart diseases, he was brought to the attention of the neurologist.

Results: After neurological examination, an electroencephalogram was performed, resulting negative for epileptic abnormalities. The carotid duplex ultrasound showed a dynamic occlusion of the left vertebral artery in hyperextension and in upright position, confirmed by cerebral angiography (DSA). The dynamic flow obstruction was caused by C5-C6 arthritic degeneration and instability, as shown by MRI and CT. After a multidisciplinary discussion, BHS was diagnosed and the neurosurgical approach was identified as the most appropriate treatment. The patient was subjected to spinal surgery with discectomy. A complete regression of symptoms and of angiographic and ultrasonographic abnormalities was obtained.

Discussion: This clinical case stresses the importance of investigating for BHS in adult patients, especially males, aged 50–70 years, with symptoms suggestive of VBI elicited by head movements. High clinical suspicion is necessary for the correct execution of routine examinations (US, CT and MRI). DSA is the gold standard for the diagnosis. Conservative, surgical or endovascular treatment could be considered on a case-by-case basis.

Conclusion: BHS represents an uncommon cause of VBI, which should be investigated by an appropriate diagnostic process, on the basis of the clinical presentation.

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DRESSING APRAXIA: A LONG TIME ISOLATED SYMPTOM IN A PATIENT WITH ALZHEIMER'S DISEASE

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Background and Aims: Dressing apraxia is defined as the condition in which voluntary capacity for daily dressing and the perception of correct body relationships are lost. Uncommonly, it has been reported as an onset manifestation of Alzheimer's disease (AD) even among the atypical forms.

Methods: A 80-year-old right handed woman, family-run-business employee came to medical attention with a 1-year history of progressive difficulties in dressing, in absence of motor disturbances. In particular, she complained about difficulty in handling buttons and arranging her clothing articles on her body without an impairment of instrumental and daily living activities. She underwent a clinical-neuropsychological assessment and cerebrospinal fluid (CSF) biomarkers of AD.

Results: Beyond a primary dressing apraxia, difficulties in exploring tactile and somato-sensory stimulus in personal space, simultanagnosia and ideomotor and constructive praxis deficits both to an ecological and neuropsychological evaluation emerged. The neurological examination disclosed mild extrapyramidal signs and TC scan revealed left asymmetric enlargement of the subarachnoid spaces. CSF analysis supported Alzheimer's disease pathology.

Conclusions: Within the heterogeneity of the onset manifestations in AD's atypical variants known to date, we described a peculiar case where dressing apraxia occurs as an initial and isolated symptom for a long time.

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DIAGNOSTIC CHALLENGES IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS POLYNEUROPATHY: A CASE REPORT

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Hereditary transthyretin amyloidosis (ATTR) is a rare cause of polyneuropathy involving peripheral sensorimotor and/or autonomic systems. Although red flags have been previously proposed to unravel this latter disease, the diagnosis of ATTR polyneuropathy (ATTR-PN) remains challenging for clinicians, particularly in the late-onset ATTRv-PN phenotype. Herein we reported a case of ATTR-PN, whose diagnosis was delayed by several confounding factors which typically affect elderly patients. A 75-years-old male was admitted to the Neurological Department with an 18-months history of lower limbs-paresthesia with tingling pain in the feet, progressively severe gait ataxia, and erectile dysfunction. The family history reported a brother who suffered from rapidly progressive sensory-motor polyneuropathy leading to death within 24 months from the onset of symptoms. The medical history of the patients was positive for hypertension and diabetes. The first neurological examination revealed mild/severe paraparesis of the lower limbs (MRC=3-4/5), overall absence of deep tendon reflexes, distal and symmetrical anesthesia of the hands and feet. During hospitalization, serum antigangliosides, oncomarkers, cerebrospinal fluid analysis (CSF), and neurophysiological tests were performed. Furthermore, a TC total body was performed to exclude a paraneoplastic etiology of the neuropathy. Serum and CSF analyses were negative. TC total body revealed the presence of an oval formation at the level of the uncinate process of the pancreas suspected of neuroendocrine tumor. Neurophysiological exams

revealed a sensory-motor severe axonal polyneuropathy in proximal and distal muscles of the upper and lower limbs. Notwithstanding the ubiquitous reduced sensory-motor amplitude in the neurophysiological study, motor distal latencies of bilateral median nerves were increased, suggesting a bilateral carpal tunnel syndrome. Based on this latter result and on the family history positive for a case of polyneuropathy with similar clinical and neurophysiological patterns, genetic test for hereditary ATTR was performed. The test revealed the Val30Met mutation of transthyretin. Herein we reported a case of patients suffering from rapidly progressive axonal sensory-motor polyneuropathy. During the hospitalization, at least two etiopathogenetic causes of polyneuropathy have arisen, as diabetic or paraneoplastic neuropathy. The family history positive for a similar polyneuropathy and the evidence of anamnestic and clinical red flags (e.g. erectile dysfunction and bilateral tunnel carpal syndrome), have led the clinicians to suspect ATTR-PN. However, the absence of documented family history occurs in 33%-100% of hereditary ATTR-PN, particularly in non-endemic areas. Distinguish between idiopathic and genetic neuropathies is challenging but important to improve screening tests and treatment strategies, available for this type of genetic neuropathy.

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SEIZURES AND WALDMANN'S DISEASE: DIRECT CORRELATION OR UNFORTUNATE COINCIDENCE?

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Background: Severe electrolyte disturbances can cause acute symptomatic seizures (ASSs) when documented within 24h by laboratory tests. Even though ASSs do not imply an enduring predisposition to develop seizures, they may reappear if the underlying electrolyte disturbance recurs. Hypocalcemia and hypomagnesemia are some of the main characteristics of Waldmann's disease (WD), a rare protein-losing enteropathy associated with intestinal malabsorption. To date, the association between WD and seizures has been poorly reported. Here we describe the case of a patient suffering from WD who experienced seizures in a picture of electrolyte disturbances and structural brain alterations.

Case report: The patient is a 33-year-old Caucasian male with intellectual disability. No familial history of neurological or genetic disorders was reported. His personal history included self-limiting febrile seizures. After the diagnosis of WD in 2019 based on clinical/laboratoristic evidence of intestinal malabsorption and bioptic confirmation of lymphangiectasia, he periodically underwent intravenous implementation of calcium and magnesium. In 2021 he experienced a focal-onset (head version to the left) to bilateral tonic-clonic seizure. After another seizure with the same semeiology few days later, the patient referred to ER where severe hypocalcemia (5.3 mg/dl, n.r. 8.5-10.2 mg/dl) and hypomagnesemia (1.6 mg/dl, n.r. 1.8-2.2 mg/dl) were detected. CT scan was unremarkable. Admitted to Neurology department, calcium and magnesium implementation was immediately adminestered. EEG showed high-voltage sharp-waves and sharps in right fronto-temporal regions and brain MRI revealed T2/FLAIR hyperintense areas in the right centrum semiovale and the homolateral subcortical white matter identified as neuroepithelial cysts. Also a dysmorphic aspect of both temporal ventricles was detected. During hospital stay, levetiracetam 1000mg/day was started. One year later the patient came to our attention at the Epilepsy Centre of Policlinico of Bari without reporting other seizures. He was still taking levetiracetam 1000mg/day and periodically underwent intravenous implementation therapy.

Discussion: This case report underlines the difficult decision-making process the clinician has to do when a seizure occurs in the emergency context. The presence of severe electrolyte disturbances, as in the case of our patient, supports the hypothesis of acute symptomatic seizures. Nevertheless, the presence of brain structural alterations could probably justify the administration of anti-seizure therapy due to the potential risk of seizure recurrence.

Conclusion: Considering that WD may predispose to frequent electrolyte disturbances increasing the risk of ASSs, is the supplementation therapy sufficient to prevent seizures or anti-seizure treatment may represent an additional measure of prevention especially in the context of coexisting potentially epileptogenic structural brain lesions?

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BROWN-VIALETTO-VAN LAERE SYNDROME: TWO CASES WITH A DIFFERENT CLINICAL COURSE

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Objective: Brown-Vialetto-Van Laere Syndrome (BVVLS) is a rare inherited neurometabolic disorder characterized by progressive pontobulbar palsy associated with sensorineural deafness and respiratory insufficiency [1]. Riboflavin transporter deficiency has recently been described as causative of the disease, due to the mutations in one of the genes (SLC52A1-3) involved in the riboflavin carrier-mediated system [2].

Subjects: We describe two female cases of BVVLS of 25-years-old and 57-years-old respectively with the same gene mutation, but with different timelines of treatment and clinical course.

Methods: The patients were evaluated with a complete neurological examination, blood tests, spirometry and nocturnal oximetry, annually. Both cases were genetically tested showing mutations in a compound heterozygosity of the C20orf54/hRFT2 gene in the first case, and in heterozygosity of the C20orf54 in the second case.

Results: In the first patient, clinical onset was characterized by sensorineural deafness at 10 years, followed by dysarthria, mild dysphonia, facial diplegia, hypotrophic left deviated tongue with fasciculation; respiratory muscles were spared. The diagnosis was made 3 years later, and high-dose riboflavin supplementation was started. After the introduction of the treatment, neurological and respiratory clinical stability was observed. The clinical onset of the second patient occurred at 43 years with sensorineural deafness, dysarthria, dysphonia, bilateral laryngeal deficit, progressive ascending hands hyposthenia, bilateral foot-drop and a progressive dyspnea and dysphagia in the following 2.5 years, resulting in the need for mechanical ventilation and enteral nutrition through stomia. Conversely to the first case, the second patient initiated the riboflavin

supplementation with a delay of 4 years from the diagnosis and 7 years later from the onset of symptoms, resulting only in a mild improvement in dysphagia and hyposthenia, while the remaining symptoms were stable.

Discussion: Riboflavin acts as a precursor of flavocofactors, involved in redox metabolic reactions in mitochondria. Reduced riboflavin transport, resulting in oxidative stress, may contribute to neurodegeneration [2]. We described two cases with different neurological clinical progression, where the greater clinical severity of the second patient could depend on: (1) the different genetic mutations involved; (2) the more severe clinical onset with respiratory insufficiency and hyposthenia; (3) the more delayed introduction of the riboflavin supplementation. Riboflavin supplementation results in clinical stabilization of both, suggesting that timely diagnosis and treatment is important to avoid irreversible neurological damage.

Conclusion: BVVLS is a rare neurometabolic disease in which an early genetic and clinical diagnosis is essential in order to treat it promptly.

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OPSOCLONUS-MYOCLONUS SYNDROME (OMS) ASSOCIATED WITH ANTI-HU ANTIBODIES: A CASE REPORT AND REVIEW OF THE LITERATURE

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Objective: Opsoclonus-myoclonus-ataxia syndrome is a high-risk phenotype of paraneoplastic neurologic syndrome (PNS), characterized by involuntary, multidirectional saccadic movements, non-rhythmic action myoclonus, frequently associated to cerebellar signs [1]. Paraneoplastic form derives from an immune-mediated reaction triggered by a remote cancer and may be associated with different antibodies [2].

Subjects: We describe the case of an otherwise healthy 29-year-old male patient admitted to our institution with opsoclonus-myoclonus-ataxia syndrome and we review the literature regarding OMS associated with anti-Hu antibodies.

Methods: Laboratory tests, electrophysiological studies, radiological and functional imaging, study of the gastroenterological tract with biopsy, haematological and dermatological examination were performed. Further, the patient underwent revision surgery of the mediastinic cavity. A literature search on PUBMED and COCHRANE LIBRARY was also provided, and a brief narrative review of findings was compiled.

Results: Clinical onset was characterized by progressive cerebellar trunk ataxia developed over the last two months, associated with oscillopsia and multidirectional nystagmus. Subsequently, episodic non-rhythmic palatal myoclonus, sleep disorders (akathisia and episodic myoclonus of the lower limbs) and involvement of peripheral nervous system with diplopia, ptosis and sensitive polyneuropathy emerged. Diagnostic examinations were performed: CSF analysis showed high titre of anti-Hu antibodies, also positive on serum; total body PET-FDG showed the presence of thymic residue. All remaining investigations were negative. Mediastinic cavity revision surgery revealed thymic hyperplasia. Therapy with IGIV was performed without benefit, followed by high-dose steroid treatment with partial improvement in symptoms and relapse after discontinuation.

Discussion: We described a case with anti-Hu seropositive PNS with the following peculiar features: (1) no clear evidence of active cancer, despite extended diagnostic tests; (2) onset of the syndrome in young age, while OMS is usually associated with neuroblastomas in children or SCLC in older adults; (3) remittent/relapsing course of the disease and its therapeutic implications; (4) idiopathic and infectious causes of OMS were excluded. Anti-Hu antibodies (ANNA-1) are high-risk onconeural antibodies directed to intracellular antigens associated with PNSs; they may present with sensory-motor polyneuropathy, cerebellar syndrome, OMS or non-specific neurological signs [1]. In adults the main cancer associated to PNS and notably to anti-Hu antibodies is the Small Cell Lung Carcinoma (SCLC). However, according to present literature, PNS and autoimmune lab findings can precede the detection of cancer by years [3].

Conclusion: This case report and literature review on anti-Hu seropositive OMS emphasize the importance of a strict follow-up in order to define a definitive diagnosis and aggressive treatment.

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INTRA-CAROTID INJECTION OF ALPRAZOLAM: AN UNUSUAL CAUSE OF UNILATERAL MULTIEMBOLIC STROKE OF UNDETERMINED SOURCE (ESUS)

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Objectives: To present a peculiar case of embolic stroke associated with self-administered intra-carotid injection of alprazolam.

Material: A 45-year-old woman with a past medical history of unipolar depression and eating disorder was admitted due to left-sided hemiplegia. She declared alprazolam abuse as a sleep inducer. The night before the admission in the Stroke Unit the patient reported right frontotemporal headache and loss of consciousness. The day after, during consciousness regaining, she showed clinical features of hemispheric syndrome including left-sided hemiplegia, hemisensory loss, left hemineglect and homonymous hemianopsia (NIHSS = 11).

Methods: Case report.

Result: MRI revealed multiple lesions in the contest of the right hemisphere scattered throughout the occipital calcarine, frontal, temporal and insular cortex, as well as thalamus and “neostriatum” but strictly limited to the right internal carotid artery territory (fetal-type posterior cerebral artery was observed in a previous CT scan). Main etiologies were ruled out (no cardiac sources of embolism, no sign of large artery atherosclerosis, intra-extracranial artery disease or autoimmune / prothrombotic disorders). Detailed inquiring, in search of a reasonable explanation of the unilateral source of multiple emboli, permitted to ascertain that, the month before the current admission, she had been evaluated in the Emergency Department for neck swelling due to injection of alprazolam on the right aspect of the neck. Although the patient initially denied drug injection into the neck, she finally admitted that just before the onset of the clinical syndrome she had injected alprazolam in the right carotid artery because of the “urgent need to sleep”. She was treated with

acetylsalicylic acid (100 mg/day) and was discharged on day 14 with complete recovery (NIHSS = 0).

Discussion: While other cases of embolic stroke after intra-carotid injection of buprenorphine were previously described [1;2], no other cases of cerebral ischemia due to intra-arterial injection of benzodiazepines were reported so far. In the present case, both embolism due to alprazolam solution (which includes ethyl alcohol and propylene glycol, being not indicated for intravenous administration) or concomitant gas embolism could be the etiologic mechanism of the reported stroke.
Conclusion: Intra-carotid injection of alprazolam is a possible cause of unilateral multiembolic stroke of undetermined source (ESUS). This case emphasizes the importance of collecting a detailed medical history and should aware clinicians about the possibility of an exogenous mechanism underling unilateral multiple ischemic cerebral lesions, even in patients who are not known to be parenteral drug users.
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RECURRENT STROKE MIMIC FLAIR-HYPERINTENSE LESIONS IN ANTI-MOG-ASSOCIATED ENCEPHALITIS WITH SEIZURES (FLAMES): THE FIRST ITALIAN CASE AND A REVIEW OF LITERATURE

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Background and aims: Flair hyperintense lesions in anti-MOG-associated encephalitis with seizures (FLAMES) is a novel entity in the spectrum of MOG antibody associated disorders (MOGAD). We report a case of recurrent FLAMES syndrome which is, to the best of our knowledge, the first Italian case, and we revise the literature.

Materials and Methods: We describe the case of a 40-year-old man with a 12-year history of alcohol and cocaine abuse. In November 2019 he was admitted to the emergency department for right hemiplegia and ipsilateral myoclonus. Brain MRI revealed two FLAIR-hyperintense lesions without gadolinium enhancement situated in the left precentral gyrus and posterior limb of the internal capsule. Patent foramen ovale was found and the patient was discharged with the diagnosis of ischemic stroke. In December 2021 he was hospitalized again for left hemiparesis. Brain MRI revealed a new FLAIR/DWI hyperintensity on the right precentral gyrus, while the previous lesions had disappeared. The patient was discharged with the diagnosis of ischemic stroke relapse and PFO surgery was suggested. Twenty days later he was admitted again because of continuous left facio-brachio-crural myoclonic jerks.

Results: Electroencephalogram showed polispikes and waves on the right central region and contralateral diffusion, clinically determining facio-brachio-crural myoclonus and independent lateralized periodic discharges at 2 Hz in the right fronto-central region, synchronous with clonus of the first left interosseus muscle consistent with multi-drug resistant epilepsia partialis continua. A lumbar puncture detected more than 6 oligoclonal bands restricted to CSF. Serum positivity for anti-MOG IgG1 antibodies on cell-based assay (titer 1:320) was detected. After an intravenous methylprednisolone bolus and five sessions of plasma exchange, MRI showed resolution of the lesion, and EEG a reduction of epileptic abnormalities, associated with improvement of epilepsia partialis continua. Left limbs myoclonic jerks, however, persisted.

Discussion: FLAMES is a rare entity in the MOGAD spectrum, characterized by FLAIR unilateral cortical hyperintensities, seizures, fever, headache, and serum positivity of anti-MOG antibodies. Anatomically, our case is characterized by recurrent side-shifting cortical and subcortical involvement. Clinically, the most peculiar features are epilepsia partialis continua, so far described in one case only, and a stroke-mimic onset. Usually, the disease is monophasic with encephalopathic features and shows a good response to corticosteroid therapy.
Conclusions: Anti-MOG disorders can present with a wide spectrum of phenotypes, including the recently described FLAMES. We broaden the knowledge about this rare condition, underlying the importance of an early diagnosis for prompt treatment.
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ACUTE ONSET OF PARANODOPATHY ASSOCIATED WITH ANTI-CASPR1 ANTIBODIES AND PROMINENT CRANIAL NERVES INVOLVEMENT

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Introduction: In the last decade, there has been a growing interest in autoimmune nodo-paranodopathies. The prevalence of antibodies to specialized perinodal domains of myelinated axons is about 5.5% in the Italian Chronic Inflammatory Demyelinating Polyneuropathies (CIDP) cohort [1].

Methods: A 38-year-old man was admitted to our Hospital for subacute-acute onset of distal numbness and proximal weakness (MRC sum score 54, Guillain- Barré Syndrome Disability Score (GBS-DS) 2). CSF analysis disclosed a slight increase in protein levels (0.54 g/L). Nerve conduction study (NCS), performed 2 weeks from symptoms onset, was unremarkable except for absent H-reflex recorded from soleus muscles. Assuming a diagnosis of "early" GBS, the patient was treated with intravenous immunoglobulin (IVIg) and discharged after few days. Three weeks later, he was readmitted to our Neurology Unit for progressive clinical motor deterioration (MRC sum score 36, GBS Disability Score 4), gait ataxia, stocking-glove pain, and cranial nerve involvement (facial diparesis and horizontal diplopia). CSF protein level further increased (3,4 g/L), NCS at 37 days from clinical onset, showed only a mild increase in the F-wave and distal motor latencies. A cervical MRI showed a mild hyperintensity in cervical roots. Onco-neural antibodies research turned out negative, autoimmune screening test and PET-TC were normal. Patient disclosed only a modest clinical response to plasma exchange

treatment (MRC sum score from 36 to 38), so that immunosuppressive treatment with Rituximab (RTX) was started.

Results: NCS performed at 2 months from symptoms onset showed demyelinating features; clinical course together with neurophysiology (EFNS/PNS criteria [2]) were consistent with a diagnosis of CIDP. Ultrasonography disclosed cervical roots and nerves enlargements with increased CSA. Additional investigations, including serum analysis for paranode antibodies, turned out negative for CNTN1 and positive for Caspr1/CNTN1 complex. Sural nerve biopsy showed mild axonal loss, rare demyelinating features localized to paraonde and no inflammatory infiltrates. After Rituximab 2 g, the patient showed a strong and constant clinical motor and sensory improvement: MRC sums core 48 and 56, GBS Disability Score 3 and 1, at one and three months, respectively, after RTX.

Conclusions: Very few cases of paranodopathy associated to Caspr1 antibodies are reported in literature [3]. Ongoing sensory-motor demyelinating neuropathy associated with severe cranial nerves involvement, pain and gait ataxia, with scarce response to IVIg, should direct to a diagnosis of paranodopathy associated with anti-Caspr1 antibodies.

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"PSYCHICALLY BLIND OF HER BLINDNESS": A COMPREHENSIVE EVALUATION OF A CASE REPORT OF ANTON'S SYNDROME

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Background: Anosognosia [1], or loss of awareness of a neurological deficit, is an impressive syndrome serving as window into consciousness. It sometimes complicates an unequivocal brain insult, most often a stroke, and can occur in a plethora of neurological impairments, with different degrees of symptoms, from lack of complaint to delusions, and various temporal features, i.e. quick recovery, persistence for years or permanence. In Anton's Syndrome (AS) [2], or anosognosia for cortical blindness, patients are completely blind at neurological assessment, but disregard or persistently deny any visual loss; hallucinate or confabulate to explain away any possible evidence of their failure; and act as though vision is intact, despite all evidence to the contrary. In the case discussed herein, I.G. a 79-year-old female with mild motor aphasia undergone to fibrinolysis, who developed within 24hours bilateral temporo-occipital hemorrhagic infarction that complicated at 48hours with abrupt transient AS, lasted for about 2days.

Materials and Methods: Comprehensive assessment was performed when AS occurred, hence closely monitored in the following days.

Results: The neurological examination showed, in preserved personal-spatio-temporal orientation and short/long term memory, the loss of all visual sensations, perception of stimuli in movement, and menace reflex, a pattern of I grade hypertensive retinal angiopathy at fundoscopic examination, and preservation of pupillary reflexes and ocular movements. Structured Awareness Interview adapted for AS evidenced maximum degree of anosognosia (3/3) with confabulation, although intact visual imagery. Non-contrast brain CT demonstrated hemorrhagic bilateral temporo-occipital lesions (R35x25 mm, L25x15mm) exerting mass effect on posterior horns of lateral ventricles, beyond a posterior parafalcial tentorial-subtentorial blood flap, and bilateral, but major right, temporal subarachnoid hemorrhage. Electroencephalogram confirmed the two lesional focalities (slow theta-band oscillations) in the temporo-occipital region of each side, with a modest presence of epileptiform elements to the right one. Electroretinogram was normal. Visual evoked potentials showed a suggestive pattern of bilateral visual cortex involvement, major at right (R:P100, 131.10 ms; P100, 114.50 ms. L:P100, 110,11 ms; P100,127.93 ms). In the following days, the patient began to gradually recover both visual deficit and awareness of it.

Conclusions: AS is a rare and fascinating complication of cortical blindness, whose rehabilitation is fundamental for the patient's good recovery. Its underlying pathophysiological mechanisms are still not entirely clear, but undoubtedly worthy for the study of the correlates of visual awareness.

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A CASE OF EARLY DISEASE REBOUND AFTER FINGOLIMOD DISCONTINUATION IN A PATIENT WITH MULTIPLE SCLEROSIS AND SARS-COV-2 INFECTION

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Background: Fingolimod is approved in Italy as a second-line therapy for Relapsing-Remittent Multiple Sclerosis (RRMS). Its withdrawal may increase the risk of relapses that typically occur after a long hiatus after drug discontinuation and usually require high dosages of intravenous steroids to be controlled. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can affects both Central and Peripheral Nervous System. Like other viruses, it can be a trigger for MS relapses. Here, we describe a case of rebound after Fingolimod discontinuation during a SARS-CoV-2 infection that interestingly appeared soon after drug discontinuation and that was effectively controlled with low dosages of oral steroids. We speculate possible mechanisms underlying this atypical course of disease rebound and postulate whether SARS-CoV-2 infection might have contributed or even caused the disease relapse.

Case report: On November 2020, a 44-years-old male with RRMS developed a mild SARS-CoV-2 infection and autonomously discontinued Fingolimod for 10 days. A scheduled MRI performed 1 month later showed a voluminous demyelinating lesion in the supratentorial white matter, with contrast enhancement. However, the patient did not present new neurological signs, so he was treated with oral steroids for few days. After 3 months, a cerebral MRI highlighted a marked dimensional reduction of the lesion with no longer appreciable contrast enhancement.

Discussion: Since radiological relapse appeared soon after drug discontinuation, a contribution of SARS-CoV-2 infection in relapse occurrence may be postulated. Indeed, as SARS-CoV-2 may cause several neurological manifestations, also acting as a trigger for new onset or flares of many immunological disease, it is unclear whether our patient's relapse was due to drug discontinuation, to covid19 infection or maybe to an additional effect of both. Moreover, the disease rebound was effectively controlled by low dosage of oral steroids, in contrast to what usually

happens with drug withdrawal-related disease rebound that need high dosage of intravenous steroids to be controlled.

Conclusions: The decision to continue or suspend a DMT during a SARS-CoV-2 infection must be individualized, but in presence of mild symptoms drug discontinuation is not recommended. Fingolimod does not seem to expose to a risk of a more severe SARS-CoV-2 infection, but the risk of aggressive rebound after discontinuation may exceed the risk of infection. In our patient is not surely defined whether the relapse was related to drug withdrawal, to SARS-CoV-2 infection, or maybe to both. However, immunization against SARS-CoV-2 should be recommended for individuals with MS.

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THE CHALLENGE OF IDENTIFY PSYCHOGENIC NON-EPILEPTIC SEIZURES (PNES) IN PATIENTS WITH DEFINED DRUG-RESISTANT EPILEPSY: A CASE REPORT

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Introduction: Epilepsy and psychogenic nonepileptic seizures (PNES) can coexist, often arousing diagnostic and therapeutic challenges.

Case presentation: We report the case of a 40-year-old man affected by drug-resistant epilepsy secondary to schizencephaly, a rare brain congenital malformation defined as a gray matter-lined cleft extending from the pial surface to the ventricle; the spectrum of cleavage ranges from a thread of cerebrospinal fluid connecting the subarachnoid space to the ventricle, which is encircled by dysplastic gray matter ("closed-lip schizencephaly"), to a wide communication ("open-lip schizencephaly").[1] In the last years the focal seizures presented by the patient were well controlled by triple antiepileptic drug therapy (valproic acid, levetiracetam, lamotrigine), while his psychiatric comorbidity progressively worsened and required the intake of risperidone. The patient came to our attention because he suffered multiple daily episodes, never experienced before, characterized by the emission of guttural sound followed by alteration of the state of consciousness and involuntary movements of the face (blinking of the eyelids, buccal movements), lasting about 30-60 seconds, which resolved spontaneously. Hence, the patient was admitted to our neurological ward to be monitored with continuous video-EEG. Serum concentration of antiepileptic drugs were in the therapeutic range. His routine interictal EEG recorded the presence of a moderate amount of short sequences of spikes and spikes-and-wave at the right frontal-center-parietal electrodes, showing spatial correlation with the cleft. During video-EEG monitoring the patient presented some episodes of suspension of the state of consciousness with buccal automatisms and involuntary eye movements, preceded by the emission of vocalizations, lasting about one minute with consciousness preserved throughout the event but with reported impossibility to react. In correspondence with the reported episodes there was no electroencephalographic correspondence.

Discussion: PNES are often challenging to differentiate from epileptic seizures, especially in patients with definite epilepsy, and continuous video-EEG monitoring is regarded as the gold standard for diagnosis of PNES.[2] Non-epileptic seizures occurs both in patients with and without epilepsy; the data suggest that patients with treatment-resistant epilepsy are at higher risk of developing PNES. The dual diagnosis should be considered in the cases of the unexpected development of new seizure types or increase in their frequency.[3]

Conclusion: This case highlights the importance of suspecting the presence of PNES even in patients with a defined diagnosis of epilepsy, especially in drug-resistant forms where overlap is relatively common. Moreover, the use of video-EEG proves to be fundamental for carrying out a correct differential diagnosis.

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NOVEL RECESSIVE TTN MUTATIONS ASSOCIATED WITH FAMILIAL PROGRESSIVE CORE MYOPATHY AND CARDIOMYOPATHY: EXPANDING THE GENOTYPE AND THE PHENOTYPE OF TTN RELATED MUTATIONS

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Objectives: To describe two novel recessive pathological TTN variants detected by clinical exome sequencing in association with a familial childhood onset, slowly progressive myopathy plus cardiomyopathy.

Materials: Pt1, a 76-year-old man, came to our observation at age 60, for a slowly progressive limb muscle weakness, with onset in childhood, with toe-walking, then predominantly affecting his proximal muscles. His 73-year-old brother was similarly affected. Their parents were non-consanguineous.

Methods: Diagnostic assessment included blood tests, CK and LDH determination, EMG studies, ECG 24-hour monitoring, echocardiography, respiratory function tests, muscle MRI and biopsy, Next-Generation Sequencing (NGS) based molecular testing on leukocytes DNA.

Results: in both siblings CK and LDH were normal, EMG showed rare myotonic discharges and was myopathic, nerve conduction was normal. Muscle MRI documented fatty degeneration, mostly in anterior lower leg compartment; echocardiogram displayed left heart hypertrophy; muscle biopsy of Pt1 revealed core-like alterations and chronic myopathic changes; desmin immunohistochemistry and acid maltase activity were normal. Muscle disease progressed over 14 years of follow-up in both siblings, with loss of autonomous walking, severe restrictive respiratory syndrome and dilated cardiomyopathy. Targeted enriched NGS panel for congenital myopathies was negative, clinical-exome sequencing (Illumina, TruSightONE) documented in both siblings compound heterozygosity for a c.2089A>T in exon 12 of the titin gene (TTN), inducing a premature stop codon (p.Lys697Ter), and a c.19426+2T>A in intron 66 predicted to affect TTN alternative splicing by in silico.

Discussion: Titin-related myopathies manifest with variable onset, severity, progression and muscle involvement. In our family, we identified two novel likely pathogenic AR variants in TTN, and actually the clinical presentation would also fit with an AR TTN mutation. A recent clinico-molecular study on a large cohort of AR TTN-related skeletal myopathies suggested that noncongenital cases would be associated with at least one pathogenic variant in one of the final three TTN exons (362–364). Further studies on patients' muscle mRNA will address how aberrant splicing would eventually affect expression of the mutated TTN allele in this family.

Conclusions: This family expands the spectrum of AR-TTN related myopathies and emphasizes the role of reverse phenotyping for addressing diagnosis of rare neurogenetic diseases assessed by NGS.

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REMINISCENCES FROM ANCIENT AGES. A CASE OF MENINGO-VASCULAR SYPHILIS

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Aims: To describe a case of meningo-vascular syphilis in order to raise clinicians sensitivity towards old re-emerging pathologies.

Materials and Methods: Case report.

Results: A 58 years-old Italian man presented to our department with vertigo, gait disturbance and speech difficulties. His medical history was significant for hypertension only. Cerebral-CT showed bilateral chronic lacunar lesions in white matter and thalami. Angio-CT revealed a pseudo-aneurysm of the right internal carotid artery (C1-level) and a focal ectasia of its sovraclinoid part. Cerebral-MRI (1.5 T) showed, on a background of diffuse leukoencephalopaty, multiple acute lesions on both cerebral hemispheries; gradient-echo sequences were positive for some microbleeds, both lobar and deep. Blood tests for autoimmune disease showed non-specific ANA 1:180 positivity, while thrombophilic screening tests, Holter-ECG, transthoracic and transesophageal echocardiography were unremarkable; no right-left shunt was found at TCCD; an angiography didn't add significant information. The patient was discharged under antiplateled therapy. After discharge a whole aorta angio-CT and a FDG18-PET were required in the suspicion of vasculitis. Angio-CT showed an ectasia of ascendent aorta, where FDG18-PET revealed focal accumulation of radioactive tracer. About two months later the patient returned to hospital with intense vertigo and gait impairment. An other Cerebral-MRI (3 T, with gadolinium) was performed, showing new DWI-positive lesions (left cerebellar hemisphere and corona radiata, bilaterally), some of which appearing as hyposignal on SWI-sequences in relation to hemoglobin degradation products; no contrast enhancements were found on nervous tissue while the vessel-wall study revealed significant enhancement on the right carotid artery sovraclinoid tract. A lumbar punture was finally performed, confirming an inflammatory state: proteins 103 mg/dl (<50), leukocytes 17/mmc (<5) 100% monomorphonucleate, IgG 21.4 mg/dl (<3.4), albumin 47.6 mg/dl (< 35), Link index 1.5 (<0.66), barrier index 14.6 (<7.4). CSF-PCR for neurotropic viruses was negative as well as bacterial and mycotic cultures. Both blood and CSF were positive for T. Pallidum infection (blood: IgM/IgG-ECLIA, TPHA 1/640 and RPR; liquor: TPHA and IgG-Western-blot). After penicillin therapy the patient has remained free from clinical relapses and no progression was seen at 6-month follow-up MRI, while CSR findings turned negative.

Discussion: Meningo-vascular syphilis is one form of neurosyphilis and can occure at any stage of disease. This is defined as the inflammation of the meninges as well as the arteries, causing thrombosis and infarction of cerebral tissue.

Conclusions: T. pallidum testing should be considered in the differential diagnosis of multifocal acute/subacute vascular events, explecially when more common causes of stroke have been ruled out.

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A CASE OF LEBRUNE SYNDROME WITH STROKE LIKE ONSET

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Background and Aims: Suspected ischemic attack is a common diagnostic challenge for physicians and it is important to identify cerebral ischemic attack promptly because of the necessity of urgent treatments. On the other hand, it is also important to identify some particular situations in which a more precise etiological diagnosis is important to avoid unnecessary investigations and inappropriate treatment. We report a case of a rare genetic mutation responsible of acute neurological symptom onset.

Method: Case report.

Results: A 42-year-old man, with a personal history of mild mental retardation, with normal daily life activities, was presented with sudden onset of right leg weakness during walking. CT scan imaging demonstrated no acute lesion in the brain, but cerebellar and basal ganglia calcifications. Full blood count showed normal values. Alteplase was not administered because it was not clear the nature of the primary disease affecting the patient. The patient was admitted to our Stroke Unit and low dosage of acetylsalicylic acid started. Three days after admission to the Stroke Unit, he recovered normal conditions. The brain MRI revealed diffuse leukoencephalopathy, calcification and cystes and a small area positive to DWI sequences located in the left hemisphere. Infectious disease, autoimmune disorders and neoplasia were excluded. He underwent to genetic examinations that revealed a SNORD 118 mutation responsible of both neurological disorders and MRI imaging.

Conclusion: The simultaneous presence of leukoencephalopathy, cystis and calcification should take the clinicians to consider the hypothesis of a rare underlying genetic mutation; the neurological symptoms, stroke like onset, are often the result of a condition of diffuse microangiopathy.

A NEW MUTATION OF THE FUKUTIN GENE IN CAUCASIC PATIENT WITH LIMB GIRDLE MUSCULAR DYSTROPHY

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Background: Abnormal O-linked glycosylation of a-dystroglycan (a-DG), are a group of clinically and genetically heterogeneous muscular dystrophies, recognized like a-dystroglycanopathies, indispensable molecule for intracellular and extracellular membrane stability. A-dystroglycanopathies are caused by mutations in several genes, including the Fukutin (FKTN) gene, resulting in several forms of muscular dystrophies with variable phenotypes. We describe a new mutation in the FKTN gene, not previously described, detected in a Caucasian family from Misilmeri in Palermo. A man, presented to our clinic with clear clinical manifestations of typical limb girdle dystrophy characterized by muscle weakness, cardiomyopathy, and increased serum creatine kinase (CK) levels.

Case presentation: The patient was a 53-year-old man, born from consanguineous parents, both with Caucasic ethnic. He had dystroglycanopathies familiarity in a cousin with a history of muscle weakness and cardiomyopathy. Our patient referred a history of cardiomyopathy with heart transplant in 2003. Three years ago, he first noticed difficulty in fine hand movements and progressive arms muscle weakness. Was also obtained increased serum CK levels (736 U/L). The neurological examination showed prominent scapular winging bilaterally and a proximal and distal weakness of both arms, in particular on right side, grade 3 of MRC scale and no evidence of calf hypertrophy. The patient had no facial and cognitive involvement. The patient underwent to a brain and cervical spinal cord magnetic resonance imaging (MRI) study, resulted normal. The DNA was isolated from EDTA blood sample and was sequenced using Sanger method. FKTN gene sequencing highlighted the variant c.1304A>G (p.D435G) of the exon 10 in FKTN gene, predicting missense mutation rs.377684183 in homozygous condition, not already described in other patients (The Human Gene Mutation Database-Professional 2020.1) and not identified in healthy controls (1000 Genomes Project, NHLBI-ESP6500 exome project). The genetic study was extended to the patents, discovering the same homozygous missense variant c.1304A>G (p.D435G) in three first-degree relatives: the patient's mother and his son and daughter. The patient's mother showed minimal dystrophic features while patient's son and daughter are asymptomatic.

Discussion and conclusions: Our patient was homozygous for a missense mutation in FKTN with a late onset milder phenotype and cardiac involvement. Considering the diversity of possible over-lapping phenotypes, the diagnosis of a dystroglycanopathy should be considered for the patients with supposed muscular dystrophy clinical manifestation and a history of familial dilated cardiomyopathy with a no clear or mild LGMD.

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BLINDSIGHT AND NORMAL PRESSURE HYDROCEPHALUS

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Objectives: Analyzing blindsight as a reliable explanation for black/white vision, and deficient color vision in Normal Pressure Hydrocephalus.

Materials: 28 Calabrian male patients (age range 51-84; mean 73.2), mean disease duration 4.4 years (range 1.0-23) admitted to National Research Council, and 28 controls matched for sex and age, were enrolled.

Method: All patients, and controls were subjected to Ishihara test, Farnsworth D-15 test, and City University test, both monocularly, and binocularly.

Results: 7/28 patients showing black/white vision were so subdivided: 4/7 patients without surgical ventricular-peritoneal shunt; 3/7 patients who carried out it. 1 patient of this last subgroup restored the normal color vision after the shunt; 2 patients showed black/white vision after the surgical shunt, too. 14/28 patients showing color vision deficiency were so subdivided: 7/14 without surgical ventricular-peritoneal shunt. In this subgroup, 3/7 showed double protanous/deuteranous, and tritanous deficiency; 2/7 patients showed protanous/deuteranous deficiency; 2/7 patients showed tritanous deficiency. 7/14 patients did not carry out the surgical ventricular-peritoneal shunt: 4/7 patients restored normal color vision after surgical shunt; 2/7 patients showed protanous/deuteranous deficiency after surgical shunt, and 1/7 patient showed tritanous color vision deficiency after surgical shunt, too. 7/28 patients at first clinical visit, showed normal color vision, as the controls.

Discussion: In the group of patients showing the black/white vision, very likely we have a compromise of the visual pathways from V1 to V4 in the middle brain. The very compromise of the primary visual area V1 does not allow that the visual stimulus can arrive to V4 area. In these patients miss the intact return pathways V4 to V1. This integrity is restored in the patient who have a new normal color vision after the surgical ventricular-peritoneal shunt. In the group of patients the red/green and/or blue/yellow axes deficiency very likely there is no a great compromise of V1 primary visive area, but only for V4 color vision area. The operational connections between the two areas are not very compromised, and it have restored after the surgical ventricular-peritoneal shunt.

Conclusion: The clinical evidence makes such a plausible suggestion because the integrity of both above areas is critical to see, and be consciously aware of having seen the colors. The return pathways from V4 back to V1 showed to be critical for the conscious awareness of the color attributes of vision. Thank Cassa di Risparmio di Calabria e Lucania Foundation for its contribute.

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RELATIONSHIP BETWEEN THE MOST STATISTICALLY SIGNIFICANT RM MEASURES AND NORMAL PRESSURE HYDROCEPHALUS

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Objectives: Analyzing the relationship between the most statistically significant RM indexes' measures and color vision results in Normal Pressure Hydrocephalus.

Materials: 21 Calabrian male patients (age range 51-84; mean 73.2), mean disease duration 4.4 years (range 1.0-23) admitted to National Research Council, and 21 controls matched for sex and age, were enrolled.

Method: All patients, and controls were subjected to Ishihara test, Farnsworth D-15 test, and City University test, both monocularly, and binocularly. All patients were subjected to RM 3TESLA (GE Discovery 750), making the weighted sequencies in T1, T2, FLAIR, on multiply scanning plains.

Results: 21 patients were so subdivided: 7/21 showing black/white vision without a surgical ventricular-peritoneal shunt so as 14/21 showing a color vision deficiency on red/green and/or blue/yellow axes. In this last subgroup, 3/14 showed tritanous deficiency; 4/14 patients showed protanous/deuteranous deficiency; 7/14 patients showed double deficiency on both above axes. RM 3TESLA indexes' measures analysis showed a statistically significant differences between the Medium Cerebellar Peduncle (t Student = 1,37; p>0,1<0.005); Callosal Angle (t Student = 3,805; p>0.001<0.005); Lateral Ventricle (t student = 4,66; p>0.0005) in B/N patients and color vision deficient patients.

Discussion: The statistical differences found by RM indexes' measurement between the two above groups of sample confirm a structural compromise in B/N patients than the color vision deficiency patients. This subsequently results in a major compromise of the visual pathways from V1 to V4 in the middle brain, demonstrated by the reduced length of the Medium Cerebellar Peduncle, too. Surely, patients with B/N vision miss the consciousness to see the colors due to blindsight.

Conclusion: Color Vision can be considered a biological marker useful to be placed side by side the Magnetic Resonance to show the peculiarities of Normal Pressure Hydrocephalus. Thank Cassa di Risparmio di Calabria e Lucania Foundation for its contribute.

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SUSPECTED LIMBIC-PREDOMINANT AGE-RELATED TDP-43 ENCEPHALOPATHY (LATE) AT PRE-CLINICAL STAGE: CASE REPORT

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Objective: To describe a patient with suspected pre-clinical stage of Limbic-predominant Age-related TDP-43 Encephalopathy (LATE).

Case report: A 72-year-old woman presented history of subjective cognitive decline and episodes of transient global amnesia. Brain MRI (December 2021) showed chronic cerebral vasculopathy and left temporal-polar and hippocampal atrophy with hyperintensity in T2. In January 2022 neurological examination resulted normal and the overall scores at neuropsychological assessment battery were normal, even with poor storage strategy of both verbal and visual-spatial material and just anxious-depressive traits. Blood test and cardiovascular evaluation (Epiaortic-ultrasound, Holter-ECG, TT-Echocardiogram) were normal. CSF biomarkers for dementia (Aβ42, Aβ40, t-tau e p-tau) were negative and the resting-state EEG was normal. Brain FDG-PET documented a single area of cerebral glucose hypometabolism at the left mesial temporal cortical level, while PET-amyloid was negative.

Discussion: This is the case of suspected pre-clinical LATE, a novel type of neurodegenerative disease described as a common TDP-43 proteinopathy associated with an amnesic syndrome. According to ATN classification of NIA-AA, the patient is classifiable as A-T-(N)+. Negative A due to the absence of amyloid deposition at PET, negative T due to the absence of CSF-tau and positive N due to neuroimaging (brain MRI and FDG-PET) findings. This latter biomarker profile, labeled "suspected non-Alzheimer's pathophysiology" (SNAP), implies evidence of one or more neuropathologic processes other than AD, and within this group the most frequent disease has been shown to be LATE. Furthermore, the neuroradiological asymmetric hypotrophy in the hippocampal regions supports the suspected LATE. Eventually, since the neuropsychological assessment resulted normal, it makes conceivable the definition of "pre-clinical" stage of LATE. Recently, a consensus working group has been published about cognitive features of LATE in advanced patients, but to our knowledge there is no study about preclinical stages in literature yet [1].

Conclusion: We report a patient with a suspected diagnosis of preclinical LATE. This new disease, still underdiagnosed, may impact on public health since it is very frequent in the elderly [2]. Future studies will be needed to further define the clinical features of LATE, with the aim of enhancing the therapeutic-assistance management of patients with this neurodegenerative disease [3].

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A CASE OF WERNICKE – KORSAKOFF ENCEPHALOPATHY ASSOCIATED TO ESOPHAGEAL ACHALASIA: INSIGHTS INTO BRAIN STRUCTURAL AND FUNCTIONAL CHANGES

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Introduction: Wernicke encephalopathy (WE) is an acute condition characterized by ophthalmoplegia, ataxia and confusion caused by thiamine (B1) deficiency. WE can evolve in Korsakoff syndrome (KS), a neuropsychiatric disorder associated with confabulation and deficits in short-term memory. The combined presence of these two disorders is diagnosed as Wernicke–Korsakoff syndrome (WKS). We describe a case of WKS in the contest of esophageal achalasia.

Case report: A 71-year-old man was admitted to our neurological ward for acute onset of aphasia. His wife reported 3 days instability with vertigo and falls along with frequent episodes of vomiting and weight loss for 1 months. His pathological medical history was otherwise unremarkable. Neurological examination revealed deficits in comprehension and verbal production, decreased voluntary movements without focal sign and spontaneous multi-direction nystagmus. Routine blood testing revealed hyperglycaemia, anemia, thrombocytopenia, B12 deficit with hyperhomocysteinemia. Brain CT scan with angio-CT and perfusional study were negative for vascular occlusion. CSF analysis showed increased protein (72mg/dl) with lymphocytic pleocytosis (11cells/ul).

PCR-CSF testing for neurotropic virus resulted negative. EEG showed generalized slowing with anterior bilateral delta waves. Brain MRI revealed hyperintensity of periaqueductal gray matter and superior colliculi extending in medial thalami. Patient was treated with thiamine (400mg i.m. daily) plus B12 (1000ug i.m. daily) and folic acid (5mg p.o. daily). He was able to eat with soft diet. His clinical condition improved during first days, his speech became more fluent but deficits in attention and short-term memory were evident (MMSE 23/30), he started walk with truncal ataxia. Brain FDG-PET showed hypometabolism in precuneus and posterior cingulate cortex, prefrontal and parieto-temporal regions. CSF biomarkers excluded amyloidopathy (T-tau:1802 ng/l, P-tau:59 ug/L, Abeta-42:625 ng/L, Abeta40:12738 ng/L). Total-body FDG-PET rule out malignancies. EGDS and barium swallow study displayed narrowing of the lower esophageal sphincter and proximal dilation of the oesophagus with chronic esophagitis. Esophageal manometry confirmed the diagnosis of achalasia. 20 days later brain MRI showed less evident midbrain abnormalities and CSF analysis was normalized. At discharge patient could walk independently, there were confabulations and memory deficits that persisted at 3-months follow-up (MMSE 25/30).

Conclusions: Acute onset of cognitive deficit in the contest of nutrient deficiency could be the onset of WE and prompt thiamine supplementation is pivotal to avoid further neurological deterioration. FDG-PET imaging could be useful to reveal a neurodegenerative-like pattern of hypometabolism and predict poor cognitive outcome.

STATUS OF CONTINUOUS EPILEPTIC SPASMS POSSIBLY PROVOKED BY VNS BATTERY DEPLETION AND RESOLVED BY ITS REPLACEMENT

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Background: Few cases of infants affected by severe encephalopathies developing prolonged clusters of epileptic spasms are described in the literature (1,2). They all had severe encephalopathies and continuous epileptic spasms (CES) were generally resistant to multiple antiseizure medications. However, CES are not specifically included in the most recent ILAE classification of status epilepticus (3), possibly due to their rareness.

Materials and Methods: case report.

Results: We describe the case of a 41-year-old man affected since the age of 3 months by a severe epileptic encephalopathy of unknown aetiology, manifesting with multiple type of seizures (epileptic spasms, atypical absence seizures, myoclonic, tonic and atonic seizures) and severe psycho-motor delay. His clinical condition mildly improved (seizure frequency reduction and increased alertness) after VNS implant at 31 years, and implementation of perampanel and brivaracetam at 35 and 38 years respectively. Several months after the latter therapeutic improvement, he manifested an apparently unexplained dramatic seizure exacerbation. He was urgently admitted to our unit, presenting with CES associated to autonomic symptoms (cold extremities and sweating) persisting for 12 hours. EEG showed diffuse background slowing with sub-continuous diffuse sharp waves and numerous epileptic spasms (up to one every 30 seconds) related to brief diffuse desynchronization followed by a single high amplitude slow wave. We administered orally lorazepam 1 mg repeated three times that day without substantial improvement. Since VNS battery proved depleted (the last function check traced back two years), it was replaced and promptly titrated (up to output current 1.75 mA, signal-on time 30", signal-off time 3' in three days). Since the device restarting only some isolated spasms (2-3 per day) were observed. Furthermore, since the day after surgery he proved to be more alert and was able to walk aided once again.

Discussion and Conclusions: CES could be considered a peculiar form of status epilepticus which can occur also in adulthood. In our case, despite the only mild response to VNS implantation, we can assume that battery shutdown triggered CES, as supported by the prompt clinical improvement after its replacement. VNS efficacy in epileptic encephalopathies may be underestimated.

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BRUNNER SYNDROME ASSOCIATED WITH NOVEL MISSENSE MUTATION IN MAOA GENE: A CASE REPORT

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Objective: Brunner syndrome is a rare cause of X-linked intellectual disability (XLID) associated with monoamine oxidase A (MAOA) deficiency. Since the first report in 1993, to date only 22 cases have been described. We herein report a case of a 39-year-old woman who was diagnosed with MAOA deficiency, after her 4-year-old child had developed mild intellectual disability and they had undergone genetic testing. A novel pathogenic mutation in the MAOA gene was detected in both the proband and his mother.

Materials and methods (case description): A 39-year-old woman had several accesses to emergency departments, within the last 15 years, for sudden, recurrent episodes of palpitations, headache, abdominal pain and swelling, treated with antispasmodics, unsuccessfully. No organic lesions were found. Past medical history was unremarkable, although the patient occasionally presented night terror, skin flushing and impulsive behaviour, never with hetero aggressiveness, since she was a child. After her 4-year-old child had been investigated for a neurodevelopmental delay, a genetic testing of the family was carried out.

Results: Whole exome sequencing detected a pathogenic variant in the MAOA gene: c.410A>G (p.Glu137Gly). The variant was found in heterozygous state in the woman and in hemizygous state in her child. It is a missense mutation, and it is classified as likely pathogenic based on ACMG criteria. The subsequent biochemical studies confirmed the MAOA deficiency in the patient: increased blood Serotonin (1861 nm/L, range 138-1080), urinary Serotonin (568 mcg/24h, range 26.6-182.2), and urinary catecholamine catabolites Vanillymandelic acid (7.7 mg/24h, range 1.8-6.7) and Normetanephrine (562.8 mcg/24h, range 162.0-527.0).

Discussion: The patient clinical manifestations, consistent with a partial serotonin syndrome, would configure her as “mildly affected”. We reported a case in which the proper diagnostic framework has been possible only following an accurate evaluation of the child, which lead to genetic testing, and to biochemical measurements. In line with current evidence, she was treated with sertraline, 50 mg od, together with

appropriate dietary restrictions. At 1-month follow-up the patient showed a reduction of headache and abdominal pain. The treatment with SSRI has proven effective, although the precise underlying mechanisms remain largely unknown.

Conclusions: Impaired MAOA activity in individuals with Brunner syndrome results in bioamine aberration, but it is currently unknown how this affects neuronal function. Our report of an adult patient exhibiting apparently inexplicable clusters of symptoms, expands the spectrum of Brunner syndrome-associated phenotypes. Clinical, genetic, and biochemical validation of these results in larger cohorts is warranted.

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THE IMPORTANCE OF EEG IN DIAGNOSING ACUTE-ONSET BACLOFEN ENCEPHALOPATHY IN AN ELDERLY PATIENT WITH ISCHEMIC STROKE: CASE REPORT

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Introduction: Baclofen, a drug commonly used in treatment of spasticity, can cause a variety of side effects including excessive sedation, respiratory depression, seizures and, rarely, severe encephalopathy.

Case Report: A 78-year old woman was hospitalized in the Department of Rehabilitation of our Hospital to perform physical therapy after an ischemic stroke of the left hemisphere. In order to manage spasticity, she was administered baclofen 25 mg daily. Two days after, she was found less responsive; neurologic examination revealed eye opening to speech, absence of verbal response, withdrawal from pain with a GCS score of 8 (E3-V1-M4) and sporadic myoclonic movements of the right arm. Pupils were normally reacting. No brain CT changes were noted. Routine hematology tests were normal, except for creatinine levels that were 1,4 mg/dl (GFR 36 ml/min). The electroencephalogram (EEG) showed marked and diffuse slowing of the basal rhythm and bi- and triphasic waves of high voltage recurring in a periodic or pseudo-periodic pattern. On the basis of EEG and clinical history, we hypothesized acute encephalopathy following baclofen administration. Consequently, the drug was discontinued and the patient was managed with intravenous fluids and diuretics. In the following days, her neurological status started to improve: at first, she was alert but confused, she was able to perform simple commands and to speak with a stereotyped language. Her spatial and temporal orientation and language then improved and eventually she was alert and oriented. A progressive improvement of her EEGs was concomitantly observed, with reappearance of alpha rhythm mixed with brief sequences of theta waves predominantly on the temporal regions.

Discussion: Baclofen, a centrally-acting gamma-amino butyric acid (GABA) agonist, has a central nervous system depressant effect. Several cases of baclofen toxicity have been reported, especially in patients with kidney failure as baclofen excretion is primarily renal; therefore it should be used with caution in elderly patients with decreased renal function. Baclofen encephalopathy is associated with a variety of EEG changes (generalised slowing, triphasic waves, burst suppression and generalized epileptiform activity). In our case, EEG was essential for a correct diagnosis.

Conclusion: Clinicians should be aware of the possible risk of severe side effects associated with the use of baclofen, particularly with concomitant renal impairment. EEG is a reliable and sensitive tool to confirm a diagnosis of baclofen encephalopathy when clinically suspected and to monitor the response to treatment.

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ISOLATED COGNITIVE RELAPSE IN A MULTIPLE SCLEROSIS PATIENT – NEUROPSYCHOLOGICAL AND NEUROPHYSIOLOGICAL CORRELATES

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Introduction: An isolated cognitive relapse (ICR) is defined as a transient decline in cognitive performance, without clinical or subjective evidence of other new neurological signs or symptoms, associated with a positive gadolinium-enhancing lesion, in patients affected by Multiple Sclerosis (MS). Acute cognitive impairment is rarely reported in patients with MS, probably because the neuropsychological evaluation is often overlooked in clinical practice.

Case description: Herein we describe the case of a 53-year-old woman with a diagnosis of Relapsing-Remitting MS, in treatment with Dimethylfumarate. She presented to our clinic complaining of confusion and memory loss. Neuropsychological examination showed low performance in both verbal and visual episodic memory, assessed through the Rey Auditory Verbal Learning Test (immediate recall, delayed recall, and recognition) and the Rey–Osterrieth complex figure delayed recall. Furthermore, low scores were obtained in language tests assessing naming of objects and semantic verbal fluency, depicting a cognitive profile characterized not only by memory impairment but also by semantic-lexical skills deficits. Brain MRI showed 5 new demyelinating lesions with gadolinium enhancement. The largest lesion had a tumefactive appearance and was localized in the left parahippocampal gyrus, 1 lesion was localized in the left medial thalamus and the other 3 were periventricular. EEG was performed and resulted as normal. The patient was treated with intravenous methylprednisolone for 5 days, with partial benefit on the symptoms. Neuropsychological tests were repeated and showed only a slight improvement. We also performed a neurophysiological evaluation to probe cortical excitability through different transcranial magnetic stimulation (TMS) protocols. In particular, we tested short-interval intracortical inhibition (SICI) and short-latency afferent inhibition (SAI). A reduction of SICI only for the left hemisphere after corticosteroid therapy was noted.

Discussion: ICRs have been associated with long-term cognitive decline in MS, thus they might be clinical markers for identifying patients at risk of developing permanent neuropsychological impairment. Neuropsychological assessment should be done more widely in MS

practice, in order to tackle ICRs and treat them promptly. Neurophysiology might help understand the underlying pathophysiology of ICRs. In our study, we found a unilateral reduction of SICI, that might indicate the impairment of excitatory interneurons during the relapse. More studies are warranted to better comprehend the pathophysiology and the actual prevalence of ICRs.

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MARKED ANTICIPATION OF A LATE-ONSET SCA 17 IN A PARENT-TO-OFFSPRING TRANSMISSION

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Introduction: Spinocerebellar ataxia type 17 (SCA 17) is a rare genetic neurodegenerative disease caused by an expansion of the CAG/CAA sequence in the TATA box binding protein (TBP) gene. The normal range of triplets is 25-42, whereas carriers with 49 or more CAG/CAA present the disease with full penetrance. There is no consensus regarding the number of triplets that cause the disease with reduced penetrance, but most authors agree with a number between 28 and 43 triplets. Also, there is heterogeneity in clinical phenotypes within this range of alleles.

Case description: We present a case of a father-to-son transmission with a number of CAG/CAA repetitions referrable to reduced penetrance. The proband's first symptoms started at 48 years of age when he was referred to the local service for psychiatric symptoms. He then developed chorea and mild ataxia. Genetic testing revealed an expansion of 45 CAG/CAA. We then extended the test to his father, an 81-year-old man, with a one-year history of mild unsteadiness and parkinsonism. Interestingly, testing revealed, like the son, a CAG/CAA expansion of 45 in the TBP gene. Sequence analysis of the expanded allele showed CAA interruptions in both family members, but stable transmission of the expanded allele in terms of repeats number and sequence configuration from one generation to the next.

Discussion: Microsatellite instability during parent-to-offspring transmission is a cause of anticipation in age at onset of disease. An uninterrupted configuration of SCA17 alleles is considered to be unstable, resulting in an age of onset anticipation, whilst an interrupted configuration confers stability during the parent-to-offspring transmission. Our probands carried both an interrupted expansion of 45 repeats, but marked anticipation occurred without any further increment in CAG/CAA repetitions. Moreover, their clinical picture was quite diverse, ranging from ataxia to rigidity, chorea, cognitive impairment, and psychiatric symptoms. SCA 17 is a very heterogeneous disease and further studies are needed to clarify the potential link between the number of repeats, the phenotype variability, and possible genetic modifiers.

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ACUTE HEMICHOREA AND STROKE, MANAGEMENT AND TREATMENT IN 2 CASE REPORTS

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Purpose: Acute movement disorders are possible symptoms of an ischemic stroke, however data in literature about their acute management are scarce.

Materials: We describe two cases of acute hemichorea treated with rTPA.

Methods: We searched in PubMed articles using the key words "Hemichorea and Stroke", looking in particular articles which explain how chorea symptoms were treated in the acute phase.

Results: First case: man, 87 years old, with history of dyslipidemia and hypertension. He was admitted to the ED of the University Hospital of Trieste with an acute onset of right hemiparesis and a prominent right hemichorea (NIHSS 4). He underwent a CT, CT angiography and CT perfusion resulting in a core area in the left caudate and a frontal area of penumbra, with no vessel occlusion. He underwent reperfusive treatment with rtPA with regression of symptoms within 48 hrs. The EKG demonstrated an atrial flutter as possible cause of the ischemic stroke. Second case: woman, 74 years old, nothing relevant in past medical history. At wake up she complained a sudden onset of involuntary movements in the right hand and foot. Admitted to ED of University Hospital of Trieste, a right hemichorea was found with no other neurological sign (NIHSS 0). CT scan with CT angiography and CT perfusion were performed and no pathological findings were observed. The patient was treated with rtPA with improvement of hemichorea's movements.

Discussion: In literature, a possible cause of choreic symptoms is an imbalance between the indirect and direct pathways or reduced input from sensory cortex [1]. The role of thrombolysis in symptom improvement is not clear, since just a few case series have been described and stroke related hemichorea often improves even with no specific treatment [2].

Conclusions: Hemichorea is a rare presentation of ischemic stroke; there is no evidence to withhold reperfusive treatment in such patients.

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COMPLEX MOTOR BEHAVIOUR DURING SLEEP: A RARE CASE OF PAROXYSMAL HYPNOGENIC DYSKINESIA

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Introduction: The most frequent etiologies of complex motor behaviour during sleep consist in epileptic or parasomnic events. The differential diagnosis between Sleep related Hypermotor Epilepsy (SHE) and NREM parasomnia is generally simple and in typical cases careful history taking can be sufficient for orienting the clinical diagnosis. However, the differentiation between some sleep-related seizures and paroxysmal non-

epileptic motor events may still be a challenge and a cause of diagnostic uncertainty. Identifying the origin of sleep-related hypermotor manifestations properly is still important for correct treatment and prognosis.

Methods: We describe clinical, video-polysomnographic (v-PSG), neuroimaging and genetic findings of atypical case of patient with complex motor behaviour during sleep.

Results: A 35-year-old male, presented with abnormal movements occurring exclusively during sleep since he was eight. The episodes, consisting of stiffening and random flailing of the arms and legs, occurred three to ten times every night lasting for three to five minutes. At the beginning, he was given a diagnosis of epilepsy and was started on clonazepam, becoming free of episodes for 5 years. After drug withdrawal, the episodes reappeared, being than resistant to treatment with topiramate and carbamazepine. He was referred to "C. Munari" Epilepsy Surgery Center with the hypothesis of a drug-resistant sleep related hypermotor epilepsy. His brain magnetic resonance imaging, cerebral 18FDG-PET and Next Generation Sequencing genetic panel for epilepsy were normal. An overnight video-polysomnography recording did not reveal any electroencephalographic (EEG) abnormalities and captured 8 sleep-related episodes characterized by choreoathetoid and dystonic movements involving primarily the upper extremities. During one manifestation he was tested being aware, oriented and able to answer. All the episodes occurred during NREM sleep and were characterized by EEG desynchronization without any epileptic discharge. On the basis of v-PSG findings, a diagnosis of suspected Paroxysmal Hypnogenic Dyskinesia was made and genetic panel for dyskinesia did not reveal any mutation.

Discussion: Paroxysmal hypnogenic dyskinesia is a rare clinical entity characterized by dystonic and choreoathetoid movements occurring exclusively during sleep, that can be difficult to distinguish from parasomnic or epileptic events. V-PSG and possibly home-made video recordings of the episodes are paramount for a correct diagnosis.

A CASE OF VERY LATE-ONSET CMT NEUROPATHY AND PYRAMIDAL FEATURES WITH TYROSYL-TRNA SYNTHETASE 1 (YARS1) GENE MUTATION

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Charcot-Marie-Tooth (CMT) neuropathies refer to a group of inherited peripheral nervous system disorders characterized by chronic sensory and motor polyneuropathy. In this case report, we described clinical and genetic data of a man with a very late-onset CMT dominant intermediate (CMT-DI) neuropathy with pyramidal features. An 82-year-old man came to our attention because of progressive walking difficulty. He had a sister with mild axonal polyneuropathy in the lower limbs. In his pathological history, he has bilateral sensorineural hearing loss. From 81 years old, he has complained of slight postural instability, which rapidly worsened, and a tingling sensation in feet soles. After seven months, he has reported walking difficulties, at the right lower limb predominantly. Neurological examination showed upper motoneuron signs in the four limbs, more pronounced in the lower limbs, with superficial and deep sensation impairments in the lower limbs and feet deformities (pes cavus and hammertoes). Blood, serum, and CSF tests were normal. Brain, cervical, dorsal, and lumbar spine MRIs were normal. Motor evoked potentials showed an increased latency and conduction time at the lower limbs. Electromyography showed signs compatible with a sensory-motor polyneuropathy in lower limbs, with motor conduction velocity in right and left tibial nerves of 33 m/s and 36 m/s respectively. Lastly, NGS exome sequencing revealed the presence of the c.273C>G heterozygous mutation in the YARS1 gene, which causes the formation of a stop codon and a truncated protein (p.Tyr79Ter). This variant is classified as pathogenic according to American College of Medical Genetics guidelines. The prevalence of hereditary neuropathies beginning beyond the fourth decade of life is usually underestimated. The late onset of neuropathy could be explained by the residual percentage of protein activity. Loss of function mutations in the YARS1 gene causes a loss of activity of the aminoacyl-tRNA synthetase and reduced YARS1 expression levels, which could correlate with the age of onset [1]. This case report highlights the connection between CMT and pyramidal syndromes. In literature, pyramidal signs in YARS1 mutation are reported [2], but they are not well documented. However, it is clear that the molecular pathological causes of CMT and hereditary spastic paraplegia (HSP) overlap at different levels [3]. In conclusion, pyramidal features could be a part of CMT neuropathy with YARS1 gene mutation. Due to the unusual late onset, this type of CMT should be considered a differential diagnosis with CIDP, paraneoplastic neuropathy, and motor neuron diseases.

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AIDP FOLLOWED BY PARANEOPLASTIC ANTI-HU SYNDROME: A CASE REPORT

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Introduction: Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) includes a group of conditions characterized by progressive areflexic paresis and mild sensory changes usually following a vaccination or an infection. Typical findings are the presence of a multifocal demyelinating process in motor nerves, characterized by conduction block or temporal dispersion documented by neurophysiological tests, and of CSF albumin-cytological dissociation. Paraneoplastic neurological syndromes are due to the production of intra- or extracellular autoantibodies in the context of neoplasms, of which they represent often the onset manifestation; among the symptoms, there are hyperkinetic movement disorders such as dystonia, athetosis and chorea, but also peripheral nerve involvement. We describe the case of a 72-years-old woman that developed a post-vaccination AIDP and, subsequently, pseudo-athetosis movements, dysarthria, sensory ataxia, diplopia and vertical ocular movement palsy, as a paraneoplastic syndrome caused by anti-Hu antibodies related to an ovarian tumor.

Methods: The diagnosis of AIDP was confirmed by clinical and anamnestic features and electromyography. Repeated neurophysiological tests showed a worsening of the condition despite therapy with plasma apheresis, administration of intravenous Ig and motor rehabilitation. Due to the sudden onset of pseudo-athetosis movements, dysarthria and

paralysis of vertical gaze movements, assuming a paraneoplastic pathology with involvement of both the CNS and the peripheral nervous system, the patient underwent a total-body CT scan that showed a massive ovarian neoformation.

Results: Consistently, Ca 125 was also markedly increased. CSF analysis was characterised by xanthromic appearance, pleocytosis, hyperprotidorachia and positive anti-Hu antibodies through cell-based investigation. Moreover, the EEG showed bilateral diffuse slow abnormalities. Brain MRI, however, was not significant.

Discussion: Despite the absence of abnormalities in the MRI, probably due to early execution, the symptoms were compatible with a paraneoplastic anti-Hu syndrome involving both the CNS, reasonably responsible for the dysarthria, ophthalmoparesis and confusional state, and the peripheral nervous system, in particular the dorsal root ganglia, with consequent pseudo-athetosis movements, probably due to marked sensory ataxia.

Conclusion: Here we emphasize the importance of early oncological diagnosis and treatment, the only option in order to get an improvement in such cases. This case will soon be discussed in a gynecological-oncological setting to assess the possibility of tumor eradication, the only decisive therapy for paraneoplastic syndromes with intracellular antibodies.

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EFFICACY OF TEMOZOLOMIDE FOR TREATMENT OF REFRACTORY STATUS EPILEPTICUS SECONDARY TO GLIOBLASTOMA MULTIFORME

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Objective: The treatment of non-convulsive status epilepticus (SE) can be very challenging. Aneddotic evidences suggest the efficacy of temozolomide on seizures on cerebral tumors [1,2], mainly on low grade gliomas (LGG).

Materials: A 67-years-old man presented to emergency room confused and with fluent aphasia due to focal SE secondary to glioblastoma multiforme (GBM). Tumor was partially resected, and the patient was already treated with radiotherapy combined with chemotherapy with temozolomide. The patient has already started therapy with levetiracetam for secondary epilepsy.

Methods: The patient underwent to careful neurological evaluation, routine serum blood tests, brain MRI, and EEG recordings.

Results: Neurological examination revealed a confusional state and fluent aphasia, without other neurological signs. Serum blood tests were normal. Brain MRI was unchanged compared to previous scans. EEG recording evidenced periodic lateralized discharges pattern suggesting SE. Benzodiazepines infusion determined temporary improvement of EEG pattern; thus it was progressively introduced antiseizure medications (ASMs) therapy with levetiracetam 3 g/day, lacosamide 400 mg/day, phenobarbital 100 mg/day, clobazam 20 mg/day and lately continuous intravenous infusion of midazolam, which did not improved the patient's clinical condition. Finally the patient started a 5-days cycle of therapy with temozolomide which determined a complete and sustained resolution of SE. In the following months the patient did continued monthly cycles with temozolomide. Neuroimaging did not show tumor progression; moreover the patient remained seizure free regardless ASM decalage for adverse events.

Discussion: Temozolomide is an alkylating agent crossing blood brain barrier, which represent gold standard for the treatment of GBM. A few studies demostrated that temozolomide might improve seizure outcome in patients with LGG, regardless tumor mass reduction [1,2]. Thus temozolomide determined the resolution of SE in our patient, and sustained beneficial on seizures at follow up independently on tumor improvement.

Conclusions: Temozolomide might improve seizures outcome in patients with GBM regardless its antitumoral effect.

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BING NEEL SYNDROME (BNS). NEURORADIOLOGICAL FINDINGS OF CNS INVOLVEMENT IN WALDENSTRÖM MACROGLOBULINEMIA (WM)

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Objectives: To illustrate MRI findings in a case of WM with CNS involvement.

Methods-Results: 58 y.o. man affected by WM diagnosed in 03/22. Symptoms began in 2017 initially interpreted as MGUS. He had fatigue and fever; asymmetric sensorimotor polyneuropathy occurred in 2019 and visual deficits in 10/21. Brain MRI in 12/21 showed left occipital edematous lesion with mass effect. CSF revealed only a high protein amount. He underwent steroid treatment with neuroradiological improvement hypothesizing an inflammatory disease. A clinical worsening (fatigue, paresthesias, visual deficits) motivated brain and spine MRI in 03/22 showing progression of occipital lesion and bi-hemispheric, infra, supra-tentorial brain and spinal lesions. Contrast-enhancement appeared in coronae radiatae, intraorbital optic nerves, extrinsic ocular muscles, sphenoid body. Thickening of the cervical spinal roots, cauda equina and left parietal dura coexisted. A direct infiltration of CNS by lymphoplasmacytic cells was suspected, suggesting a BNS. Further exams revealed serum anti-MAG+, presence of MYD88+ (L265P) mutation, 70% cellularity in bone marrow, diffuse interstitial infiltrate of B lymphocyte-like elements with plasmocytic differentiation. In CSF plasmocytic lymphocytes and MYD88+ mutation were found. BNS diagnosis was therefore formulated. He was treated with Methotrexate, Rituximab and repeated medicated lumbar punctures. Neurological symptoms improved progressively. Recurrence of gait disturbances and visual deficit were successfully treated with steroids. MRI in 04/22 showed bilateral subdural effusions, worsening of dural thickening, involvement of cavernous sinuses and sellar region, progression of the left occipital and right temporal lesions. Therefore he underwent brain biopsy in 05/22 which did not reveal malignant lymphoplasmacytic cells but abnormalities in white, gray matter and leptomeninges, perivascular infiltrates of T-cells with rare hystiocytes. Post-operative MRI in 06/22

showed edema regression and contrast-enhancement reduction, persistence of dural thickening and subdural fluid collections. The patient is still under treatment and follow-up in accordance with hematologists.

Discussion-Conclusions: BNS is a rare complication of WM seen in about 1% of patients, resulting from direct infiltration of CNS by malignant lymphoplasmacytic cells. The presence of MYD88+ (L265P) somatic mutation in CSF proved to be useful for the diagnosis and monitoring of the disease [1]. Definite diagnosis requires histological biopsy which may be biased by prior treatments, as in our case. Brain and spine MRI can highly support the diagnosis identifying two typical patterns: diffuse leptomeningeal thickening or tumor-like [2,3] thus allowing distinction from other possible diagnosis (ie CNS lymphoma, inflammatory or infective leukoencephalopathy).

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DISSEMINATED NOCARDIOSIS WITH CEREBRAL LESIONS IN IMMUNOCOMPETENT PATIENT

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Background: Nocardiosis is an uncommon, life-threatening, opportunistic infection usually found in immunocompromised patients. The causative bacteria is an aerobic actinomycete in the genus Nocardia, an unusual gram-positive. The most common disease sites are lungs, central nervous system and skin. Systemic disease (2 or more non-contiguous sites +/- pulmonary focus) presents usually in more than one third of patients, among these about 40 percent show central nervous system (CNS) symptoms. In immunocompetent patients with CNS involvement parenchymal abscesses are typical hallmarks and can occur in any region of the brain.

Case Presentation: An 86-year-old immunocompetent woman with no significant anamnestic history except for previous diagnosis of asthmatic bronchitis and no continuative medication was admitted to our emergency department with a few months-history of progressive motor disorder with gait impairment and subsequent onset of altered mental status with difficulties in verbal expression. During anamnestic collection the patient developed a generalized seizure and brain CT scan showed two focal alterations in the left semioval center of suspicion heteroformative nature. The patient was admitted to Neurology Ward, where mild right hemiparesis was found. In the hypothesis of brain metastases, chest and abdomen CT scan was performed revealing multiple lesions located in lungs, left kidney and spleen. Brain MRI scan started raising the suspicion of the abscess nature of the left frontal lobe lesions, thus lumbar puncture was carried out showing elevated CSF protein concentration. Tests recommended by the infectious disease specialist were all negative and the follow-up brain MRI scan revealed a new colliquation area. Meanwhile patient's clinical conditions were getting worse with appearance of aphasia, psychomotor agitation and oppositional attitude. Given the difficulty in making a diagnosis, the patient was moved to Neurosurgery Department to execute drainage of the brain abscess for evacuation/cultural purposes: drained material was positive for Nocardia Cyriacigeorgica. Since the introduction of appropriate antibiotic therapy (imipenem and trimethoprim-sulfamethoxazole first, linezolid then + a two-week course of amikacin), slow but progressive improvement of radiological and neurological picture was observed, with gradual regression of aphasia, echolalia and focal neurological deficits.

Conclusions: Nocardia can disseminate to virtually any organ and has special tropism for CNS. Patients affected by Nocardia brain abscesses can present symptoms suggesting mass lesion, without typical infectious signs, which can mimic primary or metastatic brain neoplasm. Diagnosis is difficult and usually requires an invasive procedure which, although questionable, allows to set up specific antibiotic therapy and to obtain complete recovery.

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THE ASSOCIATION OF CACNA1A VARIANT AND GENERALIZED DYSTONIA

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Objectives: Mutations in the CACNA1A gene have been correlated with episodic ataxia type 2, spinocerebellar ataxia type 6, and familial hemiplegic migraine type 1. Dystonia is not enlisted among the typical clinical manifestations of CACNA1A mutations. We report the case of patient with a novel missense mutation of the CACNA1A gene presenting headache, head and arm tremor, slowly progressive dystonia associated with episodic painful focal dystonic attacks, and unexplained falls.

Materials and Methods: A 57-year-old woman was referred because of neck dystonia associated with head and arms tremor since the age of 15 years. At the age of 47, in 2012, she presented an increase in tremor amplitude led to suspect an essential tremor. In 2019 she showed mild dysarthria, right torticollis with dystonic head tremor and both arms, adiadochokinesia without limb ataxia, gait with dystonic head posture, and no cerebellar features. Moreover, she reported paroxysmal dystonia attacks (3-4 per week) of the left paravertebral muscles and lower extremity with intense pain occurring without apparent provoking factors. The BFMDRS score was 14, and she tried therapy with levodopa/benserazide up to 300 mg/die with no improvement. Dystonia genetic panel showed a heterozygous mutation in the CACNA1A gene (NM_023035.2:c.1630C>T p.(Arg544Trp). In 2020 due to worsening dystonia (BFMDRS score 29,5), she underwent evaluation for GPi-DBS surgery. However, brain MRI showed cortical atrophy, and she was excluded.

Discussion: We report a case of progressive generalized dystonic syndrome due to a novel CACNA1A missense mutation. The patient presents troublesome dystonic head and arm tremor associated with headache and mood deflection, which is not responsive to medical therapies. Moreover, she developed over time painful paroxysmal focal dystonic episodes and sporadic unexplained falls. Several studies support the critical role of structural or functional cerebellum abnormalities in the genesis of dystonia. Specifically, abnormalities in networks related to the strict

interplay between basal ganglia, cerebellum, and cortical motor areas are now considered the pathogenic underpinnings of dystonia. Nowadays, few studies report on dystonia in patients with CACNA1A mutations, with only a little evidence supporting this association.

Conclusion: CACNA1A mutations are associated with a broad spectrum of neurological manifestations, with a frequent overlap of headache and neurological signs related to the involvement of the cerebellum. Few dystonic symptoms have been reported so far; however, the link between dystonia and CACNA1A mutations is increasingly evident, although the prevalence, incidence, and pathogenesis still need to be elucidated.

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AN ITALIAN PATIENT WITH SPINOCEREBELLAR ATAXIA 11 (SCA11): A CLINICAL AND GENETIC STUDY

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Objectives: The spinocerebellar ataxias (SCAs) represent a group of autosomal dominant inherited disorders. SCA11 accounts for <1% of SCAs in Europe. It is caused by mutations in TTBK2 gene, encoding for the protein tau-tubulin kinase 2 which seems to be involved in ciliogenesis. A progressive cerebellar ataxia is the most common clinical presentation, usually accompanied by abnormal eye movements, dysarthria and dysphagia. The aim of this study is to investigate the genotype-phenotype correlation in an Italian patient affected by SCA11.

Patient and Methods: We studied a 60-year-old woman presenting with progressive walking impairment since 6 years. Clinical examination showed ataxic walking, signs of cerebellar dysfunction, vibratory sensory impairment at the lower limbs and reduced ankle jerk reflexes. Molecular analysis of genes involved in some of the most common SCA forms (SCA1, SCA2, SCA3, SCA6) were negative. Neuroimaging, neurophysiological and NGS genetic studies were conducted to achieve a diagnosis.

Results: Brain and spinal cord MRI showed mild atrophy of the cerebellar hemispheres with widening of the peri-cerebellar cerebrospinal fluid spaces and a mild spinal cord atrophy. Sensory evoked responses were absent at the four limbs. ENG study revealed a sensory-motor axonal neuropathy with more pronounced sensory involvement (SAPs of sural, median and ulnar nerves were absent); neurogenic signs were present at EMG. NGS analysis by using a panel of genes related to hereditary ataxias (including ACVR2B, CCDC11, CITED2, CRELD1, FOXH1, GDF1, LEFTY2, NKX2-5, NODAL, ZIC3) displayed the novel heterozygous variant c.1360C>T in exon 12 of TTBK2 gene causing the amino acid substitution p.(Arg454Cys).

Discussion: 37 subjects with SCA11 belonging to six families (4 from Europe,1 from Pakistan, 1 from China)1-3 have been described so far; they all presented frameshift mutations (clustered in exons 12 and 13), except the Chinese family displaying a missense mutation (in exon 15). The mutation found in our patient involves the C-terminal conserved domain and is predicted as "probably damaging" according to PolyPhen-2. Neuropathy has not been described in any of the previous cases. Neurogenic signs at EMG have been reported in the Chinese family, but the ENG data are not available.

Conclusion: To our knowledge, this is the first report of a SCA11 case in Italy. In addition to typical features as ataxic gait and cerebellar signs, our patient showed clinical and electrophysiological evidence of a mainly sensory peripheral neuropathy, which appears to be a novel finding and should be considered in the phenotypical spectrum of the disease.

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A STROKE DUE TO SPONTANEOUS CAROTID DISSECTION IN A WOMAN WITH C.2371C>T HETEROZYGOUSE MUTATION OF COL4A3 GENE: A CASE REPORT

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Fibromuscular dysplasia is a systemic vascular disease, frequent in young women, commonly involving renal and carotid arteries, which represents a rare cause of juvenile stroke [1]. Here we report a case of recurrent spontaneous vascular dissections in a woman with a mutation of COL4A3 gene. A 50-year-old woman, referred to our emergency department for a sudden onset of non-fluent aphasia. Brain CT scan did not reveal ischemic or hemorrhagic lesions. Angio-CT scan showed an occlusion of the distal M1 tract of the left middle cerebral artery. Collaterally, a fibromuscular dysplasia of both carotid arteries and left vertebral artery and a dissection of the right internal carotid artery were found. Systemic intravenous thrombolysis was performed, with a complete remission of the symptoms. Carotid angiography was performed, showing a complete reperfusion of middle cerebral artery, with a distal micro-embolization which did not require endovascular treatment (TICI:2b). The patient was then admitted to our Stroke Unit. Past medical history revealed two myocardial infarctions, the second one due to a right coronary artery dissection, for which our proband undergone to coronary stenting and subsequent treatment with aspirin. Moreover, the patient presented familiarity for breast cancer (half sister) and stroke (her mother and maternal grandmother died prematurely at age 50 and 56 for

cerebrovascular events, respectively). Blood and urine laboratory test were unremarkable. A whole-body angio-CT evidenced multiple alterations in mesenteric blood vessel walls. A breast nodule, studied by mammography and needle-biopsy, revealed a bilateral invasive ductal carcinoma. Based on the phenotype and the family history, an exome sequencing was performed and showed a heterozygous c.5266dupCp. pathogenic variant of BRCA1 gene and a heterozygous c.2371C>T pathogenic variant in COL4A3 gene, classified as probably pathogenic. After the discharge the patient underwent bilateral quadrantectomy with radiotherapy. She did not suffer from other vascular events. COL4A3 is a gene which codify for the alpha 3 chain of the type IV collagen. Mutations of this gene lead to Alport syndrome, a disease characterized by ocular disturbances, neurosensorial hearing loss, and prominent renal involvement [2]. To date, only a study had reported a COL4A3 mutation in a patient with a spontaneous dissection of a cervical vessel [3], leading to the suspicion of a role of this gene in vascular integrity. This case report highlights the importance of a genetic work-up of cryptogenic stroke and spontaneous dissection, especially in young patients. Clinical exome sequencing is a useful tool for patients with suggestive clinical history.
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APPARENTLY ISOLATED CNS INVOLVEMENT IN ERDHEIM CHESTER DISEASE: CASE REPORT

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Objective: Erdheim–Chester disease (ECD) is an uncommon, multisystem pathology, characterized by the accumulation of monocyte-derived macrophages in multiple organs and tissues. The clinical manifestations are different, and the course varies depending on the degree of involvement of organ and systems. Central nervous system (CNS) involvement is associated with poor prognosis.

Materials: We present the case of 48-year-old woman presenting with clumsiness, dysarthria and gait imbalance.

Methods: We studied the case by medical history, neurological examination, laboratories, MRI, CT and biopsy.

Results: A 48-year-old woman, presented with two years of progressive and sneaky clumsiness of the right hand and difficulties in writing; involving after one year, difficulty in language articulation, dysphagia, mainly for liquids, and gait imbalance. Neurological examination revealed: slightly ataxic gait with difficulties in tandem; negative Romberg test; dysarthria with slurred speech; slight clumsiness in fine movements and dysdiadochokinesia of the right hand; hyperreflexia in the lower limbs; Epstein sign. Blood laboratory analyses, demyelinating and neo-paraneoplastic screening, plasma cholestanol, hypothalamic-pituitary hormones were normal. MRI documented T2/FLAIR hyperintense lesions in the cerebellar peduncles and dentate nuclei bilaterally, with homogeneous intense gadolinium enhancement. Thoraco-abdominal CT scan with contrast medium was negative. Whole body MRI showed osteosclerotic lesions in the left humerus, the distal epiphysis of both femurs and the body of both tibias which appeared hypointense in T1 and T2, where the hyperintense rim is evident. The patient underwent a CT-guided bone biopsy that confirmed the suspect, showing: an infiltrate of histiocytes with foamy cytoplasm, with associated fibrosis; positive immunostaining for CD68; negative immunostaining for CD1a and S100; negative immunohistochemistry mutation-specific determination for BRAF V600E. The diagnosis of Erdheim Chester were done.

Discussion: The abnormal signals, found at the level of the dentate nuclei and the middle-superior cerebellar peduncles, required the exclusion of several pathologies, which could mimic the neuroradiological picture. Differential diagnosis includes demyelinating, autoimmune, neoplastic-paraneoplastic, genetic disease as Cerebrotendinous Xanthogranulomatosis and Langerhans cell histiocytosis. On the other hand, the lack of systemic manifestations required, through different instrumental examinations, the necessity to identify secondary disease's localizations which could be biopsied to confirm the diagnosis.

Conclusions: ECD is a histiocytic neoplasm with different clinical presentation making it one of the most difficult diagnostic challenges, especially for his rarity. In our case, in absence of systemic symptoms, the neurological manifestations with MRI support guided the diagnostic protocol.

MIND THE JERK: RECURRENT FALLS MAY BE THE ONLY CLINICAL SIGN OF CORTICAL-SUBCORTICAL MYOCLONUS

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Background: Myoclonus is characterized by sudden, brief, involuntary jerks of a muscle or a group of muscles, caused by muscular contraction (positive myoclonus) or interruption of muscle activity (negative myoclonus). It can be classified into peripheral, spinal, subcortical, and cortical forms. Some authors use the term cortical-subcortical myoclonus to identify a specific type of myoclonus, which differs from classical cortical myoclonus in that the abnormal excessive neuronal activity spreads between cortical and subcortical circuits, producing diffuse excitation. As a result, the EEG shows generalized spike-and-wave discharges that correlate with the myoclonic jerks.

Materials and methods: We report the case of a 79-year-old patient with a history of right thalamic hemorrhagic stroke, with favorable evolution. Fifteen years later he was readmitted to the emergency department for episodes characterized by sudden falls without loss of consciousness. An EEG with EMG recording channel on the anterior tibialis muscle was performed, which documented frequent diffuse spike-wave and polyspike-wave discharges, temporally related to myoclonic jerks in the

lower limbs. Brain MRI showed the persistence of a small right thalamic hemosiderin residue at the site of the previous hemorrhage. Antiepileptic treatment with levetiracetam up to 1000 mg/day was started, with rapid clinical and electroencephalographic improvement. After three years of follow-up, Levetiracetam therapy was reduced to 500 mg/day in the absence of cortical myoclonus recurrence.

Discussion and conclusion: Our patient developed a clinical and neurophysiological picture resembling cortico-subcortical myoclonus, which is commonly found in genetic generalized epilepsies (GGE), including juvenile myoclonic epilepsy (JME). Recent multimodal MRI studies show the presence of structural and functional cortico-subcortical alterations in patients with generalized epilepsy, particularly at the level of the thalamus. Indeed, thalamocortical network alterations have been observed in patients with GGE, particularly in JME patients. These disfunctions may underlie the genesis of myoclonic and tonic-clonic seizures in GGE patients. Therefore, our case may represent a lesion model of generalized epilepsy with myoclonic seizures. However, our patient presented with lower limbs myoclonus, which is not the typical manifestation of myoclonic epilepsies, and is more commonly found in myoclonus of subcortical origin. Therefore, despite the presence of a consistent EEG correlate, we can assume that the axial-subcortical component was more represented. Finally, our case highlights that lower limb myoclonus of cortical-subcortical origin may be an underestimate cause of gait disturbances and postural instability. Then, it is reasonable to include the EEG in the diagnostic work-up of patients with recurrent falls.

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ACUTE BULBAR PALSY PLUS SYNDROME AS A RARE SUBTYPE OF GUILLAN-BARRÉ SYNDROME: A CASE REPORT

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Background: Acute bulbar palsy plus (ABPp) syndrome is a rare regional Guillan-Barré syndrome (GBS) variant that express common features of Miller Fisher (MFS) and Pharyngeal-cervical-brachial syndromes. Generally, it is characterized by multiple cranial nerve deficits, with or without ataxia, but in absence of limb and neck weakness.

Case report: A Caucasian 58-years-old woman with a medical history of Non-Hodgkin Lymphoma, ischemic heart disease and anxious-depressive syndrome complained sudden onset of diplopia and blurred vision upon awakening. Her neurological examination revealed left lateral and inferior recti muscles palsy which caused her double vision in the left gaze with preserved deep tendinous reflexes (DTR) in both upper and lower limbs. Then, she was discharged from a primary level hospital and prescribed with oral low dose of steroid therapy. In the following days, she developed left eyelid ptosis, hypophonia with nasal tone and dysphagia to liquids, which brought her to our attention. The patient reported a single episode of hyperpyrexia and nausea four weeks prior to hospitalization that spontaneously regressed after few days. Her neurological examination was characterized by an ataxic gait, complete ophthalmoplegia, left eyelid ptosis, nasal voice, dysphagia with nasal regurgitation of liquids and left hemisomatic hypoesthesia. The DTRs were ubiquitously increased (NINDS 4) with an extension of the reflexogenic area. After one week from the onset of the symptoms, she underwent lumbar puncture (no albumin-cytological dissociation was found in her CSF), contrast-enhanced brain and medulla MRI (negative), blood tests (positives for anti-Ganglioside, anti-GT1a and anti-GQ1b antibodies). Her electromyography, carried out 10 days after her admission, was suggestive of a minimal demyelination of left and right external popliteus sciatic nerves in the lower limbs with no acute denervation signs. Intravenous immunoglobulins (2 g/Kg over 5 days) were promptly started. At discharge, residual diplopia in the extreme lateral gaze, minimal left facio-crural hypoesthesia and instability in the tandem gait were still present. At the outpatient follow-up, two months after admission, her neurological objectivity was within normal limits.

Discussion: ABPp syndrome can be considered a distinct subtype of GBS with ophthalmoplegia, facial palsy, ataxia and presence of anti-GT1a and anti-GQ1b as distinctive features, rather than a mere overlap subtypes of GBS and MFS. Typically, subclinical neuropathy beyond cranial nerves could be present. This case report underlies the importance of a quick diagnosis and a prompt therapy, considering the potential serious complications including aspiration pneumonia and airway obstruction.

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THE CASE OF TWO SISTERS CARRYING GRN P.R298H MUTATION

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Introduction: Progranulin (PGRN) is a secreted glycoprotein encoded in humans by the GRN gene, located on chromosome 17q21. Several nonsense and missense pathogenetic GRN mutations have been described. To date, GRN p.R298H mutation was only reported in two papers and its pathogenetic role is still considered to be defined [1,2].

Objective: We herein present the case of two sisters carrying a GRN p.R298H mutation with extremely different clinical phenotypes and family history of dementia and behavioral disorders.

Methods: Patients underwent a multidimensional assessment including neurological and neuropsychological evaluation, structural and functional imaging, and genetic screening.

Results: The older sister presented at the age of 63 with severe depression of mood and apathy. She had a rapidly progressive and markedly asymmetrical parkinsonism and dementia. At the age of 65 years, she was anarthric and she developed severe dystonias prevalent in the left side of the body and in the cephalic district. She was bedridden at the age of 66 years. She was diagnosed with corticobasal syndrome. The younger sister presented at the age of 64 with dysphonia, dyspnea and inspiratory

stridor. Soon afterward, she developed urinary urgency and sporadic episodes of urinary incontinence. The only clinical feature common to both sisters is frontal cognitive dysfunction. Their father died at 52 years due to diabetic complications. Two paternal aunts were diagnosed with dementia and behavioral disorders.

Conclusions: Our cases strongly support the pathogenicity of the GRN p.R298H mutation, which is first detected in two members from the same family, both with clinical manifestations. Our findings suggest that this mutation may be associated with an extremely variable phenotype. This wide clinical variability among the members of the same family has been frequently reported as features of GRN mutations [3]. More importantly, we report the first case of an FTD-associated mutation manifesting with inspiratory stridor.

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PURE MOTOR AXONAL NEUROPATHY FOLLOWED BY THE SYRINGOMYELIA-LIKE PHENOTYPE: A NOVEL PRESENTATION OF TANGIER DISEASE

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Aims: Peripheral neuropathy is observed in approximately 50% of patients with Tangier disease (TD) and may present with two different phenotypes: an early onset form, characterized by a multifocal sensory-motor neuropathy with a spontaneously remitting course and an adult-onset chronic progressive syringomyelia-like neuropathy (SMLN). We herein describe the clinical features of two brothers with neuropathy and TD associated to a novel mutation of ABCA1 gene.

Materials and methods: We describe two brothers with TD: one presented with the classic SMLN form while his brother showed a unique two-stage clinical course, with a subacute, remitting polyneuropathy at the age of 21 years followed by chronic progressive syringomyelia-like manifestations 20 years later. Furthermore, in our patient clinical and electrophysiological features of the first episode were consistent with a pure motor axonal neuropathy with distal symmetric distribution.

Results: In both sibs we found a homozygous p.Tyr573Ter in the ABCA1.

Discussion: The early-onset TD neuropathy usually presents as a multifocal neuropathy in which conduction alteration at electrophysiological examination are a frequent finding. In these cases myelin alterations in the paranodal region of nerve fibers are supposed to be the cause of conduction blocks which underlie the reversible motor/sensory deficits, most likely. In our patient the distal symmetric neuropathy pattern was the result of multiple acute/subacute focal events, most likely. On the other hand, clinical, electrophysiological and pathological features were consistent with a pure motor axonal neuropathy which has never been described so far in Tangier disease. Axonal distal symmetric sensory-motor neuropathy with acute onset have been described in rare cases of TD disease, in which ischemic factors were suggested to play a major role. However, reported data supporting alteration of vasa nervorum in Tangier disease are not conclusive. Involvement of only motor fibers was a unique feature in our patient but whether or not this may have occurred by chance remains unclear.

Conclusions: This is the first case reported in the literature in which p.Tyr573Ter mutation in associated to polyneuropathy. The discovery of a novel clinical phenotype associated with this mutation may help to delineate new frameworks of genotype-phenotype association in Tangier disease.

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TREMOR SYNDROMES IN THE ELDERLY: THREE CASES

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Targets: We report three patients who presented a late onset, slowly progressive tremor syndrome associate to mild parkinsonian, cerebellar and psychiatric features.

Materials: PATIENT 1: 82 years old man who presented with gait and balance disturbances associated with bilateral hand tremor, with onset 2 years ago. On examination, we can appreciate mild cerebellar ataxia, dysmetria of left arm and intentional tremor of both hands. PATIENT 2: 63 years old man who reports tremor of both hands, mild depressive symptoms and behavioral issues which started ten years ago. On examination, he showed bilateral rest and action tremor, mild clumsiness on finger tapping and difficulty in tandem gait walking. PATIENT 3: 60 years old woman generalized tremor syndrome, which started 8 years ago. On examination, she showed mild bradykinesia in finger tapping bilaterally and rest and action tremor on the four limbs, head and chin. She also reported anxiety and mild depression.

Methods: The patients underwent Brain MRI, routine laboratory testing, neuropsychological assessment and FMR1 genetic test.

Results: Laboratory workout showed normal findings. Neuropsychological and behavioral assessment of patient 2 reported a control disorder and decrease of motivation without cognitive issues. Brain imaging of patient 1 and 2 showed diffuse cerebellar atrophy and hyperintensity of middle cerebellar peduncles. MRI of patient 3 showed diffuse supratentorial atrophy associated with white matter hyperintensity. Therefore, they underwent genetic testing for Fragile X-associated tremor/ataxia syndrome (FXTAS), that revealed a CGG expansion in the permutation range in FMR1 gene (respectively 88, 106 and 100 CGG repeats). Only the third patient reported family history of fragile-X syndrome (FXS).

Discussion: Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late onset neurodegenerative disorder characterized by progressive

ataxia, tremor, cognitive involvement, neuropathy, and autonomic dysfunction. The clinical features usually begin in the sixth decade with an action or intention tremor followed by cerebellar ataxia. Symptoms can mimic other movement disorders or neurodegenerative diseases, so misdiagnosis is frequent. Individuating the disorder is important also to identify the gene mutation in family members.

Conclusion: The diagnosis of FXTAS should be considered in elderly patient who present these clinical features with or without family history for Fragile X syndrome (FXS). Brain MRI can provide an important support for diagnosis that must be confirmed by genetic test.
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COMBINATION TREATMENT WITH CYCLOPHOSPHAMIDE, RITUXIMAB AND CORTICOSTEROIDS TO ARREST A RAPIDLY PROGRESSIVE TUMEFACTIVE PRIMARY CNS VASCULITIS: A CASE REPORT

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Background: Pseudotumoral presentation of primary CNS vasculitis represents a diagnostic challenge. Rapidly progressive primary CNS vasculitis often has a fatal outcome [1]. In the absence of evidence-based guidelines an aggressive disease course, refractory to common immunosuppressive drugs, may require off-label treatment combinations. For this reason, case reports describing effective treatments of a rare diagnosis and disease course are of paramount importance.

Case description: In January 2020 a 35-year-old male was referred to our Neurology Department for acute onset of superior left field quadrantanopsia and headache. Brain MRI showed a right occipital FLAIR hyperintense lesion associated with hemorrhagic infarct and cortical Gadolinium enhancement. Autoimmune and infectious disease screening, CSF analysis (comprehensive of oligoclonal bands), magnetic resonance angiography and cerebral angiography were normal. Brain MRI in the next months showed progressive lesion expansion with cortical gadolinium enhancement, cortical hemosiderin deposits, petechial hemorrhages and edema. Brain biopsy in June 2020 revealed perivascular and transmural inflammation, suggesting a primary CNS vasculitis. He was treated with high dose methylprednisolone iv followed by oral prednisone (PD) 1 mg/kg and Cyclophosphamide (CTX) 750 mg/m2 (monthly pulse dose iv). Three months after starting CTX he presented complete left-sided homonymous hemianopsia and brain MRI showed further disease expansion in the occipital, temporal and parietal right lobes with brain edema and gadolinium enhancement in the most recent inflammatory lesions. CTX was interrupted and Rituximab (RTX) 1g iv every 6 months was started in December 2020. Brain MRI performed 3 months later showed further disease expansion in the left basal ganglia and hippocampus with gadolinium enhancement. Due to the failure of both immunosuppressants used separately, combination therapy already applied in systemic aggressive ANCA-associated vasculitis [2-3] was adopted. After starting combination treatment with CTX (10 mg/kg day 0-14, then 500mg at week 4-6-8-10) plus RTX (1g every 6 months) plus PD (1mg/kg for one week, followed by gradual tapering) patient showed clinical and neuroradiological disease activity remission. Since then, the patient presented no relapses and brain MRI performed every 6 months reported disease stability in the 16-month follow-up.

Conclusion: We present the case of a young male affected by tumefactive-variant of primary CNS vasculitis refractory to common immunosuppressive treatments. Disease showed incessant progression despite steroid treatment associated initially with Cyclophosphamide and then with Rituximab. In our case report, combination therapy used in systemic aggressive ANCA-associated vasculitis (Cyclophosphamide+ Rituximab+Prednisone) proved to be effective also in primary CNS vasculitis.
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LONG-COURSE OF SPORADIC CREUTZFELDT-JAKOB DISEASE MIMICKING STEROID-RESPONSIVE ENCEPHALOPATHY ASSOCIATED WITH AUTOIMMUNE THYROIDITIS

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Aims: Sporadic Creutzfeldt-Jakob disease (sCJD) is a fatal neurodegenerative syndrome, characterized by rapidly progressive cognitive decline, psychiatric manifestations, myoclonus and cerebellar ataxia [1]. Periodic sharp wave complexes (PSWCs) are characteristic in sCJD and may exceptionally disappear in the terminal stage of the disease, because of the flattening of EEG activity [2]. Inflammatory disorders of the central nervous system must be considered in the differential diagnosis, especially in young and middle-aged patients. We report a patient with long-course of sCJD mimicking steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT).

Case: A 53-year-old man had a four-month history of behavioural and personality changes with memory disturbances. Two years earlier, he already began to manifest severe depression and anxiety disorder. Neurological examination showed partial orientation in time and space with multi-domain cognitive impairment including verbal, short and long-term memory, executive and visuo-spatial functions with constructional apraxia. Blood tests were normal, except for high titer of thyroperoxidase antibodies (TPOAb) (>1300U/ml, n.v.:<60U/ml). Cerebrospinal fluid examination only revealed high proteins (480mg/dl, n.v.: 150-450mg/dl). EEG revealed PSWCs associated with diffuse slowing. Brain MRI revealed hyperintense signal in the bilateral caudate nuclei and putamina on FLAIR and to lesser extent DWI sequences. Because of history of subacute cognitive impairment, psychiatric disturbances, and elevation of TPOAb, highly suggestive of SREAT, we attempted a therapy with intravenous methylprednisolone (at the total dosage of 5 g), followed by a 5-day (0.4gr/kg/day) intravenous immunoglobulin. Afterwards, repeat EEG showed a remarkable improvement of brain activity with disappearance of PSWC. After 24 months from the clinical onset, patient's cognitive profile has remained stable, even if he

developed complex visual hallucinations. A real-time quaking-induced conversion in cerebrospinal fluid was performed and tested positive. There was no mutation of PRP gene; a 129-codon Met-Val polymorphism was identified. According to CDC criteria [1], a diagnosis of probable sCJD was made.

Discussion: The survival time of sCJD is about 6 months from diagnosis, although longer anecdotal cases have been described [3]. Our case emphasizes the need to consider CJD in the diagnostic panel of cognitive decline, even in long clinical course disease and subtle clinical presentations. The significance of the marked and persistent EEG improvement after immunotherapy remains uncertain.

Conclusion: sCJD may occasionally have an atypical course with very slow progression. Diffusion-weighted imaging alongside other neuroimaging and cerebrospinal fluid real-time quaking induced conversion can aid diagnosis in atypical cases. The diagnosis of SREAT should only be considered after exclusion of other causes.

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NEUROSARCOIDOSIS PRESENTING AS ISOLATED MYELITIS

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Myelitis includes a spectrum of inflammatory disorders of the spinal cord that might result in devastating neurologic pictures. Sarcoidosis-associated myelopathy (SAM) refers to spinal cord involvement within sarcoidosis. This expression of neurosarcoidosis is reported to be extremely rare and represents a challenging differential diagnosis among myelitis. SAM carries indeed clinical and radiologic features in overlap with other inflammatory spinal cord disorders, such as neuromyelitis optica spectrum disorder (NMOSD), rendering so the diagnosis particularly difficult. Here we described a 71-year-old woman who presented with subacute diffuse weakness with both limbs and axial involvement, accompanied by a progressive dorsal hyper-kyphosis, dorso-lumbar pain with radiation to the anterior surface of the thigh and knee, and difficulties in ambulation. Her previous medical history was unremarkable, and she was taking no medications at the moment of hospital admission. Magnetic Resonance Imaging (MRI) of spinal cord showed multiple lesions interesting the cauda equina, the antero-lateral portion of the medulla oblungata and the spinal cords at different levels with a more extended lesion affecting the C2-C7 cervical tract, with contrast enhancement. Brain MRI showed no supratentorial CNS involvement. ENG/EMG analysis revealed an electrophysiological picture of chronic motor and sensitive axonal polyneuropathy. CSF analysis findings were a mild pleocytosis with moderate increase in CSF proteins. Whole body computer tomography (CT) and positron emission tomography (PET) pointed out the existence of mediastinc lymphadenopathy. The levels of serum ACE were mildly increased (82 IU/L). The patients so underwent thoracotomy with lymphonodal biopsy that showed non-necrotizing granulomas characterised by the presence of multinucleated giant cells and T lymphocytes, predominantly CD4 positive. Hence, it was possible to make a diagnosis of probable neurosarcoidosis based on the Neurosarcoidosis Consortium Consensus Group Diagnostic Criteria. Immunosuppressive therapy with prednisone was immediately started without further progression of neuroradiological findings and symptoms over the following years. Radiological findings within SAM can be extremely aspecific and the anatomical site is not easily accessible for biopsy, in presence of clinical suspect, the assessment of the other most commonly involved apparatus is fundamental in collecting systemic evidence of disease necessary for the diagnosis. Actually, no firm guidelines on whether, when and how treatment should be started, but immunosuppressive therapy is strongly suggested. SAM is a condition that must be taken into account in the differential diagnosis of myelitis and tempestive diagnosis, treatment and multidisciplinary management lead to better outcome.

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TREATMENT RESISTANT MITOCHONDRIAL-RELATED MIGRAINE EFFECTIVELY REVERTED AFTER CGRP MONOCLONAL ANTIBODIES THERAPY: IS THERE A ROLE OF CGRP IN GLYCOLYTIC PATHWAY?

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Background: Migraine affects nearly 55% of patients with mitochondrial disease, representing a significantly higher prevalence compared to general population. Migraine mechanisms, characterized by the imbalance between brain demand and energy resources, may be shared also by patients with mitochondrial disease (MD), where dysfunctional glucose metabolism works as a key pathophysiological substrate for migraine attacks. Furthermore, in patients with MD, migraine attacks seems to be more treatment resistant compared to patients with migraine without MD. However, the migraine response to monoclonal antibodies acting on the pathway of CGRP (CGRP-mAbs), proven effective and safe in the preventive treatment of patients with episodic and chronic migraine, is unknown, to date.

Materials: Monthly subcutaneous galcanezumab 120 mg have been administered as preventive treatment in two women with genetically proven neuropathy, ataxia, and retinitis pigmentosa syndrome (NARP) and progressive external ophthalmoplegia (PEO), suffering from chronic migraine, respectively without and with medication overuse. Both patients had failed three previous medication classes.

Methods: Patients underwent a monthly follow-up for six months in order to assess galcanezumab effectiveness, safety and tolerability. Headache diary were used for monitoring the number of migraine attacks, migraine duration (hours), headache intensity, number of painkillers intake and pain killers response (hours to pain free). Tolerability and safety were evaluated considering patients reported information.

Results: After the third galcanezumab administration, both patients reported a significant reduction in monthly migraine headache days (>50%). Specifically, a reduction from an average of 20 migraine days/month to 2 migraine days/month, and from an average of 30 migraine days/month to 14 migraine days/month was observed in respectively the patient with NARP and patient with PEO. Furthermore, headache intensity, number of pain-killers intake and pain killers response (hours to pain free) showed a significant improvement compared to the baseline. No tolerability or safety concerns emerged in the course of six-month treatment.

Discussion: Preclinical observations demonstrated a multifaceted role of circulating CGRP in energy metabolism, being able to reduce glycolytic capacity as well as fatty acid oxidation in primary white adipocytes. We speculate that the improvement of migraine severity observed in our patients with mitochondrial diseases could be due to a CGRP-mAbs-related remodulation of glycolytic pathway.

Conclusion: CGRP-mAbs could represent an effective and safe preventive therapeutic strategy in patients with genetically proven mitochondrial disease complaining migraine attacks. Future studies with a larger sample of patients will further support our observations.

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MYOCLONUS EPILEPSY IN A PATIENT WITH DOWN'S SYNDROME– A CASE REPORT

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Late-onset myoclonic epilepsy in Down's syndrome (LOMEDS) should be considered in the differential diagnosis of adult progressive myoclonic epilepsies due to their common characteristics (myoclonus, generalized epilepsy and neurological deterioration). Here we report a case of a 47-year-old woman with Down's syndrome admitted to our hospital because of worsening of her neurological condition. Her clinical history was unremarkable except for intellectual disability and psychiatric symptoms. She apparently never experienced seizures. Her sister reported a loss of the ability to perform daily activities, apathy, and unsteadiness during the previous 6 months. Involuntary movements of the limbs occurred as well. On admission, the patient was not collaborative, mutacic and unable to walk. Neurological examination revealed myoclonic jerks of the left lower limb. Because of her clinical condition, Mini-Mental State Examination was not administrable. CT scan revealed diffuse cerebral atrophy; MRI was not performed due to cardiac pacemaker. The analysis of the cerebrospinal fluid showed a reduction in Aß42 and Aß40 levels, whereas t-TAU and p-TAU were normal. EEG/EMG were performed. EEG showed a slow background activity with intermittent spike-waves or diffuse polyspike-waves complexes during wakefulness. Physiological sleep patterns were absent. Myoclonic jerks occurred especially upon wakefulness without EEG correlates. Intermittent photic stimulation at 18-21-24 Hz increased the paroxysms without clinical correlation.
Valproate was administered and myoclonus decreased, so the patient was able to walk again. Considering the clinical characteristics, the instrumental/laboratory findings, and chromosome 21 role in myoclonic epilepsies, a diagnosis of LOMEDS was made.

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POMALIDOMIDE-ASSOCIATED PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) IN A PATIENT WITH IGG-K MULTIPLE MYELOMA (MM)

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Introduction: Progressive multifocal encephalopathy (PML) is a severe demyelinating disease of the central nervous system (CNS) caused by the John Cunningham virus (JCV), which affects mainly immunocompromised individuals. Although several cases of PML have been described in individuals with multiple myeloma (MM), few are associated with pomalinomide treatment.

Case description: A 76-year-old woman suffering from multiple myeloma IgG-κ (stage ISS II) since 2005, came to our observation due to a sensory-motor left hemisyndrome which had arisen about two months earlier. The symptoms had started subtly, with a slowly progressive course. At the time of admission the patient was on the third line of therapy with a pomalidomide-dexamethasone-cyclophosphamide regimen (XVIII cycle). Magnetic resonance of the brain showed a bulky and uneven hyperintense lesion in the T2/FLAIR sequences, extending to the subcortical white matter of the right hemisphere, with typical well-defined border towards the cortex and involvement of the U-fibers. An initial spread to left hemisphere was already present at that time. The lesion was hypointense in the T1 sequence, and showed no gadolinium contrast-enhancement. The diagnosis of PML was therefore defined by the detection of the JC virus in the CSF using PCR technique.
Despite the discontinuation of the immunosuppressive therapy, in the next week there was a progressive clinical worsening, with severe spastic tetraparesis, dysarthria and dysphagia, and finally impaired consciousness. The patient eventually died about two months after a definite diagnosis was made.

Discussion and conclusions: PML is a well-known, potentially devastating disease of the CNS caused by reactivation of the JCV, and is often underdiagnosed. No effective therapy is currently available. In the last decades PML cases have increased, due to the wider use of immunosuppressive therapies, mainly linked to oncological and autoimmune diseases. Since the only effective intervention is the timely withdrawal of the responsible drug (see Natalizumab-associated PML in multiple sclerosis),

it is mandatory to establish an effective prevention, through well-defined screening programs in subjects at risk for this disease (e.g. routine JCV serology test).

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SPINAL CORD NEUROSARCOIDOSIS

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Introduction: Neurosarcoidosis occurs in less than 10 percent of patients with sarcoidosis, yet it can cause significant neurologic impairment. Basilar meningeal involvement with an associated cranial neuropathy (usually involving the facial nerve) and leptomeningeal involvement, either focal or diffuse, may be observed. Isolated neurosarcoidosis of the cauda equina is uncommon and neurologic disability with poor prognosis derives from delayed diagnosis.

Case report: A 70-year-old Caucasian man presented in June 2021 with a 2-month history of progressive walking impairment, weight loss and confusional state. CT scan and brain MRI were normal. Cerebrospinal fluid (CSF) examination showed raised protein 254 mg/dL, low glucose level 24 mg/dL, mononuclear pleocytosis (72 cells-79% mononuclear). CSF-restricted oligoclonal bands immunoglobulin with elevated (Ig) G index were found. Cytogenetic abnormalities of the lymphoma cells in CSF were not found. Overall CSF PCR were negative (West Nile Virus, Koch Bacillus, Parvovirus, Criptococcus, Herpes Viruses) as well as paraneoplastic and autoimmune antibodies. A MRI scan of the spine detected an abnormal mass with high contrast enhancement at L5 level with inflammatory-granulomatous aspect. Whole body PET was normal. Extensive search for malignancy including chest and abdominal CT and MRI scans was all negative. The biopsy of the intracanalar lumbar lesion was aspecific. CSF levels of IL-2 was 2038 pg/mL (negative in blood) and chitotriosidase 56.2 nmol/h/ml (normal in blood). A diagnosis of neurosarcoidosis of the cauda was advanced. At this stage a brain MRI showed meningeal contrast enhancement at brain stem. Desametasone 8 mg ev BID was started but the presence of multiple infections limited the increase of the therapy. The patient died three months later for massive subarachnoid haemorrhage.

Discussion: Neurosarcoidosis of the cauda equine was a challenging diagnosis in this patient because of the lack of extraneurological involvement. CSF examination and the MRI results support the differential diagnosis with others causes of involvement of the cauda equine as tuberculosis and lymphoma. The failure of the biopsy and the long time for second level exams processing delayed the starting of immunosuppressive therapy, also limited by the presence of nosocomial infection. A leptomeningeal truncal vasculitis as a second relapse of sarcoidosis developed only 8 weeks after the admittance and in course of corticosteroid therapy.

Conclusions: Spinal cord sarcoidosis occurs in less than 1% of all cases of this disease. The lack of consensus diagnostic criteria and algorithm are the main obstacle to the rapid and successful diagnostic achievement.

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EMICHOREA FOLLOWING AN ACUTE HYPEROSMOLAR HYPERGLICEMIC STATUS: CASE REPORT

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Objectives: To present a case report of an emichorea, occurred in a patient without history of previous acute cerebrovascular accidents.

Material: A 83 years-old female developed postural instability in association with a concomitant hyperglicemic status. CT and MRI scan of the brain showed a lesion in the right putamen, attributed to a dysmetabolic origin. The patient was then hospitalized with the diagnosis of hyperosmolar hyperglicemic status. Meanwhile she developed COVID-19 with an asymptomatic course. The Patient was discharged from the Hospital one month after and started suffering from "jerks" along the left side of the body with brachio-crural distribution. She was further hospitalized for more precise diagnosis and then treated with multiple doses of tetrabenazine up to a total dose of 200 mg per day, then reduced to 100 mg per day, with a completely resolution of the intrusive choreic-atetosic movements.

Methods: Brain MRI scan, EMG/ENG and EEG study, polysonnography, thoracic-abdominal CT scan, oncologic markers and lumbar puncture with particular investigation of neurodegenerative biomarkers, antibodies for autoimmune encephalitis and onconeural antibodies.

Results: New brain MRI scan was superimposable to the previous one. Polysonnography demonstrated complete absence of movements during sleep. The EEG study did not show any epileptic related elements. The EMG/ENG and the results of lumbar puncture were substantially unremarkable. Taking into consideration the hypotesis of a paraneoplastic syndrome, oncologic markers were investigated and a thoracic-abdominal CT scan was performed, resulting in an isolated elevation of chromogranine A and no evidence of tumors.

Discussion: Non-ketotic chorea (NKC) has been described in literature and it is recognized as a clinical entity related to a concomitant non-ketotic hyperglicemic status in less than 1 per 1,000,000 patients with diabetes, particularly elderly women. Proposed pathogenetic hypotesis may be hyperglicemia and glucose toxicity, concomitant hyperviscosity and local microhemorrages. Compared to other metabolic disorders, non-ketotic chorea has usually a unilateral onset [1,2]. Intercurrent SARS-CoV-2 infection may play a role [3].

Conclusion: Discussing the present case with the available literature, we confirm the potential link with a poorly controlled diabetes and, in particular, with an acute hyperosmolar hyperglicemic status.

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REVERSIBLE VASOCONSTRICION SYNDROME AS A RARE COMPLICATION OF GUILLAIN BARRÈ SYNDROME

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Background and Aims: Reversible Cerebral Vasoconstriction Syndrome (RCVS) is a clinical and radiological entity characterized by thunderclap headache with or without other neurological deficits associated with segmental constriction of cerebral arteries that resolves within 3 months. The pathophysiology is unknown, but alterations in cerebral vascular tone induced by sympathetic overactivity, endothelial dysfunction and oxidative stress are thought to be the underlying mechanisms. RCVS has been associated with various conditions, including vasoconstrictive drugs, blood products, migraine, pregnancy, and post-partum state. We present a case of RCVS complicating Guillain Barrè syndrome.

Materials and Methods: A 39-year-old woman, at 4 months postpartum and with history of migraine with aura, was admitted for acute inflammatory demyelinating polyneuropathy (Guillain Barrè syndrome) with cranial nerves involvement (bilateral facial and trigeminal nerves), confirmed by serial electrophysiological studies and cerebrospinal fluid analysis. Intravenous immunoglobulin 2 g/kg were administered over 5 days. No signs of dysautonomia were reported during continuous monitoring of vital parameters. 6 days after the admission, she developed recurrent episodes of severe headache, poorly responsive to nonsteroidal anti-inflammatory drugs.

Results: A head CT scan was performed, showing bilateral subarachnoid haemorrhage overlying the occipital lobes. Transcranial doppler ultrasound revealed elevated mean flow velocities in the left and right middle cerebral arteries and in the left posterior cerebral artery. Brain MRI and MRA confirmed vasoconstriction involving anterior and posterior circulation and excluded other causes of subarachnoid haemorrhage. Oral nimodipine (60 mg every 6 hours for 7 days) was administered to treat vasospasm, and opioid analgesics for pain management. 18-days-MRA follow-up showed complete resolution of cerebral vasoconstriction.

Discussion: Our patient meets the proposed diagnostic criteria for RCVS, with acute headache, cerebral vasoconstriction demonstrated by transcranial doppler sonography and MRA, complete normalisation of vascular abnormalities within 12 weeks. Up to our knowledge, few cases of Guillain Barrè syndrome complicated by RCVS have been reported. Previously proposed mechanisms involved increased cerebral vascular tone due to dysautonomia with arterial hypertension, and endothelial dysfunction provoked by elevated levels of cytokines and systemic immune activation. Post-partum state and intravenous immunoglobulin therapy have been independently associated with RCVS. We hypothesize that demyelination of trigeminal nerve and its cerebral blood vessels afferents could lead to a dysregulation of trigeminovascular system, acting as a risk factor for RCVS.

Conclusion: RCVS is an uncommon complication of Guillain Barrè syndrome, and neurologists should be aware of its occurrence.
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ANTI-GLUR3 LIMBIC ENCEPHALITIS: A RARE CASE OF NSAS

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Introduction: Neuronal surface antibody syndromes (NSAS) are a growing group of autoimmune neurological illnesses characterized by autoimmune encephalitis (AE), which mainly affect the medial temporal lobe. The well-known NSAS include those associated with anti-NMDAR, anti-LGI1, and anti-CASPR2 antibodies, whereas other forms are uncommon. Apart from the typical encephalitis symptoms of altered awareness, fever, and focal neurological abnormalities, limbic encephalitis can also cause neuropsychiatric signs and seizures [1]. We present an unusual case of limbic encephalitis with anti-GluR3 antibodies positivity.

Case report: We describe a patient who presented fever, convulsions and behavioural abnormalities following bilateral interstitial pneumonia. His medical history was significant for sarcoidosis, diabetes, hypertension, and a COVID-19 pneumonia three months before. T2-hyperintense bilateral lesions in the temporal cortex and bilateral lesions in the anterior frontal-insular cortex were seen on contrast-enhanced brain MRI. An electroencephalogram resulted widely slowed without focal alterations. Lumbar puncture presented high protein and glucose values, a negative microbiological exam, high value of Link-index and Tourtellotte index, elevated IgG, numerous oligoclonal bands. Anti-GluR3 antibodies positivity in was discovered. We also performed several blood and radiological exams to exclude neoplastic or infective sources, but no significant data were found. We started an antibiotic and an antiviral treatment for this patient for a possible infectious etiology, and then we moved to an immunosuppressive treatment with methylprednisolone, but we had to stop this drug for multiple infectious comorbidities appeared during the hospitalization.

Discussion: Anti-GluR3 antibodies are uncommon in adult patients' cerebrospinal fluid (CSF), but they were found in children with autoimmune epilepsy, particularly in Rasmussen encephalitis [2]. They have unique properties and generate many pathogenic effects in vitro and in vivo. They are discovered in a considerable number of patients with unexplained and intractable epilepsy - especially GluR3B peptide antibodies.

Conclusions. Anti-GluR3 encephalitis is a poorly defined neuropathological condition that should be addressed when assessing NSAS in adults, especially if the more common antibodies are not present in blood or CSF examination. Due to the lack of data on this clinical entity, it is unclear whether Anti-GluR3 encephalitis has a worse prognosis than other more prevalent NSAS.
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AZYGOS ANTERIOR CEREBRAL ARTERY CAUSING LEFT MEDIAL FRONTOPARIETAL AND BILATERAL OCCIPITAL INFARCTS

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Objectives: Acute ischemic stroke usually presents as a clearly defined clinical syndrome with evidence of brain infarction at neuroimages in specific vascular territories. Atypical clinical and neuroradiological presentations may occur, especially due to a vascular variant. Here, we described an atypical presentation of ischemic stroke in a patient with azygos anterior cerebral artery (AACA).

Materials: A 74-year-old man was admitted to our Section for an acute onset transient clinical picture characterized by stereotyped, rhythmic and involuntary movements of the head ('no-no' like) and of the right trunk (twisting), categorized as focal aware seizures. A transient right hemiparesis, lasting 30', had occurred the day before. His medical history was relevant for high blood pressure. At hospital admission, neurological assessment was unremarkable. Brain CT showed a recent ischemic left pericallosal lesion. Neurological condition worsened the day after, with the occurrence of acute-onset severe right hemiparesis, apraxia, difficulty in right-left discrimination, and dyscalculia.

Methods: The patient underwent brain magnetic resonance imaging (MRI) with magnetic resonance angiography (MRA), doppler ultrasound of carotid and vertebral arteries, precordial echocardiography, electrocardiogram, 24 h-cardiac rhythm monitoring and electroencephalogram. Results: Brain MRI showed recent ischemic lesions in the left medial hemisphere involving the callosal body, semioval center and parietal lobe. Also, bilateral occipital infarcts were evident. On MRA, an AACA with stenotic, atherosclerotic narrowing before pericallosal artery emergence was detected. The other examinations showed no relevant findings. A double antiplatelet treatment was started.

Discussion and conclusions: AACA is a rare anatomical variant, characterized by the presence of only one anterior cerebral artery: two A1 segments of the anterior cerebral artery join to form a single vessel, and no anterior communicating artery is present [1]. Since a single AACA supplies territories of both anterior cerebral arteries, a stroke in the AACA territory can result in bilateral frontal infarcts [2,3]. In our case, AACA stroke was associated to an atypical presentation, with unilateral medial fronto-parietal lesions and bilateral occipital lesions, probably due to a peculiar cerebral collateral circulation and to the involvement of watershed territories.

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AN ITALIAN FAMILY WITH MOTOR NEUROPATHY AND HEARING LOSS CAUSED BY A MYH14 MUTATION

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Objective: To report on an family with distal muscle weakness and a previous diagnosis of non-molecularly characterized distal myopathy with autosomal dominant inheritance.

Materials and Methods: Clinical, laboratory, neurophysiological, muscle pathology, muscle imaging and genetic data of two affected family members (the proband and his brother) were analyzed. In addition, full audiological examination of both siblings was performed.

Results: The patients had onset in their adolescence with distal lower limb weakness, starting in the anterior compartment, followed by involvement of intrinsic hand muscles. Serum CK were normal or slightly elevated. Electrophysiological studies were consistent with chronic motor axonal involvement. Scapular girdle and lower limb muscle MRI showed extensive fatty replacement of lower leg muscles both in anterior and posterior compartments, with a "muscle island" pattern. Muscle biopsy was compatible with chronic neurogenic damage with a slight increase in internal nuclei. Since they complained of hearing loss, audiological examination was performed and confirmed a bilateral, moderate to severe sensorineural (cochlear) deafness. Based on these findings, a targeted NGS panel covering genes for hereditary neuropathies/motor neuron diseases was performed and showed the presence of a heterozygous variant in the non-muscle myosin heavy chain gene 14 (MYH14), c.2822G>T; p.R941L, segregating with the disease.

Discussion: Mutations in MYH14 are commonly associated with pure, non-syndromic autosomal dominant deafness. However, this variant, which has been previously described only in four families (two Korean and two Northern American), was also associated with an axonal neuropathy phenotype. In the two Korean families the patients presented, in addition, myopathy and hoarseness, and minor concomitant myopathic findings were present in our patients as well.

Conclusion: We describe the first European family carrying the R941L mutation in MYH14. MYH14-opathy is an ultra-rare disease that should be considered in the differential diagnosis of patients with neuro(myo)pathy and sensorineural deafness.

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MULTIFOCAL CONTRAST-ENHANCING BRAIN LESIONS IN A PATIENT WITH RECENT SARS-COV 2 INFECTIONS: A CHALLENGING CASE

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Background: Brain MRI, together with clinical and laboratory findings, usually helps in differential diagnosis between neoplastic and tumefactive demyelinating lesions (TDLs). However, glioblastoma may evade this

paradigm, representing a diagnostic challenge. We herein present an insidious case of infiltrating, multifocal glioblastoma that mimicked TDLs.

Case presentation: A 68-years old otherwise healthy woman was admitted to our Clinic for diplopia, dizziness, and left hemianesthesia and dysesthesia which came up a month before, soon after the administration of COVD19 vaccination. The clinical picture severely worsened ten days before admission, after SARS-CoV2 infection. At neurological examination, she presented bilateral rotatory nystagmus and limitation in vertical conjugated eye-movements. A brain MRI showed a tumefactive T2-FLAIR-hyperintense, T1-hypointense lesion in the midbrain and right thalamus with homogeneous contrast-enhancement. Perfusion showed high rCBV-values and there was a rise of choline with modest reduction of NAA. A similar smaller lesion was described in left frontal lobe. On CSF analysis, a mild protein increase (57 mg/dL) was found, with no other abnormal findings on microbiological investigations, IgG index and isoelectrofocusing. CSF NfL was 1157 pg/mL, serum and CSF AQP4 and MOG antibodies tested negative, as well as serum ANCA, ANA, Anti-citrullin antibodies. A chest-abdomen CT scan and a total body 18FDG-PET were performed, only showing a mild prevalence of 18FDG uptake in right thalamus. Considering these findings and the history of recent SARS-CoV2 infection and vaccination, IVMP 1 g/daily for 10 days was started with initial benefit. A control brain MRI showed reduction in size and in contrast-enhancement of the lesions. We started an oral tapering with prednisone 1 mg/kg, but in few days clinical conditions worsened. A brain MRI showed an increase in contrast-enhancement and an enlargement in size of all the lesions. We proceeded with plasma exchange (5 exchanges in10 days), without improvement. Due to the appearance of obstructive hydrocephalus, an external ventricular drainage was applied. A biopsy of the frontal lesion eventually led to the diagnosis of glioblastoma IDH-wildtype, grade four (WHO 2021).

Discussion and conclusions: Inflammatory demyelinating diseases have been described after SARS-CoV2 infection or vaccination. In our case, the history of recent SARS-CoV2 vaccination and infection, led to consider an inflammatory nature of brain lesions. However, the diagnostic work-up led to diagnose glioblastoma. When no better explaination is available, clinicians should keep in mind the possibility of neurological sequelae of SARS-CoV2 infection but differential diagnosis with SARS-CoV2 unrelated diseases should always be performed.

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A CASE OF DELAYED PRES IN A NORMOTENSIVE PATIENT WITH MULTIPLE POSSIBLE ETIOLOGIES

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Posterior reversible encephalopathy (PRES) is a clinico-radiological entity first described in 1996 [1], characterized by headache, altered mental status, seizures, nausea, vomiting and visual abnormalities associated with typical neuroimaging findings. Its pathophysiology has not been completely explained, but endothelial injury, neurotoxicity and impaired cerebral autoregulation are most probably involved. We present the case of a 71 years old female, with NHL, treated with rituximab and methotrexate until February 2022. Three weeks before the admittance to the emergency room she had COVID, with cough, asthenia, myalgia. Besides she has chronic pain, with episodic analgesic overuse. The last chemotherapy administration was in February 2022; two months later she developed severe headache and general malaise and then she was admitted to the emergency room with a tonic- clonic seizure. On admission and during the hospital stay blood pressure was normal. Cerebral CT with angio-CT and CT perfusion showed ischemic-like left temporal lesion, narrowing of left M4 with decreased local perfusion. EEG showed global slowing without epileptic abnormalities. Severe mental status alteration persisted; lumbar punture was performed and revealed slightly elevated protein level (76.5 mg/dl); absence of polymerase chain reaction tests for virus detection, including SARS-CoV-2; autoimmune encephalitis and paraneoplastic syndrome were excluded, as well as the presence of malignant cells. Brain MRI showed bilateral, subcortical parieto-occipital T2 /FLAIR hyperintensities, no restriction in DWI, no contrast enhancement, with a radiological pattern suggestive of PRES. During the first days in the hospital the patient showed confusion, behavioral abnormalities, visual and other sensitive misperceptions and aphasia; no other focal signs. Then she gradually improved until complete recovery ten days later, with supportive therapy alone. The brain MRI after two weeks was completely normal. She was discharged with the diagnosis of PRES, according with the clinico-radiological criteria [2]. Our report highlights that PRES should be considered even when neurological symptoms occur months after the administration of chemotherapy, widening in this way the spectrum of chemotherapy-induced PRES. Anyway we can't exclude in this case that other triggers, such as the recent COVID infection, could precipitate neurotoxicity: in fact PRES cases are increasingly being reported in patients affected by COVID-19, although generally during the acute phase of a severe clinical impairment [3].

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NEW ONSET REFRACTORY STATUS EPILEPTICUS IN LIMBIC ENCEPHALITIS RESPONSIVE TO ANAKINRA AND BRIVARACETAM: CASE REPORT

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Objectives: To report the efficacy of anakinra and brivaracetam in inducing persistent seizure remission in a case of seronegative limbic encephalitis with new-onset refractory status epilepticus (NORSE).

Materials and Methods: A 47 years-old female patient was admitted to our hospital due to a first generalized tonic-clonic seizure. A contrast-enhancement CT scan excluded acute lesions and venous thrombosis. The following days she became unresponsive due to nonconvulsive status

epilepticus. She was then admitted to Intensive Care Unit. The MRI scan showed bilateral, symmetrical T2-hyperintensity in the mesial temporal lobes and external capsules, without contrast enhancement. CSF findings, including viral PCR, resulted to be normal. A second CSF analysis showed protein increase without pleocytosis. A wide panel for serum and CSF surface and onconeural antibodies was negative. Total-body CT scan and PET showed no malignancies. She underwent therapy with high-dose IV corticosteroids and IV immunoglobulin, followed by oral steroids, with no significant improvement. Due to persistent electrographic status epilepticus despite multiple antiepileptic therapy with high-dose phenytoin, lacosamide and levetiracetam, intravenous barbiturate was started without any improvement. One month after clinical onset, anakinra 100 mg subcutaneous twice daily was started. Levetiracetam was shifted to brivaracetam.

Results: After few days, EEG and vigilance significantly improved. One month after the therapeutic switch, the patient was discharged from ICU and readmitted to Neurology ward. MRI showed progressive resolution of the temporal lobes hyperintensity and the patient improved in both neuromotor and neuropsychological functions. EEG showed no ictal activity nor interictal epileptiform discharges. She was then transferred in rehabilitation facility due to residual memory and frontal functions deficit.

Discussion: Non infective, antibody-negative limbic encephalitis represents a diagnostic and therapeutic challenge. Timely administration of immunotherapy could help preventing irreversible sequelae as cognitive impairment. Status epilepticus may represent the main clinical symptom of this syndrome. Treatment of autoimmune encephalitis includes first-line (steroids and IVIg) and second-line therapies (rituximab or cyclophosphamide). Anakinra, an IL-1 receptor blocker, has been recently shown to be an option for unexplained cerebral inflammatory syndromes and autoimmune encephalitis. It has also been shown to control seizures in Rasmussen's Encephalitis, FIRES and NORSE. Brivaracetam is a third-generation anti-epileptic drug effective in reducing seizures in drug resistant epilepsy. In our patient, the combination of the two drugs allowed to achieve seizure control and remission of autoimmune encephalitis.

Conclusion: Anakinra represents a valid option in NORSE in autoimmune encephalitis. Novel AEDs as brivaracetam may help achieving additional seizure control.

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A CASE OF BING-NEEL SYNDROME AS THE FIRST MANIFESTATION OF WALDENSTROM MACROGLOBULIEMIA

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Introduction: Waldenstrom macroglobulinemia (WM) is a rare type of non-Hodgkin lymphoma and the Bing-Neel syndrome is a neurological complication of WM which results from direct infiltration of the central nervous system by malignant lymphoplasmacityc cells, leading to heterogeneous and non specific clinical presentations which often make the diagnostic work-up a challenge. Here we present an interesting case of Bing-Neel syndrome as the initial presenting feature of WM.

Case presentation: A 60 year-old man presented to our clinic on February 2022 with a 6-month history of progressive visual acuity abnormalities, ataxic gait, episodes of confusion, short-term memory impairment and severe weight loss. He had a transitional grade I left frontotemporal meningioma symptomatic for aphasia the year before. He was an active heavy-smoker. Brain MRI showed a diffuse hemispheric and subtentorial leptomeningeal enhancement as well as of the optic nerve, trigeminal and vestibular roots. In the suspect of a neoplastic meningitis, with the aim of finding the primitive tumor, he underwent a total-body CT scan which showed the presence of a presacral mass, followed by an 18-FDG-PET which revealed an abnormal high glucose uptake in the pelvis and in the bone marrow in the vertebral column. A spinal MRI detected leptomeningeal infiltration of the cauda equina. Further workup included cerebro-spinal fluid analysis showing high WBC count (176/mm3) and elevated protein level (615 mg/dL) reflecting blood-brain barrier disruption. Flow cytometric analysis of CSF showed a clonal B lymphocyte population. Serum electrophoresis revealed the presence of an IgM kappa protein of 7,6 g/L. The patient finally underwent a biopsy of the vertebral lesions and bone marrow examination (infiltration by lymphoplasmacytic lymphoma). The final diagnosis was WM with Bing-Neel Syndrome as presenting symptom. He was treated with 2 cycles of Rituximab followed by Ibrutinib monotherapy with progressive improvement of his neurological condition.

Conclusion: This case represented a diagnostic challenge since the underlying hematological disease presented with heterogeneous neurological symptoms. We have to take in mind BNS in the differential diagnosis of neoplastic meningitis of undetermined origin.

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LOEYS-DIETZ SYNDROME AND OVERLAP EHLERS-DANLOS/ OSTEOGENESIS IMPERFECTA MOSAICISM: A RARE CASE OF YOUNG ADULT STROKE

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Purpose: The incidence of ischemic stroke (IS) increases exponentially with age. Stroke also occurs in children and young adults, resulting in significant morbidity and mortality. The identification of IS cause in young adults is mostly challenging unlike in the elderly, IS in young adults more often can be due to rare causes and infrequent risk factors. Guidelines and recommendations are lacking in the diagnostic process and clinical approach for these patients. We present the following case report in order to underline the rarity of young adult IS causes and the diagnostic difficulties.

Methods and Materials: A thirty-year-old female had personal history of knee dislocation and mild scoliosis. She was admitted to Stroke department for outpatient assessment because of a right occipital IS of undetermined causes, occurring three years before with sudden onset of visual disturbance and left body paresthesia. We performed laboratory and instrumental tests for IS cause identification: supra-aortic vessels and transcranial Doppler ultrasound; holter ECG monitoring, transthoracic and transesophageal echocardiography; brain CT and MRI; autoantibodies panel and a thorough genetic screening.

Results: The instrumental assessment did not reveal large vessels atherosclerosis, cardiovascular diseases or brain vessel abnormalities. ANA, LAC and IgG antiphospholipid antibodies were altered to a single measurement. Repeated assessment did not confirm these findings, but Basedow thyroiditis was later diagnosed. Genetic panel for Fabry, MELAS and MERRF was unremarkable. Nevertheless, genetic screening detected C.128delA variant in heterozygosity and apparent mosaicism on the COL1A gene and c.1195A> G variant in heterozygosity on TGFB2 gene. Physical examination revealed blue sclerae, elastic neck skin, long and thin fingers. Bone mineral density test showed osteoporosis at the rachis.

Discussion: Considering the clinical features and the genetic findings, we diagnosed the coexistence of Loeys-Dietz syndrome (LDS) and Overlap Ehlers-Danlos syndrome (EDS)/ Osteogenesis imperfecta (OI) in mosaicism. Since these conditions have extremely variable expressiveness, the clinical symptoms of both diseases could occur simultaneously in an unpredictable manner. In addition, the mutation detected on TGFB2 gene has never been previously described. According to literature, we believe that the IS may be related to LDS, while phenotypic picture is related to the Overlap EDS/OI mosaicism.

Conclusion: LDS is characterized by vascular alterations and skeletal manifestations, and the clinical spectrum is so variable, requiring neurological and cardiovascular follow-up. We assume that in young adult strokes, genetic testing for LDS should be performed in addition to Marfan and Ehlers-Danlos syndromes and other monogenic diseases.

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AN UNWANTED GUEST: A CASE OF SKELETAL MUSCLE TOXOPLASMOSIS

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Objective: To highlight the importance of muscle biopsy in a case of rapidly progressive muscle weakness with rhabdomyolysis in a HIV-positive patient with previous identification of cerebral Toxoplasma Gondii (TG) infection.

Materials: Patient's medical history, laboratory tests, electrodiagnostic and imaging tests; quadriceps muscle biopsy workout, including PCR detection and immunohistochemical staining for TG.

Methods: Review of the patient's medical history, clinical assessments and laboratory tests.

Results: We report a case of a 58-year-old Rumanian man with a recent diagnosis of AIDS, active CMV infection and TG cerebral localization proved by DNA finding in CSF. He was adherent to antiretroviral therapy and to trimethoprim-sulfamethoxazole as secondary prophylaxis. After three months since first diagnosis, he accessed to the Emergency Department for psychomotor slowing and rapidly progressive muscle weakness. At neurological examination proximal weakness without myalgias and absent tendon reflexes were observed. Laboratory tests showed marked serum CD4 lymphocytopenia and high serum CK levels (14x). A nerve conduction study proved a chronic sensory-motor axonal neuropathy. Following a negative screening for myositis-specific and myositis-associated antibodies, TG prophylaxis was switched to pyrimethamine and sulfadiazine and ganciclovir was added for elevated CMV DNA titers. A cycle of IVIg therapy was performed without significant benefit; a muscle biopsy of the right quadriceps was performed, after considering different etiologies, namely a seronegative autoimmune necrotizing myopathy, an antiretroviral toxic myopathy, a para-infectious myopathy. TG in different stages was identified in muscle tissue; this finding was further confirmed by positive PCR detection of TG DNA and immunohistochemical staining for TG on muscle sample. Scattered CD8 lymphocytes infiltrates with myopathic changes, consistent with inflammatory alterations, were also observed. After the histological confirmation, therapy with medium dosage intravenous corticosteroids, followed by oral maintenance therapy, was started, assisting to a progressive improvement of clinical conditions and normalization of CK levels.

Discussion: Toxoplasma Gondii is known to be responsible for opportunistic infections in HIV-positive individuals [1]. Tachyzoites may be able to invade and to transform into cyst-forming bradyzoites in CNS and skeletal muscle [2]. Cysts are scarcely responsive to primary and secondary pharmacotherapy, possibly leading to relapses [3]. In our case, muscle biopsy permitted to discriminate among differential diagnosis of the acute weakness and to confirm a diagnosis of para-infectious myositis.

Conclusion: Muscle biopsy represents a useful tool for the differential diagnosis of rapidly onset weakness: the identification of the protozoan confirmed a complex diagnosis and implied therapeutic decisions, leading to clinical improvement.

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A CASE OF MYELORADICULONEURITIS IN A PATIENT WITH STAPHYLOCOCCUS AURES SYSTEMIC AND CEREBRAL INFECTION AND AN AUTOIMMUNE DISEASE

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Objectives: Staphylococcus aureus (SA) infections are particularly challenging both in management and treatment. Patients suffering from SA infective endocarditis may have bacterial dissemination to the central

nervous system (CNS) with consequent brain or less frequently spinal cord involvement.

Methods: Here we present the case of a 76 year-old female patient who was hospitalized for paraparesis with also heart and respiratory failure. She suffered from atrial fibrillation treated with anticoagulants and in the past she underwent biologic mitral valve replacement.

Results: Echocardiography showed a normal ejection fraction and a mitral valve insufficiency. Spinal cord MRI showed a dorsal medullary lesion (from D3 to D7), brain MRI disclosed bilateral parenchymal lesions. The day after fever with worsening of paraparesis so we performed blood cultures and lumbar puncture that showed a Staphylococcus aureus infection. We performed another cardiologic evaluation that disclosed the presence of infective endocarditis. She was treated with intravenous vancomycin, cephalosporins and dexamethasone with regression of fever and improvement in cerebrospinal fluid and blood exams. Meanwhile autoimmune screening performed during hospitalization disclosed the presence of Lupus anticoagulant (LLAC) and ENA antibodies. Despite therapy we observed a worsening in paresis with also arm involvement and tendon reflex reduction. A new spinal cord MRI was performed but there was no progression of the dorsal lesion, cervical lesions were absent. Electromyography showed acute axonal sensory motor neuropathy. She was treated with intravenous immunoglobulin with only partial response.

Conclusions: Here we present a rare case of a patient affected by parenchymal lesions and dorsal myelitis due to Staphylococcus aureus endocarditis and a new diagnosis of an autoimmune disease. SA myelitis is a rare condition with few cases reported in literature. Direct bacterial myelitis is considered a possible but very rare mechanism. The presence of Staphylococcus in cerebrospinal fluid suggests a possible direct damage; another possible mechanisms in our patient, who also suffered from an autoimmune disease, could be a parainfectious damage with an abnormal immune response to infection with consequent medullary involvement. Moreover we diagnosed an acute axonal sensory motor neuropathy of uncertain etiology that can be a consequent complication of immune response or also secondary to sepsis and hospitalization.

INTRA-ARTERIAL THROMBOLYSIS DURING THROMBECTOMY TREATMENT IN PATIENT WITH ISCHEMIC STROKE DUE TO LARGE VESSEL OCCLUSION: CASE REPORT

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Objective: To discuss the safety and efficacy of intra-arterial thrombolysis (IAT) associated to endovascular thrombectomy (EVT) in ischemic stroke.

Case report: A 64-year-old smoker woman with systemic hypertension was referred to our hospital with a wake-up stroke. She got up at 5.30 a.m. with right hand numbness worsening in the next hours. Last time seen well at 22 pm. The patient presented with a severe dysarthria, right hemiplegia, mild sensory loss, right hemianopia, right inattention and forced gaze palsy (NIHSS score was at 19) at clinical neurological examination. The brain CT scan showed a mild left hypodense lesion of the internal capsule, while CT-angiography the occlusion of left internal carotid artery (l-ICA). Due to the uncertain time of onset a brain MRI was done showing a DWI- FLAIR mismatch. Therefore, intravenous thrombolysis was started and concurrently the endovascular thrombectomy was begun. Arteriography confirmed embolic occlusion of l-ICA's siphon; a single attempt of thromboaspiration was done with reperfusion of distal portion of l-ICA and occlusions of l-ICA after ophthalmic branch, left medial carotid artery (MCA) parietal branch and left PCA P2-P3 branch. At this point, 20% of rTPA was directly infused in l-ICA reaching a complete reperfusion of distal branch of MCA. After reperfusion therapies the neurological examination showed a great improvement with NIHSS score at 3. The patient was discharged at home after seven days of hospitalization fully recovered.

Discussion: There are several benefits associated with concurrent use of mechanical thrombectomy (MT) and IAT such as decreasing clot burden, exposing the inner core of clot to the thrombolytic agents. According to latest metanalysis (1), in acute ischemic stroke with large vessel occlusion, the use of IAT together with MT may achieve better functional outcomes and lower mortality rates. However, all studies included in the meta-analysis were observational in nature, limiting the validity of these findings, more real life data are needed.

Conclusion: Intra-arterial thrombolysis during thrombectomy may be an effective and safe method that provides better recanalization than the conventional mechanical thrombectomy alone, especially for refractory clot in patients with embolic large-vessel occlusion.

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FDG/PET AS DIAGNOSTIC TOOL IN ATYPICAL CASE OF HUNTINGTON DISEASE

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Objective: Huntington disease is an autosomal dominant neurodegenerative disease characterized by progressive movement disorder associated with cognitive decline (frontal pattern) and behavioral changes. CAG repeat expansion of 37 or longer in the huntingtin (HTT) gene is considered pathogenic and diagnostic. Here we describe an atypical case with the aim to emphasize the role of brain FDG/PET to suspect Huntington disease.

Material and methods: We present the case of a 48-year-old who developed slowly progressive behavior disorder characterized by apathy and delusional psychosis, associated with mild cognitive decline (parietal pattern), parkinsonism and alteration of rhythm and prosody of the language.

Results: Routine blood and cerebrospinal fluid (CSF) analyses, including plasma progranuline dosage, were all in the range of normality. CSF Tau, phospho-tau and Amyloid Beta-42 were normal too, while 14.3.3 protein western blot was ambiguous. Just non-specific cortical and subcortical atrophy was present in brain MRI. DAT-scan showed diffuse and bilateral moderate reduction of striatal distribution volume values, slightly more pronounced in the putamen. Brain FDG/PET showed a marked bilateral diffuse reduction of relative glucose metabolism in the striatum, slightly more evident in the caudate, and a widespread relative glucose hypometabolism in the parieto-occipital and and dorsolateral-medial frontal cortical regions bilaterally. Only on the basis of FDG-metabolic patterns and in particular of the reduced striatal relative hypometabolism, genetical analysis of the HTT gene was performed that disclosed a CAG repeat expansion by 40; thereby the patient was diagnosed with Huntington disease.

Discussion: Here we present a Huntington disease patient showing a very atypical phenotype characterized by parkinsonism and cognitive impairment dominated by and alterations of parietal functions along with mild prefrontal involvement, in absence of choreic movements: just the brain PET/FDG led to suspect Huntington disease.

Conclusions: Huntington's disease is a condition that exhibits widely varying spectra of presentation, sometimes very challenging. Therefore in

case diagnostic suspicion arises, it is necessary to integrate with instrumental examinations and FDG/PET which can be determinant in atypical case, being capable to show early not only the striatal dysfunction even when structural imaging is normal, but also disclosing widespread reduction of tracer distribution in cerebral cortex.

A CASE OF ALS AND PD: TWO SIDES OF THE SAME COIN?

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Purpose: Simultaneous presence of two neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS) and Parkinson's Disease (PD) is very rare and has been observed mainly in some inhabitants of Guam (known as ALS-Parkinson Dementia Complex) and the Kii Peninsula in Japan.
Here we report the case of a patient who presented with clinical and instrumental findings of both PD and ALS.

Materials and Methods: A 51-year-old man with a personal history of Brugada syndrome type I, left frozen shoulder after traumatic injury and an unremarkable family history for neurodegenerative disorders has developed a progressive weight loss associated with asthenia, within nine months. Patient underwent a gastroenterological consult with esophagogastroduodenoscopy (EGDS) and Helicobacter pylori gastritis and seronegative celiac disease were diagnosed. Therefore, he started a gluten-free diet and eradication therapy for H. pylori. Persisting asthenia, associated with inappetence and arterial hypotension, patient turned to our clinic.

Results: At the neurological examination patient presented with normal spatial-temporal orientation, bradykinesia with facial masking and slow speech, severe generalized muscular atrophy and weakness with spastic rigidity in the lower limb and cogwheel rigidity in the upper limb, especially to the left side. Fasciculations were clinically evident in the shoulder girdle muscles bilaterally. Epstein's, Hoffmann's and Babinski's signs were present. Sensitivity deficit was not found.
Electromyography (EMG) and Nerve Conduction Studies showed second motor neuron involvement. Brain MRI showed tenuous hyperintensity of cortico-spinal tract on both sides. Reduction of dopaminergic uptake in both striate nuclei was found at DATSCAN. Levodopa challenge test was performed with poor response. At a new gastroenterological evaluation, previous diagnosis of Celiac Disease was denied: diet with gluten was resumed without complications.

Discussion and Conclusions: ALS and Parkinson's disease can be difficult to distinguish clinically, since some ALS signs can mask parkinsonism manifestation. However, histopathological features of these diseases could suggest a common pathophysiological pathway. Extrapyramidal signs in patients with ALS must be sought, as the simultaneous presence of Parkinson's disease must be excluded. In selected patients, it is useful to perform DATSCAN to confirm the diagnosis: according to the literature, use of therapy with L-DOPA improves symptoms in these patients. However, our patient had a poor response, probably because motor neuron disease had already led to a significant reduction in motor performance.

PSYCHOGENIC NON-EPILEPTIC SEIZURES (PNES) IN THE COVID-19 PANDEMIC ERA: A SYSTEMATIC REVIEW WITH INDIVIDUAL PATIENT DATA ANALYSIS

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Purpose: Psychogenic nonepileptic seizures (PNES) resemble epileptic seizures but are not due to an underlying epileptic activity; they often coexist alongside epilepsy. We described and summarized the clinical characteristics of patients with PNES as reported in the literature from the outbreak of the COVID-19 pandemic. We evaluated differences between patients with a diagnosis made immediately prior the pandemic (pPNES) and those who were newly diagnosed during it (nPNES).

Methods: Systematic search with individual patient analysis of PNES cases published since the outbreak of the COVID-19 pandemic. MEDLINE (accessed through PubMed), EMBASE, and Google Scholar were searched from December 2019 to November 2021. Differences between pPNES and nPNES were analyzed using Chi-square or Fisher exact test.

Results: Eleven articles were included, with a total of 133 patients (30 males), 106 pPNES (79.7%) and 27 (20.3%) nPNES. In the pPNES group, PNES frequency increased during the COVID-19 pandemic in 20/106 (15%) patients, whereas in 78/106 (58.7%) the frequency remained stable or decreased. No similar data was available for the nPNES group. Compared to the pPNES group, nPNES was associated with a higher risk of SARS-CoV-2 infection (1/106 versus 3/27; $p<0.0001$) and epilepsy diagnosis (33/106 versus 16/27; $p<0.0001$), whereas psychiatric comorbidities were less frequent (76/106 versus 1/27; $p<0.0001$).

Conclusions: During the pandemic, most patients with pPNES remained stable or improved, whereas nPNES were associated with a lower risk of psychiatric comorbidities. These findings might suggest that the COVID-19 pandemic does not negatively affect PNES, possibly due to lower social exposure, with reduced stress. Although probably and inevitably affected by reporting bias, these intriguing findings suggest that, at least in some patients, the COVID-19 pandemic may not necessarily lead to a worsening in the frequency of PNES and quality of life. These results could justify performing observational studies to further elucidate this issue.

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THE IMPORTANCE OF PRE-HOSPITAL HISTORY: A RARE STROKE MIMIC CONDITION

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Objective: In the present case report a rare cause of "stroke-mimic" is reported.

Materials and methods: A 79 year old woman was admitted to our emergency room with an altered mental state with speech disturbance, acutely onset one hour after lunch. On admission the examination showed normal vital signs, pupils reactive to light, language dysfunction, confusion and mild doubtful right limbs weakness. Routine laboratory tests, including blood glucose, electrolytes, and ammonium were unremarkable. Brain CT showed no abnormality. As a presumptive diagnosis of cerebrovascular disease was considered, she was treated with actylise (rTPA) 50 mg according to weight (55 kg). During rTPA infusion, patient experienced facial and four limbs involuntary movements, therefore RT-PA treatment was discontinued. After few hours the patient developed psychomotor agitation, confusion and visual hallucinations unresponsive to benzodiazepines; chlorphenamine was therefore successfully administered. The day after the patient presented fully asymptomatic. Both a brain Magnetic Resonance Imaging (MRI) and electroencephalogram resulted normal. The morning after her admission, the patient's husband was found at home in a comatose state. The admission of the second patient of the same family with similar neurological acute symptoms, prompted the ER team to investigate medications, drug use, and possible poisoning factors, revealing in both patients an ingestion of wild mushrooms picked in a yard, such mushrooms were ingested in other family members in the previous days resulting in a large spectrum of symptoms: from sleep disorders, to vomiting and agitation. Therefore, the second patient was treated with supportive care and gastric lavage resulting in clinical regression of neurological signs and symptoms.

Results: A cross-check with poisoning center allowed to identified the mushroom species as Amanita Pantherina (AP), a common ubiquitous mushroom in mediterranean areas.

Discussion: AP shows a Central Nervous System (CNS) depressant effect due to muscimol which is rapidly absorbed by gastro-intestinal tract and crosses the blood-brain-barrier. Muscimol acts as a gamma-aminobutyric acid (GABA) receptor agonist and has a depressant effect on CNS. Clinical picture of AP poisoning includes visual hallucinations, confusion, psychoses, behaviour disorder, disorientation, myosis and mydriasis, ataxia, seizures and coma. To reduce toxic mushroom absorbition gastric lavage, activeted carbon and purgatives are recommended. Symptomatic psychotic syndrome treatment with benzodiazepines and barbiturates is required.

Conclusions: In patients presenting with unexplained confusion and neurological symptoms, once more common causes are excluded, mushroom poisoning should be considered and subsequentely investigated with the patient friends and relatives.

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RAPIDLY PROGRESSIVE DEMENTIA WITH NORMAL BRAIN MRI, EEG AND CSF FINDINGS, DUE TO ANTI-CV2/CRMP5 ENCEPHALITIS

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Introduction: Anti-CV2/CRMP5 paraneoplastic syndrome usually manifests as encephalomyelitis, sensorimotor neuropathy, cerebellar ataxia, chorea, uveitis, and optic neuritis. Herein, we describe a case of anti-CV2/CRMP5 encephalitis presenting with rapidly progressive dementia (RPD) and prominent neuropsychiatric symptoms with negative general work-up.

Case presentation: A 65-year-old woman was admitted to the neurology department due to depressive and cognitive symptoms of subacute onset. She presented with anhedonia, feeling of guilt, fatigability, clinophilia, insomnia, loss of appetite and subtle executive and memory dysfunction evolving over the past two months. Seven days prior to admission, her relatives reported a brief episode of acute confusion and psychomotor agitation, with delusions of persecution. Neurological examination revealed global cognitive impairment with prominent executive and memory dysfunction. Cerebrospinal fluid (CSF) analysis, electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) were normal. Pending results for autoimmune/paraneoplastic encephalopathy, the patient was transferred to the psychiatric clinic for symptomatic treatment. Work-up revealed positive anti- CV2/CRMP5 antibodies. The patient was treated with intravenous methylprednisolone 1gr/day for 5 days with no improvement. She was administered intravenous immunoglobulin (IVIG) 2gr/kg with significant clinical improvement. Further investigation for primary tumor, including positron emission tomography (PET)-CT scan was negative.

Conclusions: We present an exceptional case of RPD due to anti-CV2/CRMP5 encephalitis with normal imaging, EEG and CSF findings that was mimicking a psychiatric disorder. In cases of autoimmune dementia/encephalitis, diagnostic vigilance and low investigation threshold are required to prevent misdiagnosis.

HIV-RELATED MONONEUROPATHY MULTIPLEX: A CASE REPORT

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Objectives: Human immunodeficiency virus (HIV) shows a remarkable tropism in the nervous system, both central and peripheral [1]. HIV-related neuropathy is one of the most common forms of neurotropic manifestation of this disease. Clinical syndromes can range from distal sensory polyneuropathy to autonomic neuropathy [2,3]. In some cases, mononeuropathy multiplex (MM) has been associated with HIV infection, thus entering the diagnostic work-up as a differential diagnosis with inflammatory or autoimmune causes.

Materials and methods: A 54-year-old male patient came to our attention complaining of hypoesthesia in the right thumb and impairment of hand and finger movements in the right hand. The first symptoms appeared about six years before the visit and have progressively worsened since then. In order to obtain a better diagnostic framing, the patient underwent a complete neurological evaluation, neurophysiological and neuroimaging examination, and detailed serum analysis.

Results: On physical examination, unilateral weakness was observed in wrist flexion/extension and finger movements of the right upper limb, together with muscle atrophy involving the forearm, thenar, and hypothenar eminences, and all interosseous muscles of the same limb. The deep tendon reflexes of the upper limbs were reduced bilaterally. Electroneurography showed motor axonal damage on the ulnar and median nerves of the right arm, while muscle denervation involving the related muscles was found on electromyography. MRI of the cervical spinal cord revealed no pathological findings that could explain the patient's symptoms. A search for onconeural antibodies and gangliosides was negative. The patient tested positive for HIV infection on serum analysis, while autoimmune markers and other routine laboratory tests were normal. Since all other possible causes were ruled out, we concluded that the patient's symptoms could be explained in light of infectious disease, and he was diagnosed with HIV-related MM.

Discussion and conclusion: MM is a very common neuropathic syndrome, usually associated with inflammatory diseases or autoimmune disorders. However, when the above causes are ruled out, a detailed virological examination should be performed as part of the diagnostic work-up of these patients in order to avoid unnecessary examinations and, most importantly, to arrive at an early diagnosis. In fact, a neurological syndrome could be the first manifestation of HIV infection, and patients should be referred to the most appropriate diagnostic-therapeutic pathway as soon as possible.
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SPONTANEOUS SPINAL EPIDURAL HEMATOMA: A CASE OF STROKE MIMIC

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Objective: Spontaneous spinal epidural hematoma (SSEH) is a rare and changeling condition as it can be a stroke mimic. It's important recognize and differentiate this clinical condition in patients treated under stroke code activation. We present a case of SSEH with hemiparesis mimicking acute ischemic stroke (AIS).

Patient and Methods: A 82-year-old woman, with a history of Hypertension, Diabetes Mellitus and Chronic Ischemic Heart disease, experienced a sudden posterior neck pain radiating to her left shoulder, after having lunch. At 2 hours after symptoms onset, she was admitted to the emergency room of our hospital. She reported taking dual antiplatelet therapy and she denied recent trauma. She was initially investigated as a cardiological emergency, but her cardiac assessment was normal. The neurological examination revealed a left Bernard Horner Syndrome (including slight drooping of the upper eyelid, miosis, sunken appearance of the affected eye but no anhidrosis on the interested side of the face) and homolateral upper limb paresis with 3/5 Medical Research Council (MRC), all other findings were within normal limits. Her National Institutes of Health Stroke Scale score (NIHSS) was 3. A cerebrovascular accident was immediately hypothesized. An emergency computed tomography (CT) scan of the brain revealed no intracranial hemorrhage. CT angiography of brain and thoracic aorta showed no evidence of major vessel occlusion or artery dissection. Complete blood exams were all normal. The patient was out of time for thrombolysis and was admitted to Neurology departed for other investigations. The following day, she complained progressive clinical worsening and also developed left lower limb paresis. Subsequent magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the brain was unremarkable, while MRI of the cervical spine showed epidural hematoma, in the left dorsal portion, from C2 to C6.

Discussion: SSEH is a rare spinal pathology. Its annual incidence is estimated about 0,1 per 100000. SSEH is caused by many factors, such as hypertension, coagulopathy, anticoagulant/antiplatelet therapy, neoplasm, vascular abnormality and idiopathic causes. Patients with cervical SSEH frequently present with sudden-onset neck pain and subsequent motor paralysis or sensory dysfunction. For this reason, it may be initially misdiagnosed as AIS. SSEH should be considered when hemiparesis is associated with neck pain and signs of Horner's syndrome and Brown-Sēquard syndrome.

Conclusion: SSEH is a rare but important desease. Prompt diagnosis and intervention are essential to prevent permanent neurologic deficits. In the suspicion of SSEH spine MRI is recommended for a definite diagnosis.
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A CASE OF SUBACUTE FLACCID PARALYSIS WITH KIDNEY AND PULMONARY FAILURE

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Objective: To describe a 74-year-old man with subacute and symmetric lower limb flaccid paralysis, kidney and pulmonary failure, who got clinical benefits from immunosuppressive therapy.

Materials and methods: A 74-year-old man was referred because of progressive asthenia and bilateral lower limb motor deficit. His past medical history was significant for blood hypertension and benign prostatic hypertrophy. The physical examination showed bilateral lower limb weakness, absent knee and ankle reflexes, without sensory loss and cranial nerves involvement. Within two weeks, he developed a flaccid and symmetric paralysis on the lower limb and became bedridden. During the recovery the patient developed acute kidney injury with elevated creatinine level (max 8.12 mg/dl) and pulmonary insufficiency. He was started on 3-times-a-week hemodialysis and high dose steroids with clinical benefits.

Results: Creatine kinase, vitamins and glycated hemoglobin level were normal. Autoimmune panels detected a slightly positivity of MPO-ANCA antibodies in two out of three different surveys. Motor and sensory nerve conduction study showed signs of a marked sensory-motor axonal suffering. Electromyography of upper and lower limbs revealed sporadic fibrillation potentials without signs of neurogenic recruitment and a myopathic recruitment pattern at the voluntary activity on proximal muscles of upper limb. Muscle MRI showed diffuse hyperintense signals of the upper and lower limb muscles on STIR sequences. A muscle biopsy showed an increased variability of fiber caliber due to the presence of hypotrophic angular fibers and rounded fibers and a lymphomonocytic infiltrate into the perimysial arterial wall. A kidney biopsy revealed pauci-immune necrotizing glomerulonephritis with tubulointerstitial nephritis. A bronchoalveolar lavage documented a diffuse alveolar hemorrhage pattern. He had been diagnosed with microscopic polyangiitis and he started immunosuppressive therapy with Cyclophosphamide and Rituximab. At 2 months of treatment, subsequent examination demonstrated improvement in lower extremity strength and in renal and pulmonary function.

Discussion and conclusion: A frequent manifestation of ANCA-associated vasculitis is a progressive sensorimotor neuropathy. In addition to serologic and electroneurophysiological tests, it is fundamental to

perform biopsy of an affected organ in order to obtain a definite histological diagnosis and to start a targeted and aggressive treatment.
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RAPIDLY PROGRESSIVE TEMPORAL ATROPHY RESULT OF ANTI-GAD 65 ENCEPHALITIS: A LINK BETWEEN NEUROINFLAMMATION AND NEURODEGENERATION

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Background: Anti-GAD 65 antibodies are related to a limited number of specific neurological syndromes such as cerebellar ataxia, epilepsy, stiff person syndrome, and rarely limbic encephalitis. Compared to other encephalitis with antibodies directed towards intracellular antigens, anti-GAD 65 encephalitis is associated with a poor response to immunosuppressive treatments and a typically unfavorable course. To the best of our knowledge, we report the first case of anti-GAD 65 encephalitis characterized by a rapidly progressive course with severe bitemporal atrophy and a perseverative speech disorder defined as palilalia.

Materials and Methods: An 81 years-old right-handed woman showed a subacute onset of confusion, palilalic speech, episodic memory deficit and erratic prosopagnosia. Brain MRI showed hyperintense bilateral inferior temporal gyrus and uncus FLAIR-T2 signal without gadolinium enhancement or DWI restriction. Cerebrospinal fluid (CSF) analysis displayed a slight increase in mononuclear cell count, oligoclonal bands intrathecal synthesis and a positive result for anti-GAD 65 antibodies, confirming the diagnosis of autoimmune encephalitis. So, we started an immunomodulatory treatment with high-dose of methylprednisolone, plasmapheresis and rituximab sequentially. Three months after the onset, the patient started suffering from behavioral and psychological symptoms resembling a Klüver-Bucy phenotype and the repetition of Brain MRI showed a significant increase in temporal lobes and hippocampi atrophy amount. We conducted a voxel-based morphometry and hippocampal subfields analysis using the CAT12 toolbox and ASHS algorithm, respectively.

Results: A severe volumetric reduction with prevalence in the left hemisphere is observed in the amygdala, hippocampus, entorhinal cortex, inferior temporal gyrus and temporal pole with less parahippocampal and middle temporal gyrus involvement. The other brain regions are substantially spared or only slightly involved in the degeneration. The hippocampal subfields analysis showed low volumetric values of the hippocampal subfields, particularly prominent in the CA1 and in the perirhinal cortex (BA 35 – BA 36) compared to an internal database used as reference.

Discussion: Neuroinflammation seems to have triggered an extremely rapid neurodegenerative process that has in common some clinical and neuroradiological features with FTD. It is historically unclear whether neuroinflammation is the cause or the consequence of neurodegeneration, and if brain-reactive antibodies' findings are causative or should be considered an epiphenomenon. Our index case supports the hypothesis that inflammation could rarely represent the "primum movens" of the neurodegenerative cascade.

Conclusion: This case study may represent a model supporting the connection between neuroinflammation and neurodegeneration and confirms the poor anti-GAD 65 encephalitis prognosis.
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A CASE OF HEIDENHEIN VARIANT OF CREUTZFELDT-JACOB DISEASE PRESENTING WITH CEREBRAL VASOCONSTRICTION

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Background and aims: Creutzfeldt-Jacob Disease (CJD) is a rare neurodegenerative disorder caused by abnormal deposits of misfolded prion protein (PrP); its tumultuous course and variable clinical characteristics constitute a diagnostic challenge in initial stages. To our knowledge, there are no reports describing the copresence of cerebral vasoconstriction, even if there are evidences of PrP deposits around cerebral vessels and altered cerebral vasoreactivity: by describing our case, we could give impulse to further investigate this association.

Methods and Results: A 54-year-old woman with a 3-year history of recurrent severe headaches followed by dizziness and nausea was hospitalized complaining unremitting and worsening symptomatology and exhibiting a brain MRI showing FLAIR and DWI hyperintensity of multiple bilateral cortical gyri in parieto-occipital and frontal regions suspected for strokes. Her neurological examination showed bilateral ataxia, hyperreflexia, fragmented speech and movements. EEG evidenced generalized theta-delta activity with runs of epileptic waves, while chemical, microscopic and bacterial CSF examination was normal. General blood test, thrombophilic, autoimmune, viral and neoplastic screening were unremarkable. Carotid duplex, transcranial Doppler ultrasound and MRI angiography showed normal findings. She was submitted to cerebral angiography, bilaterally showing a threadlike appearance of the distal tract of anterior, middle and posterior cerebral arteries and posterior inferior cerebellar arteries. Steroid and later vasodilative therapies (supposing a primary cerebral vasculitis and a cerebral vasoconstriction syndrome respectively) were not effective, while patient's condition steeply worsened in the first two weeks, with Balint and Gerstmann syndrome, bradykinesia, diplopia, nystagmus and bilateral Babinski sign. In a second MRI slight swelling and hyperintensity of right caudate and lenticular nuclei appeared. The high suspicion of CJD was supported by a new EEG, revealing more pronounced delta activity, interrupted by triphasic waves sequences. A cerebral 18F-FDG PET showed marked cortical hypometabolism, mostly in posterior regions. Completion of CSF analysis showed high levels of tau, low ß1-42 amyloid and absent 14.3.3 protein, while RT-QuIC was positive for PrP. At the third week the patient appeared lethargic and abulic, with ophthalmoplegia, diffuse plastic hypertonia and dystonia, apraxia, ataxia and myoclonus; a follow-up EEG registered diffuse triphasic delta waves.
The patients was eventually transferred to another facility, were her conditions progressively worsened until death. A post-mortem Western Blot analysis of the cerebral autoptic specimens was positive for PrP.

Conclusion: Our observations constitute the first report of cerebral vasoconstriction associated to CJD. More observations are needed in order to shed new light on the disease pathogenic mechanisms.

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SPINAL DURAL ARTERIOVENOUS FISTULA PRESENTING AS ACUTE AREFLEXIC BILATERAL LIMB WEAKNESS

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Introduction: Spinal dural arteriovenous fistula (SDAVF) is an uncommon cause of myelopathy mostly affecting middle-aged men, in which anomalous arterio-venous connections develop at the level of dura mater with medullary edema deposition and venous congestion [1]. Symptoms often include lower limb weakness, variably associated with radicular-like-pain, sensory and sphincter-disturbances [1,2]. SDAVF can lead to permanent disability if left untreated; endovascular embolization represents the principal treatment option.

Case: A 71-year-old man presented to our attention complaining of lower leg weakness with acute-onset 10 days before. The symptom was associated to back pain and urinary incontinence without sensory involvement. Neurological examination showed difficult gait, possible with bilateral support, reduced proximal limb strength (ileo-psoas had value of 3/5 at Medical Research Council grading system), with normal distal leg strength. Lower-limb deep-tendon reflexes were absent. Upper limbs examination showed normal strength and reflexes. No sensory deficit was found. Blood tests were normal. Cerebrospinal fluid analysis revealed raised albumin levels with 27 white-blood-cells. Electromyography showed fibrillation potentials in the vastus medialis, anterior tibialis and gastrocnemius caput medialis muscles, bilaterally. Nerve conduction study in the four limbs showed decreased femoral, peroneal, and tibial Compound Muscle Action Potential amplitudes with absent tibial-peroneal F-response and tibial H-reflex. No sensitive abnormalities were found. Spine MRI showed longitudinal T2-Short-TI Inversion Recovery (STIR) hyperintense columnar central-medullary edema extending from D5 to medullary cone with late phase contrast enhancement. Serpiginous dorsal and lumbosacral peri-medullary vessels were noted at T2-STIR sequences. Spinal angiography revealed a SDAVF at D12 level. Endovascular embolization treatment was performed with near complete limb weakness resolution over the course of 15 days.

Discussion: SDAVF is a rare neurological disease associated with misleading clinical presentation. Symptoms often develop insidiously, but acute/subacute presentations are rarely reported [1,2]. MRI often shows spinal T2-dependent hyperintense columnar edema with late contrast-enhancement and dilated serpiginous peri-medullary vessels with flow void signal [1,3]. SDAVF should be considered in the diagnostic evaluation of lower limb weakness when more common causes of spinal/nerve involvement have been excluded, especially in light of the potential reversibility when promptly treated [1,2]. Diagnosis can be especially challenging in case of SDAVF with acute presentation, potentially mimicking other causes of acute onset weakness such as Guillain-Barrè syndrome or transverse myelitis. In these occasions a careful spinal MRI evaluation aimed to highlight SDAVF peculiar features can play a crucial role addressing the diagnosis [3].

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DEMENTIA AND AGING

EFFICACY OF COGNITIVE TELE-REHABILITATION TREATMENTS IN PATIENTS WITH PARKINSON'S DISEASE OR POST-STROKE

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Introduction and Objectives: Tele-rehabilitation (TR) treatments, based on cognitive stimulation (CS), have been recently proposed as useful approaches to improve or stabilize cognitive functions in patients with mild or moderate cognitive impairment [1,2]. The aim of the present study was to investigate whether CS delivered by a TR system in patients with Parkinson's disease (PD) or post-stroke, with mild to moderate cognitive impairment, may improve cognitive performances and/or stress of caregivers. The present study was founded by a national grant titled MULTIPLAT_Age (cod. NET-2016-02361805).

Methods: Consecutive patients were enrolled in the present study (8 with PD and 10 post-stroke, 12 males/6 females; mean age, PD group: 65.1± 3,5; post-stroke: 58,1± 3,8; years of education, PD group: 9,67± 2,9; post-stroke group: 9,5± 2,2). The CS was delivered for 1 hour/day, 5 times/week, for 4 consecutive weeks. The system consisted of two PC-based workstations, using the Virtual Reality Rehabilitation System (VRRS, Khymeia, Italy), one installed at patient's home and the other in the rehabilitation center. All exercises were organized by cognitive domain: memory, attention, praxia, mathematics, logic. At baseline and after the treatment, a complete cognitive, mood and quality of life assessment was performed in all patients. For the family member, Caregiver Burden Inventory (CBI) was performed.

Results: The preliminary results showed a significant improvement in both PD and post-stroke patient groups in cognitive abilities, after the CS performed by the TR protocol in comparison to baseline evaluation. Specifically, there was a significant improvement in both PD and post-stroke patient groups, in the constructive praxis task ($p=0.029$ for PD group; $p=0.021$ for post-stroke group) and in the visual attention ($p=0.044$ for PD group; $p=0.017$ for post-stroke group). Post-stroke patients also reported significant improvement in learning and short- and long-term memory of verbal information ($p=0.039$) and a significant decrease in severity of depression and caregivers stress (BDI: $p=0.038$; CBI: $p=0.002$). The study is still ongoing and data collection is in progress.

Conclusions: The preliminary results of this study suggested that CS performed by a well-defined virtual reality TR tool for cognitive rehabilitation may be efficacious in improving the cognitive functioning of patients with PD or post-stroke with mild/moderate cognitive impairment. This treatment may also reduce patients' depression levels and stress levels of caregivers. If confirmed in the larger cohort of patients, these

data are going to be of particular value for patients living in all geographical areas, such as Calabria, characterized by a scarcity of specialized rehabilitation services.
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EEG ENTROPY IN ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT

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Objective: To evaluate whether the non-linear algorithm multiscale entropy (MSE) for the analysis of the electroencephalographic (EEG) signal in patients with Alzheimer's Disease (AD) and mild cognitive impairment (MCI) can be a novel approach to reveal potential new AD biomarkers.

Materials: 9 AD and 6 MCI patients aged 59 to 81 (6 men and 9 women) were included after clinical and neuroradiological assessment, comprehensive of cerebrospinal fluid dosage of biomarkers. Cognitive impairment was assessed with the Montreal Cognitive Assessment (MoCA).

Methods: We collected consecutive 60-seconds epochs of EEG signal andanalyzed them using the MSE algorithm. MSE evaluates the regularity of the signal based on the parameter "sample entropy" computed on multiple temporal scales ($\tau max = 30$). We quantified the non-linear measure through slopes computed on MSE curves obtained by plotting values of sample entropy against the temporal scales at which such values were estimated. We then compared results between groups and tested correlations with MoCA scores.

Results: The slopes demonstrated lower values of entropy in AD than MCI at smaller scale factors (i.e. $1 \leq \tau \leq 7$). Conversely, at larger scale factors (i.e. $\tau \geq 8$) AD patients had higher values of entropy than those with MCI. Lower values of entropy correlated with lower MoCA scores at small scale factors and with higher MoCA scores at larger scale factors.

Discussion: Entropy is lower in AD than MCI at smaller scale factors, while higher at larger scale factors. We found a correlation between the quantity of entropy and MoCA scores at different time scales. Previous studies compared AD and healthy controls, demonstrating lower entropy in AD at smaller scale factors, but also increased entropy at larger temporal scales [1,2]. This is the first study demonstrating an analogous behavior between AD and MCI thus suggesting that MSE can provide a novel EEG biomarker in MCI.

Conclusions: Our analysis implements current knowledge regarding the dysfunction of networks in AD. The importance of these results resides in the possibility of defining different profiles of loss of nonlinearity as a biomarker using EEG. Our approach could represent a novel method to predict the evolution towards AD.
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ALZHEIMER'S DEMENTIA EARLY DIAGNOSIS, CHARACTERIZATION, PROGNOSIS AND TREATMENT DECISION VIA A SOFTWARE-AS-MEDICAL DEVICE WITH AN ARTIFICIAL INTELLIGENT AGENT

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Objectives: TRACE4AD (DeepTrace Technologies s.r.l, Italy) is a machine learning-based software-as-medical device able to predict the conversion to Alzheimer's disease (AD) dementia of subjects at risk within 24-months exploiting automatic processing of T1-weighted MPRAGE brain MRI study and neuropsychological tests [1]. TRACE4AD provides a report with the predicted individual risk of conversion to AD dementia, specific cognitive deficits, and suggestions supporting neurologists in diagnosis and characterization, prognosis, and decision-making. We tested TRACE4AD in the clinical setting in its ability, at baseline, to: a) predict amnestic Mild Cognitive Impairment (MCI) conversion to AD dementia within 24-months; b) characterize cognitive deficits; c) support neurologists' decision-making. Reference standards were: a) the neurologist's clinical diagnosis at 24-months, b) the neuropsychological assessment at the baseline, c) the agreement with the neuro exam and intervention decision time and type defined by neurologists at the baseline.

Materials: We retrospectively included 92 subjects (mean age 73.12 ±7.6, 46% female): 32 patients from two Italian centers where TRACE4AD was implemented after user training; and 60 subjects from the ADNI dataset [2].

Method: All patients had a brain MPRAGE study at baseline, 77/92 patients (83.7%) also performed a neuropsychological assessment at baseline, 75/92 patients (81.5%) had a stable clinical diagnosis at 24-month. TRACE4AD extracted the gray matter map from MPRAGE and used it (combined with cognitive measures when available) to make inferences.

Results: TRACE4AD accurately predicted conversion/non-conversion to AD dementia in 93.3% of patients based on the MRI study alone, and in 96.6% based on MRI and cognitive measures. Cognitive deficits characterized by TRACE4AD were found in agreement with the neuropsychologists' assessment for all patients except one who presented with major depression. We found disagreement between the neurologist's decision at baseline and the tool in only two patients, defined with normal cognition by the neurologist and predicted at high risk of AD dementia conversion by the tool. TRACE4AD supported neurologists' decision by 12 months in 15/17 patients for the prompt decision at baseline: 6 patients with cognitive complaints, defined with normal cognition by the tool, had no interventions; 9 patients with subtle cognitive deficits, recommended for treatment by the tool, had a tailored intervention.

Discussion: AI can be used to support neurologists in characterizing the diagnosis, prognosis, decision and timing of intervention. TRACE4AD requires training for its use in clinical practice.

Conclusion: TRACE4AD is promising, safe, and effective in supporting neurologists in the clinical practice of MCI across different centers.
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GENERAL PSYCHOPATHOLOGY SEVERITY IN PSYCHOGERIATRIC PATIENTS WITH MILD BEHAVIORAL IMPAIRMENT

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Aim: Mild Behavioral Impairment (MBI) is a neurobehavioral syndrome characterized by late-onset neuropsychiatric symptoms associated with an increased risk of developing cognitive decline and progressing to dementia. MBI can be evaluated by means of the MBI-Checklist (MBI-C), an assessment scale which has been developed based on the ISTAART research diagnostic criteria for MBI [1]. The aim of this study is to evaluate differences in general psychopathology severity between psychogeriatric patients diagnosed with or without MBI.

Materials and methods: We recruited 191 patients aged 50 years or more and referred to the psychogeriatrics outpatient service of the Second Psychiatric Unit at Pisa University Hospital. 47 patients diagnosed with neurodegenerative parkinsonism and 31 diagnosed with major neurocognitive disorders were excluded. The sample (N=113) was then subdivided based on the presence of MBI according to the MBI-C cut-off (≥8). The Brief Psychiatric Rating Scale (BPRS) 4.0 was used to assess general psychopathology severity features at baseline [2]. Four subscale scores (i.e., depression/anxiety, psychosis, negative symptoms, and activation) were computed based on the factor structure suggested by Velligan et al. [3]. Comparative analyses were conducted using Wilcoxon rank sum test. Median and interquartile range were used as descriptive statistics. A statistical significance level of $p < 0.05$ was set for all tests.

Results: MBI was found in more than one third of the sample (N=40, 35.4%). MBI patients showed a significantly higher BPRS total score compared to other psychiatric patients (40 [15.2] vs. 34 [9], r=0.22, p=0.02). While no significant differences between the groups were found for depression/anxiety (r=0.00, p=0.99), activation (r=0.13, p=0.17) and psychosis subscales (r=0.10, p=0.31), MBI patients had a significantly higher score on the negative symptoms subscale (8 [3] vs. 6 [3], r=0.25, p<0.01), including blunted affect, psychomotor retardation and emotional withdrawal items.

Discussion and conclusion: MBI patients show a more severe clinical picture compared to other psychogeriatric patients, in particular as regards symptoms related to apathy. Apathy is a neuropsychiatric transnosographic syndrome characterized by cognitive, affective, and behavioral manifestations. It is commonly detected in prodromal stages of Alzheimer's Disease and it has been related to the progression of cognitive deficits along the neurodegenerative continuum. According to our results, being able to detect this symptom may be useful in correctly identifying patients at higher risk of neurodegeneration. Further research and longitudinal evaluations are needed to expand and validate these preliminary results.

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COGNITIVE DUAL-TASK COST DEPENDS ON THE COMPLEXITY OF THE COGNITIVE TASK, BUT NOT ON AGE, NEUROLOGIC DISEASE OR MOTOR-COGNITIVE FUNCTIONAL STATUS

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Objective: Dual-tasking (DT) while walking is common in daily life and can affect both gait and cognitive performance depending on, e.g., age, attention, task complexity and neurologic condition. To the best of our knowledge, there is no study to date that has investigated the effects of motor-cognitive DT, involving a motor task relevant to everyday life (combined straight walking and turning) and at different levels of cognitive complexity, on cognitive DT cost (DTC) in subjects of different ages and patients with various neurological diseases and in different motor-cognitive functional status.

Material and Methods: Ninety-one participants including younger and older healthy participants as well as patients with Parkinson's disease, Multiple Sclerosis, Stroke and chronic low-back pain performed a simple reaction time (SRT) task and three numerical Stroop tasks under the conditions congruent (StC), neutral (StN) and incongruent (StI). Tasks were performed under both standing (single task, ST) and walking (DT) conditions, and DTC were calculated. Patients were also grouped on the basis of Short Performance Physical Battery (SPPB) (S+: >9; S-: <= 9) and Montreal Cognitive Assessment (MoCA) (M+: >25; M-: <= 25) leading to 4 groups (S+M+, S+M-, S-M+; S-M-). Mixed ANOVAs were used to determine the effect of groups and task complexity on cognitive DTC.

Results: A higher response time in DT, compared with ST, was observed during SRT. However, response time was lower for DT when performing Stl. DTC decreased with increasing cognitive task complexity. No significant effects of age, disease and functional status on cognitive DTC were found.

Discussion: DT while walking has a different effect on cognition depending on the complexity of the cognitive task. More complex tasks and involving executive functions showed lower cognitive DTC and even better cognitive performance in DT than in ST. Underlying mechanisms could involve task prioritization, cross-talk interaction, or a combination of learning processes and interference between the two tasks. Age, neurologic condition and motor-cognitive status have no relevant effect on DTC in our cohort.

Conclusions: Our results suggest that, regardless of age, neurologic disease and motor-cognitive functional status, simple cognitive tasks

show the largest and most stable cognitive effects during DT. This may be relevant for the design of future observational studies, clinical trials and for application in clinical routine.

STRUCTURAL CORRELATES OF COGNITIVE AND MOTOR SCREENING SCALES IN NORMAL PRESSURE HYDROCEPHALUS

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To date a number of different scales have been proposed to assess motor and cognitive deficits subjects with suspected normal pressure hydrocephalus (NPH). Here we decided to explore the relationship between cognitive and motor screening scales and brain volumetric measures in this population to evaluate their ability to capture degenerative changes in this population. Twenty subjects with NPH (age: 75,8 ±5,6, sex: 14 male, 6 female) were included in the study and asked to undergo volumetric T1 MRI imaging and an extensive cognitive-motor battery. Motor assessment examined gait and equilibrium through the use of Berg Balance Scale (BBS), Short Physical Performance Battery (SPPB), Time Up & Go (TUG) and Timed Up & Go dual task (TUG dual task). Concerning cognitive assessment, Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Frontal Assessment Battery (FAB) were administered. MRI images were segmented in grey matter, white matter and CSF maps using SPM12, which were then used to compute parenchymal fraction and normalized grey, white and CSF fractions volume. Descriptive statistics and Spearman's correlations were obtained through IBM SPSS version 26.0. Results showed a positive correlation at baseline assessments between gray matter volume and FAB (rho = ,673; p = .004) score and between brain parenchymal fraction and FAB (rho = ,762; p = .001), while no other correlations was significant. When corrected by age and schooling, correlations between gray matter volume and brain parenchymal fraction and FAB score remained significant No correlations were found with motor data. Gray matter, as well as parenchymal, volumes show correlation with FAB scores at baseline assessment but not with other well-known cognitive screening tests or motor tasks, pointing to the value of this scale to capture relevant cognitive changes in this population. Although sample size is limited, parenchymal volumes correlate with cognition of patients with suspected NPH.

IDENTIFYING VARIANTS OF POSTERIOR CORTICAL ATROPHY USING CLINICAL CLASSIFICATION OR MR-BASED MACHINE LEARNING

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Objectives: To detect variants of posterior cortical atrophy (PCA) using clinical classification or a data driven machine learning approach based on MRI network metrics.

Materials: Thirty-six PCA patients and 69 healthy controls were consecutively recruited at two specialized centers. All subjects underwent neurologic and cognitive examinations, lumbar puncture and a 3T MRI (3DT1-weighted and resting-state functional MRI).

Methods: Patients were first categorized in ventral (vPCA, N=19) and dorsal (dPCA, N=17) variants according to the prevalence of specific visuo-perceptive and visuospatial symptoms based on the current diagnostic criteria. Sociodemographic, clinical, cognitive as well as topological brain network properties and regional functional connectivity using graph analysis and connectomics were compared between groups. Second, k-means clustering was performed on the whole group of patients considering both demographics and graph metrics of the occipital, temporal, and parietal lobes, as informative features. Sociodemographic, clinical, cognitive and CSF characteristics of the two clusters were compared.

Results: vPCA and dPCA were similar for age, sex, education, MMSE, disease duration and CSF levels. Relative to controls, only vPCA patients showed alterations of all global, temporal, and parietal metrics. Common alterations were found in terms of nodal strength, path length, and local efficiency within the occipital area in each PCA group compared with controls, but no differences were observed between PCA variants. At the regional level, compared to controls, dPCA patients showed a focal parieto-occipito-temporal functional connectivity breakdown, while vPCA had a more widespread reduction additionally involving frontal, basal ganglia, and sensorimotor connectivity. The k-means analysis identified two clusters of 26 and 10 subjects, respectively. These groups were similar for clinical and cognitive features. However, patients belonging to Cluster 1 were significantly younger and had significantly lower levels of CSF amyloid-ß compared to Cluster 2 patients.

Discussion: Although the two clinical variants were similar for sociodemographic, clinical and biological (CSF) features, vPCA patients showed a more severe pattern of functional connectivity breakdown. On the other hand, an MRI-based machine learning approach, albeit unable to capture clinical phenotype differences, provided indications about underlying disease pathology. Our findings suggest the potentially high sensitivity of graph-analysis and connectomic in capturing signs of neurodegeneration in PCA

Conclusions: These findings offer new potential biomarkers for non-invasive diagnosis of neurodegenerative conditions and for predicting disease trajectories.

Funding. Italian Ministry of Health (#GR-2010-2303035; #GR-2011-02351217), Philippe Chatrier and France Alzheimer Foundations, Fondation pour la Recherche sur Alzheimer.

TENÈPSIA: A TELE-NEUROPSYCHOLOGY PLATFORM FOR THE REMOTE ASSESSMENT OF MILD COGNITIVE IMPAIRMENT

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Objectives: Telemedicine offers many possibilities, such as remote monitoring of patients and following them up through the development of the disease, giving support to them and their caregivers. The need for a telemedicine approach to the early diagnosis of Alzheimer's disease (AD) is widely acknowledged. Neuropsychological testing is a crucial component of the assessment of mild cognitive impairment (MCI) and represents a gateway to biomarker assessment for prodromal AD diagnosis. The aim of TENÈPSIA project is the development of a high quality, tablet-based remote neuropsychological assessment platform.

Methods: The Italian Neurological Society (SIN), the Italian Neuropsychological Society (SINP) and the Italian Neurological Society for Dementia (SINDEM) promoted the organization of a Working Group (WG) of experts in the clinical and neuropsychological assessments of dementia. The WG is in charge for the selection of scales and tests, their digital validation and implementation. The project is a partnership between Biogen Italy and SIN; in particular, Biogen provides digital, scientific and communication support, funding the development of digital platform through REPLY, which is the software developer of platform, and INSIDE AI that manages the in-silico test required for the certification as medical device.

Results: The WG selected a battery of rating scales and neuropsychological tests widely used in Italian clinical practice and suitable for a digitalization approach. These include questionnaires for the assessment of depression and functional status and tests of long-term memory, language, visuo-spatial abilities, executive functions, and social cognition. Software development took particular care in the usability of the platform and to the possibility of remote control of subject performance by the examiner.

Discussion: The TENÈPSIA platform will enter the phase of beta testing in June 2022; in silico testing is proceeding in parallel with software development. In October 2022 it will be issued to the Notified Body to get the certification as Medical Device II A by December 2022. The subsequent phases will be dedicated to the collection of normative data in healthy subjects and validation on MCI and early AD clinical samples.

Conclusions: Tele-neuropsychology is an area of research in constant progress, which has received an accelerated demand for tools and services to support clinical practice during the pandemic. A scientifically validated, digitalized platform, allowing a high level of automation in the procedures of stimuli administration, response collection, score correction and interpretation will favor the possibility of remote assessment with benefits for patients, families, and treatment centers.

A CASE OF LATE-ONSET RESISTANT DEPRESSION TREATED WITH INTRANASAL ESKETAMINE: COGNITIVE AND EYE-TRACKING STUDY

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Aim: To analyze the changes of eye movements and of performance in cognitive tests in a elderly patient with a history of resistant depression undergoing antidepressant treatment with intranasal Esketamine.

Materials and methods: Using an eye tracker (Eyelink 1000 Plus, SR Research) recordings of eye movements were performed during a free-viewing task consisting of the observation of 20 images with emotional and / or neutral content that were presented on a PC screen for 10 seconds. Eye movements were recorded at the baseline (before the start of the cycle of therapy), and on 0, 3rd and 6th month administration of Esketamine. The following main descriptive parameters were extracted: saccades (e.g., amplitude, velocity), blinks (e.g., blink rate), fixations (e.g., duration of fixations) and pupillary dilation. At the same time, the neurocognitive status was monitored through neuropsychological tests (MOCA and specific batteries for executive and visuospatial functions, and memory), and the clinical characteristics of the depressive disorder was determined using the following assessment tools: Mini-International Neuropsychiatric Interview (MINI), Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), Maudsley Staging Model (MSM), World Health Organization Disability assessment Scale (WHODAS 2.0 12 item).

Results: A 79-year-old woman was suffering from recurrent, 'late onset' major depressive disorder. The depressive episode didn't show a response to 4 subsequent antidepressants. At baseline depression was moderate-severe (HDRS: 25, MADRS: 34, MSM: 9) with persistent and significant impairment of personal, relational and cognitive functioning (MoCA value at baseline was 18/30 with impairment of executive functions, psychomotor speed, verbal and visual memory, lexical access skills, visuoconstructive functions). The patient underwent intranasal Esketamine treatment up to maximal doses as early as the first 4 weeks, in addition to Venlafaxine (225mg / day). The recording of eye movements showed improvement towards the values of age-matched healthy controls for blink-rate, increased speed of saccadic movements and reduced pupillary dilation.bGlobal cognitive improvement was observed from baseline to 3-6 months (MOCA raw scores T0-T1-T2 = 18-19-24/30). Most cognitive domains were better over time. Moreover, a significant clinical response was documented already after one month, and a complete remission of depression.

Conclusions: Cognitive dysfunction associated with depression represents a clinical challenge for the differential diagnosis with neurodegenerative disease. The stable improvement of depressive symptoms and cognitive deficits, along with neurophysiological markers of whole brain efficiency such as eye movements, underlines the need of a careful selection of patients who could benefit of Esketamine.

NOVEL LIKELY PATHOGENIC Y106N VARIANT IN PSEN1 GENE IN A PATIENT WITH FAMILIAL EARLY-ONSET ALZHEIMER DISEASE

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Objectives: More than 200 mutations in PSEN1 gene have been described so far, causing most of dominantly inherited early-onset Alzheimer disease (EOAD). Most of them have been identified in exons 3-12, mainly involving the transmembrane domains of presenilin 1, the catalytic unit of γ-secretase complex, with consequences on the production of Aβ peptides [1]. Here we describe the clinical and radiological features of a patient with familial EOAD carrying a new variant in PSEN1 gene.

Materials and methods: The patient underwent clinical and radiological assessment and a clinical follow-up. Molecular analysis of PSEN1, PSEN2 and APP genes has been performed as previously described [2].

Results: The patient was a 45-year-old man who presented with marked anxiety and depression progressively associated with memory and attention deficits. Four years later he was hospitalized and his MMSE score resulted 16/30 with severe memory impairment, executive deficits, constructional and ideomotor apraxia. Brain MRI showed bitemporal mesial atrophy, predominant on the right side. FDG-PET showed severe hypometabolism in temporo-parietal areas and precuneus. CSF analysis revealed elevated tau, p-tau and low Abeta42 levels, consistent with AD. He developed severe behavioural disorders and was untestable after 6 years from onset. His father presented at age 45 with a rapidly evolving cognitive decline initially involving memory and attention and died at the age of 56. In our patient, the molecular analysis of PSEN1 gene showed the presence of the Y106N variant that was absent

in the GnomAD database of controls. Based on in-silico analysis using multiple prediction tools (Revel, Mutation Taster, Provean, Polyphen2), the Y106N variant may be considered most probably damaging. PSEN2 and APP analysis did not show any mutations.

Discussion and conclusions: We report the case of a patient with an EOAD carrying a new variant in the PSEN1 gene, located in exon 4. This variant alters a highly evolutionary conserved residue, the Tyr at codon 106 and should thus affect the hydrophilic loop-1 (HL-1) of presenilin-1. HL-1 is considered a key-region for the correct γ-secretase catalytic activity and is a known hot spot for familial AD [3]. Unfortunately, parental DNA was not available to study the segregation of the disease. However, previous evidence, the in-silico prediction and the absence of the mutation in controls, according to the guidelines of the ACMG, allow us to consider the Y106N variant as likely pathogenic. Functional studies are needed to confirm the pathogenicity of this new PSEN1 variant.
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EEG CORRELATES IN THE THREE VARIANTS OF PRIMARY PROGRESSIVE APHASIA

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Objective: The three clinical presentations of primary progressive aphasia (PPA) reflect heterogeneous neuropathological substrates which are difficult to be recognized in vivo. Resting-state electroencephalogram (EEG) is promising for the investigation of brain electrical activity in PPA. In this study we aim to explore the resting-state EEG cortical sources in the three variants of PPA.

Materials and methods: A resting-state 19-channel EEG was obtained in 48 patients diagnosed with PPA (21 nonfluent/agrammatic variant PPA [nfv-PPA], 18 logopenic variant PPA [lv-PPA], 9 semantic variant PPA [sv-PPA]) and in 21 age-, sex- and education-matched healthy controls. Using Exact low-resolution brain electromagnetic tomography (eLORETA), EEG current source density (CSD) values were estimated at voxel-level and were compared among groups of patients and controls.

Results: The groups of patients were similar in terms of age, sex, education and MMSE. Patients showed a low-to-moderate cognitive impairment (MMSE [mean±SD]: nfv-PPA 23.0±6.1, lv-PPA 19.9±5.4, sv-PPA 20.1±8.6; p=0.26). Lv-PPA cases showed a higher delta density over the left frontal, central and temporal regions when compared to sv-PPA subjects, and in left precuneus and posterior cingulate when compared to nfv-PPA patients. They also displayed a higher delta density in left frontal, parietal and temporal regions than healthy subjects. Theta density was significantly higher in lv-PPA patients than in healthy and sv-PPA subjects over the left frontal regions. Alpha1 band was significantly lower in the left occipital regions of lv-PPA cases compared with the other patient groups. Lv-PPA patients also showed reduced alpha2, beta1 and beta2 density over the left occipital regions when compared to healthy subjects. No significant differences were found in terms of CSD among sv-PPA, nfv-PPA and healthy subjects.

Discussion and Conclusions: Consistently with our previous studies, [1,2] findings in PPA patients suggest that Alzheimer's disease (AD), but not fronto-temporal degeneration (FTD), might induce a characteristic disruption of the cortical electrical activity, detectable by EEG. Coherently with the focal nature of PPA-related pathology, moreover, EEG alterations appear asymmetrically distributed over the two cerebral hemispheres. EEG might thus help in the differential diagnosis between AD-related and FTD-related PPA variants, especially between lv-PPA and nfv-PPA, frequently showing overlapping clinical features in their early stages.
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SERUM LEVELS OF IL-6 ARE RELATED TO COGNITIVE IMPAIRMENT IN THE SALUS IN APULIA POPULATION-BASED STUDY

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Aim: Growing evidence suggests that inflammation contributes to brain aging and neurodegeneration [1,2]. This study investigates the relationship between global cognition as well as executive function and serum levels of inflammatory markers such as IL-6, CRP, and TNF-α in an elderly population of Southern Italy.

Materials and methods: In this population-based study, all participants were enrolled from the "Salus in Apulia study", a public health initiative funded by the Italian Ministry of Health and Apulia Regional Governmen and conducted by the National Institute of Gastroenterology IRCCS "Saverio De Bellis" Research Hospital [3]. All study participants underwent clinical and neuropsychological evaluation with Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB), as well as laboratory examination, including the measurement of serum levels of IL-6, CRP, and TNF-α. Rank-based regression models were performed to investigate the relationship between inflammatory markers and cognitive function, considering major demographic and clinical confounders for adjustment.

Results: In this study, 1929 subjects aged between 65 and 95 years (median=72, IQR= 10; 50.5% males) were enrolled. Multivariate linear regression analysis revealed that higher serum levels of IL-6 were

associated with lower MMSE (β= -0.10; 95% CI: -0.12 to -0.08) and FAB scores (β= -0.05; 95% CI: -0.07 to -0.03), even after adjustment for demographic data and cardiovascular risk factors. No significant associations were found between cognitive functioning and serum levels of CRP and TNF-α.

Discussion and conclusions: Our results show that higher levels of IL-6 were related to cognitive impairment in an elderly population of Southern Italy, suggesting that neuroinflammation mediated by IL-6 might play an important role in cognitive decline. Further evidence is needed in order to assess if IL-6 serum levels might help to detect individuals at high risk for dementia, and whether anti-IL-6 drugs, such as tocilizumab, are able to improve cognitive function in people with cognitive decline.

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EUROPEAN INTER-SOCIETAL DELPHI CONSENSUS FOR THE BIOMARKER-BASED ETIOLOGICAL DIAGNOSIS OF NEUROCOGNITIVE DISORDERS

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Background and Objectives: Cerebrospinal fluid (CSF) and imaging biomarkers are necessary for the aetiological diagnosis of neurocognitive disorders, but evidence on their rational use in the clinic is incomplete. Since November 2020, a European multidisciplinary task force of 22 experts from eleven relevant scientific societies has defined a diagnostic workflow for the efficient use of biomarkers, filling the evidence gap on biomarker prioritisation with a formal Delphi consensus procedure. This abstract reports the preliminary results as of April 2022.

Materials and Methods: A modified Delphi method was used to create consensus. Group members participated in virtual Delphi rounds and voted on specific questions regarding the diagnostic workup of neurocognitive patients, based on their experience and evidence from the literature. Consensus was reached at a threshold of 70% agreement, or 50%+1 when a question required rediscussion.

Results: Six rounds have been completed so far. Panelists agreed on the clinical workspace of the workflow (specialist outpatient service), the stage of application (prodromal and mild dementia), and the patient age window (biomarker use strongly encouraged below 70 years and of limited usefulness over age 85). The workflow is patient-centred and features three levels of assessment (W): W1 defines eleven clinical profiles based on the integrated results of neuropsychology, MRI atrophy patterns, and blood tests; W2 describes the first-line biomarkers according to W1's clinical suspicion; and W3 suggests the second-line biomarker when the results of first-line biomarkers are inconsistent with the diagnostic hypothesis, uninformative or inconclusive. More specifically, CSF biomarkers are first-line in the suspect of Alzheimer's disease (AD) and when inconsistent neuropsychological and MRI findings hinder a clear diagnostic hypothesis; dopamine SPECT/PET for those leading to suspect Lewy body spectrum. FDG-PET is first-line for the clinical profiles leading to suspect frontotemporal lobar degeneration and motor tauopathies

and is followed by CSF biomarkers in the case of atypical metabolic patterns, when an underlying AD etiology is conceivable.

Discussion and Conclusions. The workflow will promote consistency in diagnosing neurocognitive disorders across countries, and rational use of resources. The initiative has an impact in preparing clinicians to work in the upcoming clinical space where etiological disease-modifying drugs are expected to be available.

OREXIN-A IN NEURODEGENERATIVE DEMENTIAS: A STUDY ON ITS DETERMINATION IN DIFFERENT BIOLOGICAL FLUIDS AND POSSIBLE CORRELATIONS WITH OTHER NEURODEGENERATION ASSOCIATED PEPTIDES

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Objective: A growing body of evidence suggests that sleep and neurodegenerative dementias (ND) have a bi-directional relationship. Orexin-A (OXA) concentration in cerebro-spinal fluid (CSF) has been found to be altered in persons with Alzheimer Disease (AD), however results have not been consistent across studies. Furthermore, OXA determination in CSF is an invasive technique. The main aim of this study is to evaluate correlations of OXA in different biological fluids, such as blood and CSF, in patients affected by several ND. The secondary aim is to evaluate OXA concentration compared to other neurodegeneration associated peptides.

Materials: Patients affected by several ND were enrolled at IRCCS Istituto Auxologico Italiano, Departments of Neurology of Milan and Piancavallo. ND diagnosis was made according to most recent diagnostic criteria based on concordance of both clinical and radiological/CSF findings. ND considered were the following: Alzheimer disease and its logopenic variant patients (AD/ADlv), non-logopenic primary progressive aphasia and behavioural variant of Fronto-Temporal Dementia (PPA/bvFTD). A group of patients with no evidence of ND served as controls.

Method: Both patients and controls underwent OXA determination in CSF and blood (ELISA). Other neurodegeneration associated peptides measured were: serum neurofilament light chain (NFL, SIMOA), CSF total-tau (t-tau, ELISA), CSF phospho-tau (p-tau, ELISA), CSF Amyloid beta 1-40 (Abeta 1-40) and Amyloid beta 1-42 (Abeta 1-42, ELISA).
Results: Sample size was the following: 10 AD/ADlv patients (pts), 19 PPA/bvFTD pts, 21 controls. Gender and age did not statistically differ between groups (p=0.6067; p=0.147). We found a positive correlation between OXA levels in CSF and blood in the whole group of subjects (ND plus controls; Pearson correlation coefficient CC= 0,32, p=0,026) with a stronger correlation in controls (CC= 0,74) than in ND (CC= 0,29). Mean OXA concentration in CSF was significantly reduced in ND than controls (p=0,04). We also found an inverse correlation between OXA and NFL in ND group (CC= -0,37, p=0,04). All CC and significance values were adjusted for gender, age and disease duration variables.

Discussion: Despite the small sample size, we found a positive correlation between OXA level in CSF and blood: this suggests that it might be useful to measure OXA in the blood in clinical practice. We also found evidence of OXA reduction in ND, together with a negative correlation between OXA and the neuroaxonal degeneration biomarker NFL.

Conclusion: OXA level in different biological fluids may represent a biomarker of degeneration in ND, especially when correlated to NFL.
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EEG ABNORMALITIES DURING DELIRIUM AS A PRODROMAL FEATURE OF DEMENTIA WITH LEWY BODIES: A CASE REPORT

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A 79-year-old woman was admitted to our Neurology Clinic for an accidental fall due to drowsiness and weakness of left lower limb. The neurological examination was normal. The Computed Tomography of the brain was negative for recent ischemic lesions. After three days from the hospitalization, the patient experienced an episode of mixed delirium, assessed by 4AT test. Therefore, a spectral analysis electroencephalogram (QEEG) was performed, which showed a Compressed Spectral Array (CSA) pattern of 2 (DF= 6.5 Hz, DFV= 2 Hz). At the discharge, after thirteen days, her neurological examination was negative. At six-month follow-up, she reported memory deficits with CF and RBD. The neurological examination revealed signs of parkinsonism (UPDRS-III=15). Cognitive performances were tested with a complete neuropsychological assessment, including the MoCA (score of 15/30). QEEG recording confirmed a CSA pattern of 2 (DF= 7.75 Hz, DFV= 2.5 Hz). The patient also performed a 18F-fluorodeoxyglucose PET/CT which reported a moderate posterior hypometabolism (occipital and temporal cortex), with relative sparing of the posterior cingulate cortex compared to cuneus/precuneus (Cingulate Island sign). The present case shows the occurrence of an episode of delirium prior to clinical diagnosis of probable DLB. Delirium symptoms are typically characterized by the presence of an altered conscious status, CF and psychotic manifestations. All these conditions tend to resemble the clinical features observed in DLB patients, which are considered as a core clinical criterium for DLB diagnosis. In DLB patients, from their prodromal disease stages, EEG studies show a progressive appearance of a pre-alpha/theta rhythm, a main hallmark of the thalamic derangement involved in DLB pathogenesis. A thalamic imbalance drives the so-called thalamocortical dysrhythmia which is supposed to be responsible for both specific EEG patterns and symptoms observed in these patients. EEG may represent a supportive and validated biomarker for prodromal DLB, especially for delirium-onset cluster.
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CSF Aß42/Aß40 RATIO PREDICTS A DIFFERENT METABOLIC PATTERN ALONG THE ALZHEIMER'S DISEASE CONTINUUM: A CSF AND 18FDG-PET STUDY

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Background: ATN system1 stratify patients within the AD continuum (ADc) according to the positivity of in vivo biomarkers, grouped into amyloid beta (Aß) deposition(A), fibrillar tau tangles(T) and neurodegeneration (N). Increasing evidence point to a complex scenario where purely amyloidopathic (A+T-) patients can reveal an heterogeneous nosological entity not different from those having the AD signature(A+T+). Decreased CSF Aβ42 represent the key feature of these patients. Although the use of the Aß42/Aß40 was introduced to increase the diagnostic accuracy in A+T+, its use in A+T- revealed unexpected scenario. Emerging evidences showed that Aβ42/Aβ40 in A+T- accounts for toxic amyloid production 2 and reveal that a subset of patients undergo neurodegenerative changes in absence of tau pathology. Here, we aimed at exploring the 18FDG-PET metabolism pattern among A+T-, distinct by exploiting CSF Aß42/Aß40.

Materials & Methods: We enrolled 26 patients with CSF diagnosis of amyloidopathy (A+T-) from the Memory Clinic of the Policlinico Tor Vergata, stratified according to the presence of either normal (A+T-nR n=10) or pathological(A+T- pR n=16) Aß42/Aß40. All patients underwent 18FDG-PET/TC; SPM 12(statistical parametric mapping) implemented in MATLAB 2012b was used for the analysis.

Results: As compared to A+T- pR patients, A+T- nR showed significant hypometabolism in bilateral parietal and temporal lobes ($p< 0.01$).On the contrary, as compared to A+T- nR, A+T- pR showed significant hypometabolism in left frontal areas mostly involving the orbitofrontal cortex($p<0.01$).

Discussion: These results allow to strengthen the idea that neurodegeneration can be related even only to amyloid(A+T-N+). Speculations can be made on the evidence of a typical AD pattern of hypometabolism along the temporo-parietal junction among patients with normal CSF Aß42/Aß40 ratio, as if this expedient might be not fully exhaustive to rule out the presence of AD. Furthermore, the different pattern of glucose consumption distribution specifically related to Aß42/Aß40 status highlights the need to reconsider the relationship between amyloid isoforms and neurodegeneration as a process. Since A+T-pR appear as more closely related to A+T+, both from clinical and biological perspectives, we suggest that early and toxic spreading of amyloid species might induce damage to non- neuronal cells in the brain like astrocytes and/or endothelium in absence of tau pathology, sufficient to develop cognitive symptoms. This would likely imply different rate of disease progression however, A+T- and A+T+ under certain circumstances remain clinically and pathologically superimposable. The results of our study show that the deeper understanding of ATN classification offer an extraordinary chance to better understand AD and to better focus on its therapeutic strategies.

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ALZHEIMER'S DISEASE CSF BIOMARKER PROFILES IN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

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Objectives: Patients with idiopathic normal pressure hydrocephalus (iNPH) frequently show pathologic CSF Aβ42 levels, comparable with Alzheimer's Disease (AD). Nevertheless, the clinical meaning of these findings has not been fully explained. We aimed to assess the role of AD CSF biomarkers (Aβ42, Aβ42/Aβ40, p-tau, t-tau) in iNPH.

Materials and methods: To this purpose, we enrolled 44 patients diagnosed with iNPH and 101 with AD. All the patients underwent CSF sampling. We compared CSF biomarker levels in iNPH and AD.

Results and Discussion: Aβ42 levels were not different between iNPH and AD, while Aβ42/Aβ40, p-tau, and t-tau were significantly different and showed excellent accuracy in distinguishing iNPH and AD. A multiple logistic regression analysis showed that Aβ42/Aβ40 was the variable that most contributed to differentiating the two groups. Furthermore, iNPH patients with positive Aβ42/Aβ40 had higher p-tau and t-tau than iNPH patients with negative Aβ42/Aβ40. Those iNPH patients who showed cognitive impairment had lower Aβ42/Aβ40 and higher p-tau than patients without cognitive impairment.

Conclusions: We concluded that positive CSF Aβ42 with negative Aβ42/Aβ40, p-tau, and t-tau is a typical CSF profile of iNPH. On the contrary, positive Aβ42/Aβ40 in iNPH patients, especially when associated with positive p-tau, may lead to suspicion of a coexistent AD pathology.

LATE ONSET FRONTAL SYNDROME: DIFFERENTIATION BETWEEN FRONTOTEMPORAL DEMENTIA AND PRIMARY PSYCHIATRIC DISORDER USING VISUAL RATING SCALES OF ATROPHY

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Introduction: Frontotemporal dementia (FTD) includes a group of neurocognitive syndromes, clinically characterized by behavioral change and altered executive functioning. FTD and psychiatric disorders can overlap in terms of clinical presentations. Furthermore, FTD is typically characterized by a young age of onset of the disease, closer to the onset of primary psychiatric disorders (PPD), increasing the difficulty in making the correct diagnosis.

Aim: The aim of the study is to identify the discriminative pattern of brain atrophy between FTD and PPD.

Methods: Among the patients followed in the CDCD of the Ospedale Maggiore Policlinico of Milan, we retrospectively selected subjects with frontal lobe symptoms with an age at onset between 40 and 75 and with mild severity at the time of MRI. All the subjects underwent extensive neuropsychological testing, neurological and psychiatric examination. Two rater, blind for all the clinical information's, applied a protocol of 6 visual rating scales of atrophy and 2 of white matter hyperintensities.

Results and discussion: A total of 52 subjects were recruited for the study: 15 FTD, 22 PPD and 15 controls. Compared to PPD, FTD cases showed higher degree of atrophy in left orbitofrontal, anterior cingulate and fronto insula, bilateral anterior and medial temporal and parietal areas. ROC curve analysis showed that left orbitofrontal scale was the most useful in the differentiation between FTD and PSY (AUC 0.88) while left anterior temporal better discriminated between FTD and CON (AUC 0.873). A score higher than 2 in left anterior temporal showed a specificity of 100% for FTD. No differences between PPD and Controls was found.

Conclusions: Visual rating scales can be useful to discriminate FTD and PPD and the left orbitofrontal showed the highest accuracy.

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MASCOD - MULTIDIMENSIONAL ASSESSMENT OF SUBJECTIVE COGNITIVE DECLINE: A NEW SCREENING FOR SUBJECTIVE COGNITIVE DECLINE

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Objectives: Subjective cognitive decline-SCD is a subclinical cognitive impairment subjectively experienced without being detectable from a diagnostic and neuropsychological perspective. Currently, only a few screening tools focusing mainly on memory complaints exist. Therefore, the aim is to present a screening tool to detect SDC and the preliminary data of its use.

Materials: A panel of experts in cognitive functioning and disorders (neurologists, psychologists, neuropsychologists) has been constituted to discuss SCD and to construct the instrument. Then, all authors reviewed the literature and started the conceptualization of the instrument. Overall, all items constituting the new screening have been discussed among the authors and they were repeatedly revised until the full consensus was reached concerning both the content and the language. The name chosen for the new screening tool is the following: MASCoD – Multidimensional Assessment of Subjective Cognitive Decline.

Methods: After its conceptualization, to evaluate the clinical feasibility, a preliminary clinical adoption of this instrument has been carried on with some outpatients during the neurological visits when the patient reported cognitive decline. A trainee psychologist compiled the items according to the answers provided by the patients. Afterward, MASCoD results have been analysed in light of the usual neuropsychological evaluation with standardised tests.

Results: The instrument is composed of a general form for sociodemographic data and the following three sections: a) risk factors for SCD; b) memory and executive symptoms; c) anxious/depressive or distressing symptoms. There are four increasing risk levels (i.e. low, medium with emotional complaints, medium without emotional complaints, high risk) of developing a severe cognitive impairment. Preliminarily, 13 patients underwent both MASCoD and a usual neuropsychological assessment for cognitive impairment. Overall, 69,24% was the convergence level of the two measurements (i.e. detection of true positive and true negative cases for developing severe cognitive impairment).

Discussion: Assessing the SCD has to be considered pivotal in the healthcare scenario in order to early detect a progressive cognitive impairment. In the international literature there are various questionnaires assessing memory complaints, but they do not address other possible features of SCD related to attention or executive abilities, as well as anxious and depressive symptoms.

Conclusions: Compared to usual neuropsychological assessment, MASCoD seems to be a promising tool for correctly detecting the most probable trajectory of developing cognitive decline over time. A bigger sample will deepen and strengthen these preliminary findings through a well-structured validation study.

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LOCUS COERULEUS MRI PREDICTS MILD COGNITIVE IMPAIRMENT PROGRESSION TO DEMENTIA

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Objectives: Locus Coeruleus (LC), the main noradrenergic nucleus of the brain, is early and dramatically involved in Alzheimer's Disease [1]; LC lesion accelerates and worsens neurodegenerative processes in preclinical models [2]. In this study, we aimed to explore whether reduced Locus

Coeruleus integrity, as assessed by MRI, is associated with a higher risk of progression to dementia in subjects with Mild Cognitive Impairment.
Materials and methods: We submitted 165 age- and sex-matched subjects (53 cognitively intact healthy controls, 73 amnestic Mild Cognitive Impairment individuals, and 34 Alzheimer's Disease Dementia patients) to a 3T Brain MRI scan with LC-sensitive sequence [3]. LC images were analyzed through a template-based post-processing approach [3]. The whole sample underwent a detailed neurological and neuropsychological evaluation both at baseline and after prolonged clinical follow-up (2.5 years). Mild Cognitive Impairment subjects were then distinguished between converters and stable ones, based on their progression to dementia.

Results: Mild Cognitive Impairment individuals who had converted to dementia at the end of follow-up showed a significant loss of integrity of the rostral part of the left LC when compared both to cognitively intact healthy controls and stable Mild Cognitive Impairment subjects. In line with this, the survival analysis showed that Mild Cognitive Impairment individuals with lower values of LC-MRI parameters had a higher risk to progress to dementia and that such association was not influenced by age, sex, APOE ε4 status, and baseline cognitive performances. Through Structural Equation Modeling we calculated an index of global LC integrity, and we found that its deterioration paralleled cognitive performance impairment and disease severity in the whole sample.

Discussion: Our findings highlight in vivo the detrimental effects that LC degeneration might have on Alzheimer's Disease. Mild Cognitive Impairment individuals whose LC integrity was more markedly compromised at baseline had a higher risk of progression to dementia, and in the whole sample, LC-MRI parameters were associated with cognitive performance and disease severity. These results are in line with the preclinical literature which supports the neuroprotective role of noradrenaline in the aging brain and that identifies LC degeneration as a key point in Alzheimer's Disease pathogenesis.

Conclusions: Our data support the role of LC-MRI as a candidate diagnostic and prognostic biomarker in the context of Alzheimer's Disease research and clinical practice, encouraging further studies to better disclose the role of the central noradrenergic system in this neurodegenerative disease.
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FLUENCY TYPE INDEX: A NEUROPSYCHOLOGICAL MARKER TO PREDICT AMNESTIC MILD COGNITIVE IMPAIRMENT PROGRESSION TO ALZHEIMER'S DISEASE

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Aim: Category fluency (CF), depending on language functions, is the ability to recall words belonging to a specific category, while letter fluency (LF), depending on attentive-executive functions, is the ability to recall words with a specific letter. LF deficit reveals mainly a prefrontal dysfunction while a CF deficit a temporal's one. Fluency Type Index (FTI = adjustedCF – adjustedLF/adjustedCF + adjustedLF) quantifies relative proficiency of each subject on CF and LF. A positive value (FTI+) suggests an attentive-executive deficit and a negative value (FTI-) a language deficit. The study aims to investigate FTI's ability to predict aMCI evolution in AD and its correlation with a CSF parameter (Tau/Aβ).

Materials: A total of 165 aMCI patients have been divided considering evolution (aMCI-E) (n=41) or non-evolution (aMCI-NE) (n = 124) to AD within 1 year.

Methods: FTI values, prevalence of FTI- and FTI+ in each group have been compared. Pearson correlation coefficient between FTI and Tau/Aβ has been calculated and the frequency of pathological (< - 0.22 and > + 0.5) and normal FTI in patients with pathological (> 0.52) and non-pathological T/Aβ has been compared with the chi-squared test.

Results: FTI values are significantly different in the 2 groups (aMCI-E < aMCI-NE, $p < .01$). In aMCI-E group prevalence of FTI- is higher that FTI+, while no difference emerges in aMCI-NE ($X^2=\ 5.36$, $df = 1$, $p < .05$). FTI and Tau/Aβ result negative correlated ($r = - 0.18$, $p = 0.05$); frequency of pathological and normal FTI and pathological and normal CSF are correlated ($X^2 = 3.45$, $df = 1$, $p < 0.05$).

Discussion: Most patients that evolved to AD had a negative FTI and values of FTI in those patients are significantly lower compared to those of patients that did not evolve to AD. Moreover, there is a correlation between FTI and CSF parameters. In our opinion, these data indicate that FTI values could help locate the disfunction in patients with aMCI and predict the evolution to AD.

Conclusion: FTI is a neuropsychological marker that, similarly to Tau/Aβ, predicts aMCI evolution to AD.
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BEYOND IMPAIRMENT OF LANGUAGE: EMPATHY DEFICIT IN LOGOPENIC VARIANT OF PRIMARY PROGRESSIVE APHASIA

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Empathy is the ability to understand (cognitive empathy) and to feel (affective empathy) what others feel, and it may be reduced in neurodegenerative diseases [1]. Evidences about empathy in logopenic variant of Primary Progressive Aphasia (lv-PPA) are rare and not conclusive [2]. The aim of this study is to assess possible empathy deficits and their neural basis in lv-PPA compared to amnesic AD. We included 18 lv-PPA and 38 AD patients. Informer-rated Interpersonal Reactivity Index (IRI) was used to explore cognitive (Perspective Taking-PT, and Fantasy-F, subscales) and affective (Empathic Concern-EC and Personal Distress-PD subscales) empathy, before (T0) and after (T1) cognitive symptoms'

onset. Ekman 60 Faces (EK-60F) Test was administered to investigate emotion recognition ability. IRI and EK-60F scores of lv-PPA and amnesic AD were compared to those obtained in 31 subjects with Subjective Cognitive Decline (SCD). Eighteen lv-PPA and 30 AD patients underwent Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) and amyloid biomarker analysis. SPM analysis on FDG-PET was performed in 16 lv-PPA and 26 amnesic AD with positive amyloid biomarkers. PD-T1 scores were higher in lv-PPA and in amnesic AD than in SCD (respectively 28.33±5.89 vs 21.04±5.51, p<0.001; 26.03±5.71 vs 21.04 ±5.51, p=0.001). PT scores decreased from T0 to T1 in lv-PPA (z=-3.43, p=0.001) and in amnesic AD (z=-4.57, p<0.001). PD scores increased from T0 to T1 in lv-PPA (z=-3.62, p<0.001), amnesic AD (z=-5.20, p<0.001) and SCD (z=-3.450, p=0.001). Lv-PPA performed poorer than amnesic AD in happiness recognition (7.54±2.18 vs 8.94±1.04, p=0.001). Delta-PT(T0-T1) negatively correlated with metabolic disfunction of right medial frontal gyrus both in lv-PPA and amnesic AD, of left cingulate gyrus in lv-PPA, and of right temporal regions in amnesic AD (p<0.005). Delta-PD(T0-T1) positively correlated with metabolic disfunction of bilateral frontal and parietal gyri in lv-PPA (p<0.005), of right middle and inferior frontal gyri and inferior temporal gyrus in amnesic AD (p<0.001). Lv-PPA presented a heightened PD as compared to SCD but similar to amnesic AD. Increase of PD and reduction of PT along time were found both in lv-PPA and in amnesic AD and may be related to hypometabolism of shared but also different brain regions. Beyond language impairment, lv-PPA patients seems to present empathy changes and difficulties in emotion recognition [3]. Similarities in empathy deficits between lv-PPA and amnesic AD may be explained by the shared neurodegenerative mechanism. The differences in metabolic disfunction might be due to a different susceptibility of specific brain regions in lv-PPA and amnesic AD.

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MITOCHONDRIAL D-LOOP REGION METHYLATION LEVELS IN PERIPHERAL BLOOD CHANGE ALONG AD SPECTRUM, A PILOT STUDY

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Objective: The role of mitochondrial impairment has long been recognized in the pathophysiology of Alzheimer disease (AD) and interest is growing in mitochondrial epigenetics. Alterations in the mitochondrial Displacement loop (D-loop) region methylation levels, which are involved in mitochondrial DNA replication and transcription, have been reported in subjects with AD, both in the brain and peripheral blood. Moreover, in animal models of AD D-loop methylation levels were shown to change along with disease progression. The aim of the present study was to assess whether differences in D-loop methylation levels exist between healthy controls (HC) and AD subjects at different disease stages, exploring their potential role as peripheral diagnostic biomarker and their eventual association with AD pathophysiological biomarkers.

Materials and methods: We enrolled 102 subjects with AD according to NIA-AA-2011 criteria (14 MCI-AD (CDR=0.5), 18 early AD (CDR=1), 70 later-stage AD (CDR ≥2)), and 105 age- and sex-matched HC among unrelated family members. CSF AD core biomarkers (β-amyloid [1-42], total-tau and phosphorylated-tau) evaluation was available for a subset of AD population (CDR=0.5-1). D-loop region methylation levels in peripheral blood were assessed by means of methylation-sensitive high-resolution melting, shown as (%, mean ±SD), and were compared among groups using ANCOVA, including age at sampling as a covariate, followed by a post hoc Bonferroni's correction. Furthermore, we assessed its diagnostic accuracy using receiver operating characteristic curves (AUROCs). Partial correlations were used to explore the association between D-loop methylation levels and CSF AD core biomarkers in MCI to early AD subjects, with age as a control variable.

Results: MCI subjects showed significantly increased the D-loop region methylation levels (6.77 ±3.74) with respect to HC (3.80±3.73, p=0.041), early AD (3.37±4.51, p=0.019), later-stage AD (2.12±2.53, p=0.0006). Using AUROC, D-loop region methylation levels showed a fair discriminating ability in differentiating MCI from other subjects (AUC=0.771 [95%CI: 0.707–0.826; p=0.0001]). A significant negative correlation was found only between D-loop methylation levels and CSF phosphorylated-tau (r=-0.64; p=0.025).

Discussion: The observed changes in D-loop methylation levels may reflect the mitochondrial activity demand at different AD stages, reflecting a compensatory mechanism in MCI subjects or representing the initial driver of mitochondrial hypometabolism that characterizes subsequent stages of AD.

Conclusions: The present study shows that peripheral D-loop methylation levels differ at different clinical stages of AD and are related to specific AD core biomarkers, reinforcing the possible role of mitochondrial epigenetics in Alzheimer pathophysiology, and could eventually be considered among peripheral diagnostic biomarkers.

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SLEEP BODY POSITION CORRELATES WITH COGNITIVE PERFORMANCE IN MIDDLE-OLD OBSTRUCTIVE SLEEP APNEA SUBJECTS

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Background: The association between sleep disturbances, cognition and neurodegeneration may be bidirectional. The characterization of sleep with cognitive performance is essential in understanding the potential neurobiological mechanisms that underlie the connection between sleep disruption and neurodegenerative manifestations and progression.

Objectives: We explored the inter-relationships between body position during sleep, which can affect cerebral glymphatic system transport and cognitive status.

Materials: All consecutive subjects greater than 18-years old attending our Sleep laboratory between June 1, 2021 to May 31, 2022 were included. We excluded patients with unreadable polysomnographic studies or uncompleted data.

Methods: All cases were evaluated according to AASM guidelines, including demographic data, clinical history, anthropometric measures, previous diagnosis of OSA, snoring, sleep quality measures, and reporting of different sleep body position (supine, prone, right and left

side) with a screening cognitive evaluation assessed by the Self-Administered Gerocognitive Exam (SAGE) to detect early signs of cognitive impairment. SAGE score was used as continuous and categorical variable [18–22, normal cognition; 15–17, mild cognitive impairment (MILD); below 14, dementia, according to literature guidelines]. We used partial correlation analysis to measure the degree of association between duration of sleep spent in a different body position and SAGE scoring controlling for confounding variables [age, body mass index, apnea-hypopnea index (AHI), oxygen desaturation index (ODI) as measures of OSA severity].

Results: Of 243 consecutive cases, 232 subjects (127 men; mean age ±SD: 65.1±14.1 years) were included. Twenty-nine (12.5%) subjects were normal, 72 (31.0%) had mild, 68 (29.3%) moderate, and 63 (27.2 %) severe OSA. We did not find any correlation between anthropometric and demographic variables, OSA severity, and sleep quality with SAGE scoring (all P>0.05). SAGE scores were correlated with minutes spent on right lateral (r= 0.228; P=0.001) but not on left lateral or prone (all p>0.05) sleep posture and inversely correlated with time on supine sleep one (r=-0.162; p=0.015). After adjusting, SAGE scoring remained positively correlated with minutes spent on right lateral (r=0.231; p=0.001) and inversely correlated with time on supine sleep posture (r=-0.167; p=0.013).

Discussion: Our observations suggest that the right lateral posture during sleep has an advantage on cognition while supine position represents a disadvantage. This effect is independent by OSA severity, clinical and anthropometric measures.

Conclusion: Our findings warrant further investigation, particularly considering the recent evidence suggesting that sleep body position may have an active role in the brain's ability to optimize the clearance of metabolic leftovers and interstitial solutes.

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DIFFERENT RELATIONSHIP BETWEEN CEREBROSPINAL FLUID ATN BIOMARKERS AND NEUROFILAMENT LIGHT CHAIN (NFL) IN ALZHEIMER'S DISEASE AND FRONTOTEMPORAL LOBAR DEGENERATION SPECTRUM

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Introduction: The paradigm shift in research criteria of Alzheimer's disease (AD) has operationalized the biomarker-based A/T/N classification system. Neurofilament light chain (NfL) has gained momentum as a candidate biomarker of neuroaxonal injury, even potentially preferable to total-tau as CSF-based (N) biomarker. CSF NfL concentration has been reported to have poor discriminatory power for AD and modest discriminatory power for frontotemporal lobar degeneration (FTLD). Objectives of this study were: to assess the role of CSF NfL in discriminating between AD and FTLD; to explore the different relationships between core CSF ATN biomarkers and NfL in AD and FTLD; to investigate the relationship between NfL and neuropsychological measures.

Materials & Methods: Fifty-three patients with a clinical-biological diagnosis of MCI due to AD(N=36) or a clinical diagnosis of FTLD(N=17) underwent neuropsychological assessment and CSF collection. Aβ40, Aβ42, total-tau, p-tau181 and NfL quantification were conducted by automated assays. Comparisons between medians of continuous variables were carried out by means of the Mann-Whitney-U-test for mean rank, while correlations between continuous variables were examined using Spearman's correlation coefficient. ROC curve analyses were carried out to assess the diagnostic utility of total-tau, NfL and total-tau/NfL ratio for determination of AD versus FTLD.

Results: Groups did not differ in age, literacy and MMSE. NfL levels were significantly lower in the AD group, while levels of total-tau were higher. In the FTLD group, a significant correlation was found between NfL and total-tau (ρ=0,632, p<0,005), but no significant correlation between NfL and neuropsychological measures. Conversely, in the AD group NfL were directly correlated with total-tau (ρ=0,355, p<0,05) and p-tau181(ρ=0,404, p<0,05), and inversely correlated with the number of words produced during a category verbal fluency task (ρ=0,381, p<0,05). In the AD group, Aβ42/40 ratio was directly correlated with total-tau and p-tau181(ρ=0,532, p<0,005; ρ=0,501, p<0,005), but not with NfL. Total-tau/NfL ratio differentiated AD from FTLD with an AUC of 0.915, higher than the individual measures.

Discussion & Conclusions: The different relationships between CSF biomarkers in AD and FTLD spectrum supports that NfL and total-tau levels reflect distinct pathophysiological mechanisms of neurodegeneration (independent and dependent of Aβ pathology, respectively). Combining NfL with a disease-specific biomarker such as total-tau may strengthen the reliability of both markers, and their ratio seems useful in distinguishing AD from FTLD. Moreover, our results yield further support to the hypothesis that lexical-semantic impairment is a hint of neurodegeneration in prodromal AD but not in FTLD suggesting the association with early and specific neuropathological changes.

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BIOMARKERS RELATED TO SYNAPTIC DYSFUNCTION TO DISCRIMINATE ALZHEIMER'S DISEASE FROM OTHER NEUROLOGICAL DISORDERS

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Objective: To study the role of Neurogranin (Ng) and α-Synuclein (α-Syn) in AD patients, in patients affected by neurodegenerative diseases (NDD), and by no- neurological disorders (DC), also considering the ratio Aβ42/Ng and Ng/ α-Syn, to clarify the role of synaptic dysfunction in AD and to discriminate AD from other neurological disorders.

Material and methods: The study was performed in a cohort of patients from Neurology Unit of the Palermo University Hospital "P. Giaccone" who underwent lumbar puncture for CSF analysis. We measured Ng, α-Syn concentrations and Aβ42 in cerebrospinal fluid CSF of 98 patients: 44 AD patients (age 66 [61-67] Sex M/F 1.16; Education 8 [5–13] years); 17 NDD (age 63 [57–71]; Sex M/F 1.8; Education 8 [5–8] years), and 37 DC (age 66 [66–74]; Sex M/F [1.8]; Education 8 [5–17]years) by sensitive enzyme-linked immunosorbent assays (ELISAs).

Results: CSF Ng levels are significantly higher in AD patients in comparison to NDD and DC ($p<0.001$). There aren't statistically difference in CSF α-Syn between the studied groups. We found a significant relationship of CSF Ng levels with diagnostic delay (rho=0.376; p=0.017) and with lower Mini Mental State Examination (MMSE) scores (rho= -0.418; p=0.007). CSF Ng levels correlates significantly with Aβ42/40 ratio, pTau, tTau, pTau/tTau ratio, and α-Syn. We also found that Aβ42/Ng ratio was statistically significant lower in AD than in NDD and that Ng/ α-Syn ratio was higher in AD than in DC.

Discussion: The aim of this study is to investigate the role of biomarkers related to synaptic dysfunction, such as Ng and α-Syn, in AD pathogenesis. Although the non-specificity of CSF Ng in discriminating AD from other neurological disorders was previously debated, we showed that CSF Ng can discriminate AD patients from NDD and DC patients. CSF Ng are also correlated with lower MMSE score and higher pTau and tTau levels, indicating the contribution of synaptic dysfunction together with neuronal degeneration in progression of disease. Furthermore, Aβ42/Ng ratio, indicated by other authors as "index of synaptic dysfunction", can discriminate AD from NDD patients with a better diagnostic performance than Ng, in terms of sensibility and specificity, and correlates with cognitive impairment in AD, but not NDD.

Conclusions: Neurogranin can represent a promising biomarker for AD and Aβ42/Ng ratio can represent a reliable index of synaptic dysfunction able to discriminate AD from other neurological conditions.

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CEREBROSPINAL FLUID CX3CL1 IN ALZHEIMER DISEASE AS A POTENTIAL DIAGNOSTIC BIOMARKER

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Objective: Our work was aimed to study the CX3 chemokine Ligand 1 (CX3CL1) as a potential diagnostic biomarker for Alzheimer's disease (AD).

Materials: We recruited 46 patients from the Clinic for Cognitive Decline, Dementia and Parkinsonism of the University Hospital Paolo Giaccone Palermo, Italy. All patients underwent a neurological examination, brain MRI and FDG-PET as well as a lumbar puncture during the diagnostic work-up.

Methods: Patients were divided into two groups, according to the AT(N) biomarkers classification. Group A consisted of 28 patients categorized as "Alzheimer's Continuum" (A+T± (N+); ge 70 ±8; F/M=0.75); Group B included 18 patients as control group (i.e. non-AD pathological changes, A-T-(N+) Age 66.7 ± 10; F/M=0.83). Also, both AD and non AD patients have been classified according to the AT(N) biomarkers classification (Clifford R. Jack, Jr 2018). Exclusion criteria for group A were: other medical condition explaining cognitive decline, other degenerative disease, cerebrovascular disease, metabolic disease and substance abuse. We also stratified Group A into two subgroups (A1 and A2) according to positivity of Tau pathology (Group A1: A+T+ (N+), Group A2: A+T- (N+)). CSF was collected during morning hours in polypropylene tubes, centrifuged at 2000 rpm for 20' and stored at -80°C until analysis.

Results: We found that CX3CL1 was present in the CSF of all subjects (0.43 ± 0.15 ng/ml), but we also found that Group A showed a greater amount of CX3CL1 (0.47 ± 0.03 ng/ml) than Group B (0.35 ± 0.04 ng/ml) ($p < 0.001$). Furthermore, we found that CSF CX3CL1 concentration A showed a greater but not significant greater concentration than Group B ($p < 0.01$ and $p < 0.05$ respectively).

Discussion: The present study highlights a more significant presence of CX3CL1 in AD continuum subjects than in non-AD continuum patients. Furthermore, from the comparison of the classic biochemical markers, Ab and Tau expression, it is highlighted that even in patients with a level of total Tau and phosphorylated Tau comparable to subjects AD continuum, there is still a presence in the CSF greater than a third of CX3CL1, compared to subjects classified non-AD.

Conclusion: Even if the data is purely preliminary and the CSF analysis of the patients is limited, the results obtained strongly suggest an involvement of CX3CL1 in Alzheimer's disease, not secondary, and place the presence of this cytokine as a potential marker in AD.

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SUBJECTIVE COGNITIVE DECLINE AND MILD COGNITIVE IMPAIRMENT AS CAUSE OF DEATH IN A RURAL SOUTHERN ITALIAN POPULATION: DATA FROM THE ZABUT AGING PROJECT

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Objectives: Subjective Cognitive Decline (SCD) and Mild Cognitive Impairment (MCI) are currently considered as risk stages for dementia and AlzheimerTMs disease (AD). However, very few and sparse data have been reported regarding the association of all-cause mortality and the above-mentioned clinical pre-dementia syndromes. We evaluated the role of SCD and MCI as predictors of death in elderly subjects living in a rural Sicilian community.

Methods: This study was carried out using data from the Zabut Aging Project (ZAP), a survey on neuropsychiatric disorders carried out on all subjects aged at years living in a rural village in southern Sicily [1]. At baseline, 2,028 subjects were examined (2001-2003), with mortality follow-up until 2014. According to clinical and cognitive data, subjects were allocated at baseline according to the current criteria in the following categories: SCD [2], MCI [3], dementia (either AD or vascular dementia [VaD]). Mortality statistics derived from the Sicilian Regional Statistical Office and ICD-9 coded death certificates were analyzed. Multivariate logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI) of the mortality predictors in the ZAP cohort.

Results: After excluding subjects with missing information at follow-up as well as significant clinical depression, a total of 1,766 subjects aged at 50 years were analyzed. Of these 545 (30.9%) deceased during the follow-up period (2001-2014) whereas 1,221 (69.1%) withdrew alive. Multivariate logistic regression showed that male sex (adj-OR = 1.48; 95% CI 1.13-1.94), age (adj-OR = 3.42; 95% CI 2.89-4.04), MCI (adj-OR = 2.92; 95% CI 1.99-4.27), AD (adj-OR = 11.71; 95% CI 4.33-31.67) and VaD (adj- OR = 17.34; 95% CI 3.91-76.80) were significantly associated with increased mortality, while a diagnosis of SCD and the apolipoprotein E4 genotype did not modify the risk of death.

Discussion and Conclusions: Our results confirm that both AD and VaD represent major predictors of death in the elderly. Furthermore, while the presence of MCI at baseline increased the risk of death nearly 3-fold, the presence of SCD did not. This latter result suggests that the diagnosis of SCD should be interpretated as a more labile construct for predicting dementia than MCI, probably representing a subjective reaction to the underlying disease. Future prospective studies need to further explore the pathway linking SCD to mortality through dementia.

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THE ROLE OF SOCIAL NETWORKS AS PREDICTORS OF DISABILITY AND QUALITY OF LIFE IN AGING

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Objectives: The research study TAPAS in Aging (Time and Places and Space in Aging) aimed to explore the role of social networks and built environment on disability and quality of life in the aging population. Here we focus specifically on social networks as they emerged to be significant predictors of the dependent variables investigated.

Materials: Data were collected through a research protocol used in previous European and Italian projects (COURAGE in Europe and the Italian IDAGIT study). The protocol was composed by a set of validated tools: World Health Organization Disability Assessment Scale 2.0 (WHODAS 2.0), World Health Organization Quality of Life Assessment in Aging (WHOQOL-AGE), Social Network Index (SNI), the Courage Built Environment Self-Reported Questionnaire (CBE-SR), and a collection of sociodemographic information and information on health system coverage.

Method: Participants aged 50+ were recruited with the collaboration of the senior association Auser, present in the Lombardy Region of Italy, where the study was conducted. A total of 431 participants (209 males and 222 females, with a mean age of 70 years) was administered the research protocol by trained interviewers.

Results: From the regression model with WHOQOL-AGE as dependent variable, SNI and Loneliness Score resulted to significantly predict QoL: in particular, higher scores of SNI predicted an increase in QoL, while higher Loneliness Score predicted a reduction in QoL. From the regression model with WHODAS 2.0 as dependent variable, Social Support Score and Loneliness Score emerged as significant predictors of disability. Specifically, higher levels of Social Support predicted a decrease in disability level and higher Loneliness Score predicted an increase in disability level.

Discussion: The results of the present study highlighted the importance of social networks for functioning and QoL in the aging process. These results are in line with previous evidence showing the positive impact of social networks on QoL as well as the significant effect of loneliness on health and QoL.

Conclusions: Given the role of social networks in the aging process and the higher risk of isolation for older adults, it is essential that public health interventions aimed at increasing functioning and quality of life in this segment of population focusing on promoting the creation and consolidation of social network and on contrasting isolation.

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MULTIMODAL BIOMARKERS ASSESSMENT IN PRODROMAL DEMENTIA WITH LEWY BODIES. PRELIMINARY DATA

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Aims: Mild cognitive impairment (MCI) is the most common presentation of prodromal Dementia with Lewy bodies (pDLB). Albeit the indicative and supportive biomarkers included in the diagnostic criteria for DLB have been

proposed for pDLB as well, evidence of their diagnostic and prognostic accuracy in early stage is sparce. We aim to assess and characterize multiple biomarkers in a prospective cohort study of patients with MCI-pDLB. We plan to enroll twenty patients in a 18-month period and to follow them with clinical and neuropsychological examinations every 6 months. Individual biomarker consistency and group comparisons with healthy controls as well as with "competitor pathologies" (Parkinson's disease and MCI due to Alzheimer) to verify the accuracy are foreseen.

Materials: Until now, we have enrolled seven consecutive MCI-pDLB patients (five males, mean age:77±7.6; mean education 9.8±4.2; mean MMSE score 26±3.7) according to the 2020 criteria.

Methods: At baseline, patients are assessed with clinical examination (including assessment of smell and of orthostatic hypotension, and MDS-UPDRS), a neuropsychological test battery, indicative (Polisomnography, dopamine transporter SPECT (DaT-SPECT), 123I-MIBG myocardial scintigraphy) and supportive (FDG-PET, MRI, EEG) biomarkers.

Results: In all patients, a significant impairment of putamen DaT uptake was found. Significant impairment of post-ganglionic myocardial innervation and Rem Sleep Without Atonia were found in two and four patients, respectively, performing the examinations so far. 6/7 FDG-PET show the typical parietooccipital hypometabolism and cingulate island sign while in one instance FDG-PET showed hypometabolism in temporolateral, temporomedial cortex and precuneus. 4/6 EEGs showed a slowing-down of the background activity together with delta waves. In the 5 MRI performed so far, the MTA score (Scheltens scale) was 2, 1 and 0 respectively in 1, 3 and 1 patients, while Koedam score was 3 in 2 patients, 2, 1 and 0 in the remaining. Orthostatic hypotension was demonstrated in 2/7 patients, while all had objective hyposmia.

Discussion: While the few litterature data stand for a limited (60-70%) sensitivity of DaT SPECT and I-123 MIBG scintigraphy in pDLB, in this preliminary series we found higher figures, similar to those in full-blown DLB, to be confirmed in the whole sample. As the follow-up protocol proceeds, we will be able to obtain useful information of diagnostic accuracy and prognostic role of each biomarker, especially toward competing pathologies.

Conclusions: Typical hallmarks of Lewy-body pathology can be detected in most patients since the earliest stages and should be assessed for a prompt diagnosis and disease management.

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CENTERS FOR COGNITIVE DISORDERS AND DEMENTIA (CDCD) AND LOCAL PALLIATIVE CARE NETWORK: A PATIENT-CENTERED INTEGRATED MANAGEMENT MODEL AS DEVELOPED IN THE DEMENTIA PDTA AUSL PARMA

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Introduction: In contrast to oncology, patients with serious neurologic illness may lose their ability to communicate early in their disease course. Patients with rapidly progressive dementia may initially retain the motor skills of speech but be unable to participate in decision making due to cognitive impairment. Surrogate decision makers are thus commonly required to serve as the voice of patients. These communication challenges demonstrate the importance of early initiation of palliative care.

Objective: In this work the objectives are: the creation of a shared care planning, to define decisions due to the evolution of the disease together with patient and caregiver; the implementation of a palliative approach to improve the quality of life and wellness of the patient and caregiver and end-of-life care.

Methods: During the last years, Centers for Cognitive Disorders and Dementia (CDCD) have structured a health pathway to take charge of the patient with dementia and the caregiver (from the communication of the diagnosis to the end of life), with a multidisciplinary approach able to intercept early signals of physical and psychic suffering and to accompany in the various decision-making phases. This approach defines the treatment strategy and the therapeutic proposals, to respect the patient's wishes and to support the role of fiduciary of the caregiver. The CDCD team has set work meetings with the RLCP team (Local Palliative Care Network), to promote information events for caregivers and multidisciplinary visits, in order to define, identificate, plan and modulate the interventions based on the disease progression and the patient's and caregiver's needs. Each visit was documented in the patient's medical records. This pathway is part of the AUSL of Parma - PDTA Dementia.

Results: During 2021, 44 families have participated in the information events; 13 out of 44 have joined the dedicated pathway characterized by several in-depth meetings with the medical staff of the multidisciplinary team. Patient's and caregiver's psychological and physical wellness can have an impact on the evolutions of the disease, therefore the timing and availability of a comparison with medical staff can allow to intercept early emerging needs.

Conclusion: Palliative approach to dementia demands a multidisciplinary taking in charge, which consents to accompany the caregiver in the different stages of disease, alongside the care planning of the patient. The consolidation of these health pathways in clinical practice requires a cultural change of health care professionals, social care professionals and citizens in general.

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A NOVEL COMPUTATIONAL APPROACH TO THE EEG THETA-TO-ALPHA TRANSITION FREQUENCY IMPROVES PREDICTION OF DEMENTIA IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT (MCI)

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Objective: To explore whether 'transfreq', a novel algorithm for the automatic computation of theta-to-alpha transition frequency (TF) which works with just one resting-state EEG (rs-EEG), correlates better with the mini-mental state examination (MMSE) in a group of patients with amnesic MCI (aMCI) than previous approaches, like the 'Klimesch' and the 'minimum' methods.

Materials: Sixteen patients with aMCI (8 males, 8 females, mean age: 70±6 years; mean MMSE score:26.5±2.13) underwent EEG recording and clinical-neuropsychological examination every 6 months for at least 3 years or until conversion to dementia. Eleven subjects converted to Alzheimer Dementia (ADD), two to Frontotemporal Dementia, and 3 remained aMCI. For the purpose of this explorative study, we considered only the 11 ADD patients and excluded unreliable EEGs (no visible alpha peak or Klimesch not applicable). We examined 7 subjects involved in 21

sessions, every EEG recording was associated with the MMSE performed at the same time.

Methods: We used transfreq to estimate the TF and we tested its correlation with the corresponding MMSE at every 6 months points. Briefly, transfreq is based on the identification of the intersection between the lowest alpha frequency in posterior leads and the fastest theta ones in frontal leads, during a routine rs-EEG recording.

Results: Transfreq positively correlated with the MMSE score ($r = 0.668$, $p<0.001$), while the correlation was weaker with TF computed with Klimesch ($r=0.42$, $p=0.058$) and was not significant with the minimum method.

Discussion: EEG power in the slow-wave frequency bands shows a renowned inverse correlation with cognitive performances. However, alpha and theta bands are adjacent and may variably overlap across subjects. TF should therefore be estimated at individual level to avoid misinterpretation of qEEG. The classic Klimesch method relies on the comparison between the power spectra of two EEG recordings, a rs-EEG and a task-related EEG, which is hardly feasible in a clinical setting in MCI patients. The minimum method approximately defines the TF as the lowest frequency found just before the individual alpha peak in cases where this point is identifiable. Transfreq requires one EEG recording only and shows promising better results as a potential marker of cognitive decline.

Conclusions: We showed that the values of TF estimated with transfreq has a better correlation with the MMSE score in patients with aMCI converted to ADD, than those estimated with both Klimesch and minimum method. An automatic computational tool-box will be freely provided with the full paper publication.

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ASSESSMENT OF APATHY BY PATIENTS AND ITS DISCREPANCY WITH ESTIMATION BY CAREGIVERS RELY ON DIFFERENT METABOLIC CORRELATES IN AMNESTIC MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE

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Background: Apathy is one of the major behavioral symptoms of Alzheimer's disease (AD) and typically involves reduced motivation in cognitive, emotional, and social domains. Previous evidence pointed out the discrepancy between the assessment of apathy by caregiver and patient was related to the severity and worsening of cognitive impairment over time and consequent higher caregiver burden.

Objective: We explored the metabolic correlates of a peculiar aspect of the Apathy Evaluation Scale (AES), expressing the discrepancy between the global valuation of apathy by informant caregiver (AES-I) and patient's self-report (AES-S) (hereafter dIS-AES).

Materials: We retrospectively selected 29 patients (21 females; age 76.2±4.9 years; education 8.7.2±4.0, MMSE score 25.9.2±1.5) with an intermediate or high likelihood of AD (23 and 6, respectively) and converted from the mild cognitive impairment (MCI) to the dementia stage over 2 years in average.

Method: We correlated the values of [18F]-FDG PET with the AES subscores (AES-I, AES-S), and AES-IS computed as the difference between AES-I and AES-S) (multiple regression analysis; nuisance covariates: age and MMSE). Both AES and FDG-PET were acquired at baseline evaluation in all MCI-AD patients, along with neuropsychological evaluation.

Results: We found significant negative correlations of metabolic values with i) dIS-AES in bilateral parahippocampal gyri and thalami, right posterior cingulate cortex and putamen, and ii) AES-S in frontal (superior and medial) and anterior cingulate areas, prominent in the left hemisphere. Conversely, the AES-I score disclosed no metabolic correlates. As a posteriori analysis, we compared the neuropsychological test scores of two subgroups of the MCI-AD group divided according to the median score of the dIS-AES (=7), finding no significant differences (two-tailed T-test). Discussion. This exploratory study confirms that patients' self-evaluation of apathy in MCI-AD patients relies on frontal-subcortical networks as previously reported in AD and other conditions. In contrast, its discrepancy with the caregiver's assessment of patient apathy involves limbic regions within the temporal lobe, thalamus, and posterior cingulate. The latter expresses an inherent unawareness of patients for their apathy, albeit unrelated to cognitive performance in severity, and relies on the neural circuits typically impaired in AD from the earliest stages.

Conclusion: Dysmetabolism in limbic areas relates to the discrepant perception of apathy in patients and caregivers and involves different neural pathways than those classically associated with apathetic symptoms.

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UNRAVELLING NEUROTRANSMITTERS IMPAIRMENT IN PRIMARY PROGRESSIVE APHASIAS

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Objectives: Primary progressive aphasias (PPAs) are a group of neurodegenerative diseases mainly characterized by language impairment, and with variably presence of dysexecutive syndrome, behavioural disturbances and parkinsonism. Detailed knowledge of neurotransmitters impairment and its association with clinical features hold the potential to develop new tailored therapeutic approaches.

Materials: In the present study, we included 103 PPA patients and 80 age-matched healthy controls (HC). We tested if the spatial patterns of grey matter volume (GMV) alterations in PPA patients (relative to HC) are correlated with specific neurotransmitter systems.

Methods: To study several neurotransmitter systems in vivo at the same time, we adopted the novel JuSpace toolbox, which allows for cross-modal correlation of Magnetic Resonance Imaging (MRI)-based measures with nuclear imaging derived estimates covering various neurotransmitter systems, including dopaminergic, serotonergic, noradrenergic, GABAergic and glutamatergic.

Results: As compared to HC, voxel-based brain changes in PPA were significantly associated with spatial distribution of serotonin, dopamine, and glutamatergic pathways ($p<0.05$, False Discovery Rate corrected-corrected). Disease severity was negatively correlated with the strength of GMV colocalization of D1 receptors ($p=0.035$) and serotonin transporter ($p=0.020$). Moreover, we observed a significant negative correlation between positive behavioural symptoms, as measured with Frontal Behavioural Inventory, and GMV colocalization of D1 receptors ($p=0.007$) and serotonin transporter ($p<0.001$).

Discussion: Disease severity was associated with progressive worsening of dopamine and serotonin circuits, and more interestingly, impulsivity and binge eating disturbances were strongly associated with GMV co-localization to these neurotransmitter systems. The core feature of PPA is the language deficit, but behavioural disturbances are frequently detected over disease course and pharmacological manipulation of specific neurotransmitters in PPA may be beneficial on behavioural symptoms, thus reducing the cost and health burden of the disease.

Conclusion: This pilot study suggests that JuSpace is a helpful tool to indirectly assess neurotransmitter deficits in neurodegenerative dementias and may provide novel insight into disease mechanisms and associated clinical features.

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PLASMA NEUROFILAMENT LIGHT CHAIN PREDICTS ALZHEIMER'S PATHOLOGY AND PROGRESSION OF COGNITIVE DECLINE IN PATIENTS WITH SUBJECTIVE COGNITIVE DECLINE AND MILD COGNITIVE IMPAIRMENT

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Objectives: Neurofilament light chain (NfL) has been suggested as a new peripheral biomarker of neurodegeneration. In a previous cross-sectional study, we demonstrated that plasmatic NfL levels change along the continuum of cognitive decline as a function of Aβ status. In the present longitudinal work we aimed to evaluate the accuracy of NfL in predicting CSF biomarker status and progression of cognitive decline.

Materials and Methods: 139 patients (35 SCD, 59 MCI, and 25 AD) underwent neuropsychological evaluation and plasma NfL measurement at baseline. 92 patients (23 SCD, 46 MCI, and 23 AD) underwent CSF biomarker analysis and were classified according the ATN classification as: ATN0 (A-/T-/N-), ATN1 (A+/T-/N-), ATN2 (A+/T+/N- or A+/T-/N+) and ATN3 (A+/T+/N+). 38 patients (14 SCD and 28 MCI) had plasma NfL measurement after two years from baseline collection.

Results: At baseline NfL levels were significantly different between the three groups (SCD vs. MCI, $p = 0.009$; SCD vs. AD, $p <0.001$; MCI vs. AD, $p = 0.025$), also after age and APOE adjustment. In SCD and MCI groups NfLs were higher in ATN3 as compared to ATN0, and ATN1 while in AD group there were no differences in NfLs between ATN1, ATN2 and ATN3. Therefore, we merge ATN0 and ATN1 as "AD–" and ATN2 and ATN3 as "AD+". By applying a maximize metric method, we found that NfL levels were able in distinguishing between AD– and AD+ with high accuracy both in SCD (cut-off = 16.66 pg/mL, AUC = 0.86, sensitivity = 86.96%, specificity = 88.89%) and in MCI (cut-off = 20.49 pg/mL, AUC = 0.822, sensitivity = 70.83%, specificity = 90.91%). During the follow-up, five SCDs (14.28%) progressed to MCI and four MCIs (6.68%) progressed to AD. We classified patients according to the identified cut-offs, and found that, in the SCD group, NfL levels predicted the progression to MCI with a good accuracy (sensitivity = 80.00%, specificity = 76.67%). In particular, NfLs showed a very high negative predictive value (95.83%). In the MCI group NfLs did not distinguish between patients who developed AD and patients who did not. Considering the whole sample, AD– and AD+ patients showed an increase of NfLs levels of 0.63 and 1.13 pg/mL per year respectively, but this difference was not significant.

Conclusions: NfLs predict ATN status with high accuracy in SCD and MCI. In the SCD group, a cut-off value of 16.66 pg/mL allows to exclude a progression to MCI after two years with an excellent accuracy.

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OPTIMAL MOCA CUTOFFS FOR DETECTING BIOLOGICALLY-DEFINED PATIENTS WITH MCI AND EARLY DEMENTIA AMONG ITALIAN POPULATION

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Aim: In patients with Mild Cognitive Impairment (MCI) and early dementia, diagnostic properties of the Italian normative cutoffs for the Montreal Cognitive Assessment (MoCA) remain unclear. We tested the clinicometric performance of normative values and provided optimal cutoffs for diagnostic purposes.

Methods: Retrospective data collection was performed for consecutive patients with clinically- and biologically-defined MCI (PwMCI) or early dementia (PwD) from the Memory Centre of the Trieste University Hospital-ASUGI. Raw MoCA scores were corrected according to (i) the conventional 1-point correction (Nasreddine) and (ii) Italian demographically-adjusting norms [1,2,3]. Diagnostic properties of the original cutoff (< 26) and normative cutoffs, namely, the upper limits (uLs) of equivalent scores (ES) 1, 2, and 3, were evaluated. Nonparametric Receiver Operating Characteristic (ROC) curve analysis was performed to obtain optimal cutoffs.

Results: On 144 eligible patients, 45 were included in the study (24 PwMCI, mean age = 71.83±6.09, mean MoCA score = 21.04±2.58; 21 PwD, mean age = 72.14±5.58, mean MoCA score = 19.00±4.60). Twenty-five age-and-education-matched healthy elderly were enrolled as controls. The cutoff of 26 demonstrated high sensitivity (0.93 [95% CI 0.84–0.98]) but low specificity (0.44 [0.32–0.56]) in discriminating between patients and controls. Nominal normative cutoffs (ES0 uLs) showed excellent specificity (SP range = 0.96–1.00 [0.88–1.00]) but poor sensitivity (SE range = 0.09–0.24 [0.04–0.36]). All correction methods had good discriminatory power (all AUCs > 0.80, $p < 0.001$; equality test, $\chi 23 = 1.56$, $p = 0.67$). The optimal cutoff for Nasreddine's 1-point correction was 23.50 (SE = 0.82 [0.71–0.90]; SP = 0.72 [0.60–0.82]). As concerns Italian norms, optimal cutoffs were 20.97, 22.85, and 22.29 (SE range = 0.69–0.73 [0.57–0.83], SP range = 0.88–0.92 [0.77–0.97]) for Conti's, Santangelo's, and Aiello's methods, respectively [1,2,3]. The ES2 uLs reported in Conti's [2] and Aiello's [1] normative studies provided a good balance between sensitivity and specificity.

Discussion: Using the quick 1-point correction, combined with a cutoff of 23.50, might be useful in ambulatory settings with a large turnout. Italian nominal normative cutoffs show a poor sensitivity. Our optimal cutoffs might offset this limitation.

Conclusion: The present study provides Class II evidence on the diagnostic utility of Italian and Nasreddine MoCA's scoring methods, when used in conjunction with specific optimal cutoffs, in discriminating PwMCI/PwD vs. healthy controls.

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EYE MOVEMENTS ABNORMALITIES IN ALZHEIMER'S DISEASE AND DEMENTIA WITH LEWY BODIES

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Background: In recent years several studies on the analysis of eye movements have been performed and strong evidence has shown significant alterations regarding oculomotor functions and viewing behavior, especially in Alzheimer's disease (AD) compared to healthy controls.

Aim: The aim of this study is to define the use of eye tracking methodologies as a mean for evaluating eye movements in AD and dementia with Lewy bodies (DLB) patients, by analyzing the differences in oculomotor performances that may represent a potential early diagnostic marker.

Materials and methods: The sample consisted of 29 AD patients, 7 DLB n= 7 and 18 age-matched healthy controls. Neuropsychological assessment for each participant was carried out with the Mini Mental State Examination (MMSE) test used as screening tool and with the Montreal Cognitive Assessment (MoCA) test. Eye movements were recorded with the video-based eye Tracker EyeLink 1000 Plus (SR Research ®), which allows registration under free viewing conditions with binocular sampling rate up to 2000 Hz.

Results: Patients with AD and DLB were comparable for demographic and clinical variables Mean duration of fixations and its standard deviation were lower in AD patients than in the control group (respectively p= 0.033, p= 0.021). In DLB two measures were different respect to controls: the Stationary Gaze Entropy (SGE) (p= 0.043) and the average saccadic amplitude were reduced (p= 0.072). In the logistic regression analysis lower average duration of fixation and its standard deviation were associated with the diagnosis of AD (p= 0.033). A reduction in the average saccadic amplitude was predictive of a diagnosis of DLB at the limit of significance (p= 0.072). A reduction of the SGE was associated with the diagnosis of DLB both in comparison with controls (p= 0.043) and with AD (p= 0.054).

Conclusions: Eye tracker studies revealed the potential of this methodology to obtain reliable eye movement data for screening diagnosis of AD and DLB in the future, representing a rapid and non-invasive method of potential utility in the diagnostic work-up. The results for AD eye fixations and SGE for DLB, together with the negative correlation between AOI and MoCA score in both groups, are encouraging; this methodology, if investigated in a larger scale, could be a valuable early diagnostic and disease progression biomarker of AD and DLB.

CURRENT EVIDENCE AND CONCERNS ON THE USE OF DEEP BRAIN STIMULATION (DBS) IN COGNITIVE DISORDERS: A SCOPING REVIEW

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Objective: Dementia affects more than 55 million people worldwide. Several technologies have been developed to slow cognitive decline: deep brain stimulation (DBS) of network targets in Alzheimer's disease (AD) and Dementia with Lewy Bodies (DLB) have been recently investigated. This study aimed to review the characteristics of the samples, protocols and outcomes of patients enrolled in clinical trials investigating the feasibility and efficacy of DBS in dementia.

Materials: A systematic search of all registered RCTs was performed on January 31st, 2022 (reviewed on May 1st, 2022), on Clinicaltrials.gov and EudraCT. In parallel, a systematic literature review was conducted on PubMed, Scopus, Cochrane, and APA PsycInfo to identify published trials.

Methods: A modified PRISMA Flow Diagram was used to report the selection process. The Cochrane risk-of bias tool for randomized trials (RoB) was then applied.

Results: The literature search yielded 2122 records and the clinical trial search 15 records. Overall, 17 studies were included. Two out of these 17 studies were open-label studies reporting no NCT/EUCT code and were analysed separately. Of 12 studies investigating the role of DBS in AD, we included 5 published RCTs, 2 unregistered open label (OL) studies, 3 recruiting studies and 2 unpublished trials with no evidence of completion. Of 3 studies investigating the role of DBS in DLB, two were completed RCTs and 1 was an ongoing OL study.

Discussion: Results showed significant heterogeneity in the recruited populations in terms of age, severity, informed consent availability, inclusion, exclusion criteria and prevalence of adverse events (SAEs: 9.10 ± 7.10%). The overall risk of bias was assessed as moderate-high.

Conclusion: The samples investigated are small and considerably heterogeneous, published results from clinical trials are under-represented, severe adverse events not negligible and cognitive outcomes uncertain. Overall, the validity of these studies requires confirmation based on forthcoming higher quality clinical trials.

INVESTIGATING THE ROLE OF SYNAPTIC PROTEINS IN ALZHEIMER'S DISEASE: SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction and objective: Synaptic disruption precedes neuronal death and correlates with the clinical features of Alzheimer's disease (AD). The identification of fluid biomarkers of synaptic alteration is emerging as one of the potential targets for early and accurate diagnosis of the disease [1]. Over the past decade, several proteins have been proposed as possible biomarkers of synaptic alteration, and the most studied synaptic proteins are neurogranin, synaptosome-associated protein 25 (SNAP-25), and synaptotagmin-1 [2,3]. The aim of this study is to conduct a systematic review and meta-analysis to determine whether fluid biomarkers of synaptic damage are altered in AD.

Methods: Pubmed, Scopus, EMBASE, and Web of Science were searched for articles reporting synaptic proteins as fluid biomarkers in AD and in cognitively unimpaired (CU) individuals. Pooled effect sizes were determined using the Hedge G method with random effects. Questions adapted from the Quality Assessment of Diagnostic Accuracy Studies were applied for quality assessment. For this study, the protocol was previously registered in PROSPERO (registration number: CRD42021277487).

Results: The search strategy identified 189 full texts that were evaluated for eligibility. A total of 22 studies were included in the systematic review and 14 studies were included in the meta-analysis. Regarding neurogranin, 827 AD subjects and 1237 CU subjects were included in the meta-analysis, which showed a significant increase in cerebrospinal fluid (CSF) in AD patients compared with CU subjects, with an effect size of 1.01 ($p < 0.001$). A significant increase in SNAP-25 levels in the CSF of AD patients was also noted.

Discussion and Conclusions: Neurogranin and SNAP-25 are possible biomarkers of synaptic pathology in AD, and other potential synaptic biomarkers are also emerging. This meta-analysis revealed in addition that there are still relatively few studies investigating these biomarkers in patients with AD or other dementias and showed wide heterogeneity in the literature.

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ROLE OF IRON METABOLISM IN ALZHEIMER'S DISEASE AND OTHER DEMENTIAS: AN EXPLORATORY STUDY

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Introduction and objective: Alzheimer's disease (AD) is the leading cause of dementia and a major scientific goal in this field is to identify accurate and early biomarkers of disease [1]. Iron is an essential element for brain metabolism and its imbalance has been associated with neurodegeneration because of its potential neurotoxic effect [2]. Recent evidence suggests an involvement of iron dysregulation in various neurodegenerative diseases [3], but its precise role in Alzheimer's disease has not yet been clarified. This study aims to compare iron concentrations in patients with AD, mild cognitive impairment (MCI), frontotemporal dementia (FTD) and in cognitively unaffected subjects (CU).

Methods: Precise quantification of total iron in the cerebrospinal fluid (CSF) of subjects included in the study was performed by graphite atomic absorption spectrometry (GF-AAS). In order to investigate possible correlations, a Person analysis was conducted between CSF iron concentrations and core AD biomarkers and key demographic parameters. A multiple linear regression model was performed to identify possible predictors of iron values.

Results: Sixty-nine participants (16 AD, 17 MCI, 22 FTD, and 15 CU neurological controls) of whom 35 males and 34 females with a mean age of 70.5 years were included in this study. Iron concentrations were significantly increased in CSF of patients with AD compared with CU ($p < 0.001$), FTD ($p = 0.003$) and MCI ($p = 0.02$). Iron levels correlated significantly with CSF levels of total tau ($r = 0.20$, $p = 0.015$), phosphorylated tau ($r = 0.36$; $p = 0.003$) and inversely with CSF amyloid β1-42 (Aβ) values ($r = -0.39$, $p = 0.001$). Multiple linear regression model identified Aβ levels as a significant predictor of iron levels (coefficient beta = -0.30, $p = 0.017$).

Discussion and conclusion: Our study confirms a significant role of iron metabolism in AD. In addition, we identified significant correlations between CSF iron values and core AD biomarkers. Our results suggest a possible specific role of iron in the pathophysiology of Alzheimer's disease. Larger studies are needed to confirm our findings.

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THE POLITICAL DISCOURSE ON ALZHEIMER'S DISEASE AND RELATED DEMENTIAS: A TWITTER CONTENT ANALYSIS

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Introduction and Objective: Improving the condition of patients with Alzheimer's disease and related dementias (ADRD) is one of the major challenges of the century. These conditions embed both social and political issues that must be addressed by the scientific community in order to meet patients and caregivers' unrequited needs [1]. Social media are widely used tools in the spreading of scientific and political content, being potentially capable of raising awareness on this devastating disease. This study investigates the media exposure of ADRD among Italian members of Parliament (MP) by analyzing the content of their Twitter public profiles.

Methods: For all MP we identified those who had a public Twitter profile active during the first days of June 2022. For each of the available profiles, we collected the number of tweets, followers, and date of account creation. In order to identify tweets referring to ADRD, an advanced search was carried out on Twitter through the use of dementia-related keywords. A qualitative analysis of the purpose of the tweet was carried out independently by 2 authors (F.R. and A.G.) and classified into "informative" or "denigrating". Next, we tested tweets for linguistic analysis using Linguistic Inquiry and Word Count (LIWC) software.

Results: A final sample of 782 MP was collected. Of them, 527 (67.4%) were Deputies and 255 (32.6%) were Senators. To mid-June 2022, current MP have shared over 4 million tweets from their public profiles. Of these, only 286 were identified as related to the topic of ADRD. More than a half had a "denigrating" content (n = 153; 53.5%); the remaining were classified as "informative". LIWC analysis showed a prevalence of terms associated with negative over positive emotions (1.51% versus 0.49%, respectively).

Discussion and conclusion: This study reveals limited media attention to the issue of ADRD by the public Twitter profiles of Italian MP. In addition, the use of dementia-related terminology had a negative emotional prevalence on both qualitative and linguistic analysis. Previous studies have highlighted how social media can perpetuate social stigma related to dementia [2], which is still a worldwide phenomenon associated with negative psychological effects on both patients and caregivers [3]. Since this study is not political in nature, no analysis was conducted based on individual MP or parties. Instead, this analysis is intended as a stimulus for increasing positive connections between the scientific community and policymakers to increase constructive synergies.

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THE MULTIFACETED INVOLVEMENT OF THE CAUDATE FUNCTIONAL CONNECTIVITY NETWORK IN AMYLOID POSITIVE MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE PATIENTS

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Objective: The functional disruption of the caudate nucleus (CN) contributes to cognitive decline over the life span. In patients with dementia, recent MRI studies demonstrated significant volume reduction of CN with the progression of AD. Moreover, neuropathology showed that amyloid and tau pathology accumulate in the CN in AD patients. The aim of this study was to investigate the resting-state functional connectivity (FC) of the CN network in amyloid positive mild cognitive impairments (MCI) and AD patients as possible future biomarker in the AD conversion from MCI.

Materials: Fifty-three controls, 21 MCI and 94 AD patients were enrolled and underwent neurological examination and resting-state functional MRI (rs-fMRI). All AD and MCI showed cerebrospinal fluid biomarkers suggestive of AD.

Methods: A seed-based FC analysis was run between the left and right CNs and the rest of the brain and was compared between groups.

Results: In MCI patients compared to controls, the seed-based analysis showed decreased FC between bilateral CNs and subcortical structures such as putamen, amygdala, and nucleus accumbens. Furthermore, increased FC was observed between bilateral CNs and cuneus and precuneus, right lateral occipital cortex and inferior parietal gyrus, and left postcentral, precentral and supramarginal gyri. Considering AD patients, they showed decreased FC between bilateral CNs and right inferior frontal gyrus, frontal, central and parietal opercula, and left inferior parietal gyrus and lateral occipital cortex relative to controls. Moreover, AD patients showed increased FC between bilateral CNs and bilateral postcentral, supramarginal, and superior parietal, lingual, fusiform, inferior temporal, left inferior frontal and precentral gyri, cuneus and precuneus, lateral occipital and posterior cingulate cortices. No FC changes were observed between MCI and AD patients.

Discussion: Amyloid positive MCI patients are characterized by an FC reduction between CN and subcortical regions compared to controls, previously identified as highly sensitive brain regions related to the development of cognitive decline and to MCI disease. Indeed, these alterations no longer persisted in the comparison between AD patients and controls. Furthermore, compared to controls, MCI patients presented higher FC between CN and sensorimotor and parietal areas which become more prominent in the AD group, involving also temporal and occipital cortices. Alterations in the FC of CN network might be a useful biomarker in the definition of the progression of AD.

Conclusions: Caudate nucleus functional connectivity network may be a sensitive biomarker in the AD conversion from amyloid positive MCI.

Supported by. Foundation Research on Alzheimer Disease.

PREDICTING MCI TO AD CONVERSION WITH MACHINE LEARNING

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Background and aim: Alzheimer's disease (AD), the leading cause of dementia, is a neurodegenerative condition driven by a multifactorial etiology. The full-blossom stage is usually preceded by Mild Cognitive Impairment (MCI), a prodromal phase [1]. MCI subjects are more prone to developing dementia than cognitively normal subjects [2]. However, no reliable predictors of incoming progression are currently validated. The aim of our study was to apply a machine learning (ML) algorithm and data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) [3] to assess the impact of clinically relevant variables on the prediction of MCI-to-AD conversion.

Methods: 587 MCI subjects from ADNI databases were included in the study. The diagnostic criteria were the ones provided by ADNI protocols. Further inclusion criteria were the completion of baseline neuropsychological assessments and a follow-up period of at least 36 months. Four classes of variables, from baseline visits, were extracted and used as predictors: AD-related biomarkers, structural MRI data, neuropsychological data, and peripheral markers. A Random Forest algorithm was then trained to classify, in a supervised manner, stable vs. converting MCI subjects within a 3-years period. Prediction accuracy, sensibility, specificity, and positive and negative predictive values were assessed for each class of variable. Then, single variables of each group were ranked according to their relevance. To assess age- and sex-related differences, the original cohort was also divided into four age quartiles and two sex groups, and then the prediction accuracy and the variable ranking were re-assessed.

Results: Our Random Forest algorithm showed good prediction accuracy for short-term conversion to AD. The combination of neuropsychological data and AD-related biomarkers achieved the best prediction (accuracy=0.86). Neuropsychological data were the best classifier as a single category. Peripheral biomarkers showed medium accuracy but high negative predictive values and sensitivity. The classification accuracy was better in younger and female subjects and decreased across age quartiles. The ranking of variables showed peculiar sex- and age-related differences. For instance, markers related to frontal dysfunction - like TMT scores and indices of regional cortical atrophy - were relevant as predictors only in male subjects.

Conclusions: This Random Forest algorithm represents a valid instrument to predict the clinical course of MCI subjects. A panel of peripheral biomarkers may represent an easy and accessible first-line assessment for prediction, especially in combination with neuropsychological data. Our results also support the notion that the MCI-to-AD spectrum underlies complex and multifactorial pathological changes that are dynamically affected by age and sex.

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EXECUTIVE-CENTRAL AND FRONTO-PARIETAL NETWORKS ABNORMALITIES ACCOUNT FOR COGNITIVE COMPLAINS REPORTED BY SUBJECTIVE COGNITIVE DECLINE

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Objective: Alzheimer's Disease (AD) is the most common form of dementia worldwide. Currently there are no disease modifying treatments available. Detecting subjects with increased risk to develop dementia is essential for future clinical trials. Subjective cognitive decline (SCD) is a condition defining individuals who perceive a decrease in their own cognitive functioning in the absence of any detectable deficit on neuropsychological testing [1]. SCD individuals show AD-related biomarkers abnormalities in CSF [2]. Aim of the present study was to assess brain functional connectivity (FC) changes in SCD individuals.

Material and Methods: 23 SCD [3] (age= 65.8+ 8.4 yrs; education: 13.5+ 3.8yrs; MMSE score=28.6+1.9; MTA score=0.71+0.7) and 33 healthy subjects (HS) (age=65.4+8.0yrs; education: 13.2+ 3.2yrs; MMSE score=29.0 + 1.5; MTA score=0.75+0.6) were enrolled. All participants underwent an extensive neuropsychological assessment and 3T-MRI scanning including a T1-w volume and resting-state fMRI (RS-fMRI). Voxel-based morphometry (VBM) was used to assess volumetrics. The independent component analysis (ICA) was used to extract brain networks (Default Mode Network-DMN; Fronto-parietal network-FPN bilaterally; Executive Central Network-ECN and Salience Network-SN) from fMRI data and run FC analyses. Two-sample t tests were used to test for between-group differences, while one-sample t tests were used to test for within-group associations between FC and cognitive measures.

Results: There were no significant between-group differences in the demographic variables. At group level SCD reported significantly lower scores than HS at the Corsi block tapping backward test (p=0.009). There were no significant between-group differences in grey matter volumes. Conversely, SCD subjects compared to HS showed increased FC in the ECN and right-FPN, and a decreased FC in the right-FPN at hippocampal level. No significant changes in FC were observed in the remaining networks. Additionally, SCD showed an inverse association between Corsi block tapping backward test scores and ECN FC in the anterior cingulate cortex. HS showed associations between Corsi block tapping backward and ECN FC (positive in the hippocampus and basal ganglia; negative in the posterior cingulate cortex-PCC), and FPN FC (positive in right-PCC).
Discussion: SCD individuals showed FC abnormalities in networks involving fronto-parietal areas that may account for their lower visuo-spatial working memory performances.
Conclusions: Dysfunctions in executive-frontal networks may be responsible for the cognitive decline subjectively experienced by SCD individuals despite the normal scores observed by formal neuropsychological assessment. The associations found in HS might express individual heterogeneity observed during normal aging likely due to cognitive reserve mechanisms.

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ALZHEIMER'S DISEASE CARE-GIVER DURING LOCKDOWN. EFFECTIVENESS OF A PSYCHOLOGICAL GROUP THERAPY INTERVENTION

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Introduction: The approach to the therapy of age-related degenerative pathologies includes attention not only for patients but also to their relatives, in fact strategies addressed to caregivers can have an impact on the evolution of the disease in patients with AD. This research, as part of the co-funded project EMPATI@, consisted of providing sessions of group psychotherapy among caregivers of patients with Alzheimer's disease. Our aim was threefold: provide psychological support through therapeutical effects of group-therapy; increase knowledge about dementia and AD, specifically on neurobehavioral disorders; put caregivers in connection and create supporting networks.

Methods: The treatment took place in groups of 6 participants each. A program was planned for each group over 10 weekly meetings, each during 90 minutes. Through all meetings, the psychologist had a moderator role, even activating interventions concerning what emerged from time to time. Unfortunately COVID-19 pandemic forced us to modify our original project; thus, we were not able to collect all the caregivers prospected by the research design. We thus defined an ad-hoc questionnaire administered to caregivers during outpatient examinations (either neurological or neuropsychological) in order to investigates the caregiver's perception during lockdown periods.

Results: Eighteen caregivers out of 24 participated to the project. With respect to the caregiver's commitment, evaluated with CBI (Caregiver Burden Inventory), we observed general stability of the global score, with a significant improvement in the CBI subscale E (emotion) (t test = 2.11; $p = .05$). Scores obtained on the Psychological General Wellbeing Inventory, showed a significant reduction of Anxiety (t test = -3,26, $p < .05$) and an improvement in "general self-perception of health" (t test = -2.13; $p < .05$). Questionnaire results, compared with 45 controls, showed that 77% of caregivers who did not have access to group treatment reported a global worsening of patients with respect to the same response given by the 50% of the caregivers treated in the group. Moreover we found significant differences in management of behavioural disorder between group participants and controls.

Conclusion: Our results, although on a small number of participants, allow us to confirm how an intervention focused on the emotional experiences of the caregiver in the context of group therapy fosters the skills to cope with the difficulties in taking care of people with a neurodegenerative pathology in its cognitive and behavioural implications, even in contexts of extreme difficulty such as those experienced during the pandemic.

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FUNCTIONAL CONNECTIVITY FROM DISEASE EPICENTERS IN FRONTOTEMPORAL DEMENTIA

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Objectives: To explore functional connectivity reorganization at increasing topological distance from disease epicenters and its relationship with atrophic changes in different clinical presentations of the frontotemporal dementia (FTD) spectrum.

Materials: Patients with behavioral variant of FTD (bvFTD, n=64), non-fluent (nfvPPA, n=34) or semantic variant of primary progressive aphasia (svPPA, n=36) and 94 healthy controls underwent 3T MRI. The peaks of atrophy of each variant (i.e., disease epicenters) were identified in an independent cohort of 42 FTD cases with high confidence of FTLD pathology and used as seed regions for stepwise functional connectivity (SFC) analyses.

Methods: SFC analyses were used to compare connectivity in regions directly and indirectly connected to the epicenters between patient groups and controls. Correlations between SFC architecture in controls and atrophy patterns in FTD patients were tested.

Results: The identified disease epicenters were the left anterior insula for bvFTD, left supplementary motor area for nfvPPA, and left inferior temporal gyrus (ITG) for svPPA. Compared with controls, bvFTD and nfvPPA patients showed widespread decreased SFC in bilateral cortical regions with direct/indirect connections with the epicenters, and increased SFC either in circumscribed regions close to the respective seed region or in more distant cortical and posterior cerebellar areas. Across all link-steps, svPPA showed SFC decrease mostly localized in the temporal lobes, with co-occurrent SFC increase in cerebellar regions at indirect link-steps. Average functional link-step distance from the left ITG in

healthy controls correlated with regional grey matter volume in svPPA patients (r=0.29, p=0.03).

Discussion: Our findings demonstrate that each FTD syndrome is associated with a characteristic interplay of decreased and increased functional connectivity with the disease epicenter, affecting both direct and indirect connections.

Conclusions: SFC revealed novel insights regarding the topology of functional disconnection across FTD syndromes, holding the promise to be used to model disease progression in future longitudinal studies.

Funding. Italian Ministry of Health (GR-2011-02351217); European Research Council (StG-2016_714388_NeuroTRACK); Foundation Research on Alzheimer Disease; US National Institutes of Health (R01-DC010367, R01-DC12519, R01-DC14942, R01-NS89757, R21-NS94684).

BAROMETER ALZHEIMER: REFLECTIONS ON THE FUTURE OF DIAGNOSIS AND TREATMENT OF ALZHEIMER'S DISEASE

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Objectives: The need for a paradigm shift in the management of Alzheimer's disease (AD) for Italian health care system (HC), especially the opportunity to enhance early diagnosis, is widely acknowledged. The Barometer addresses this issue by providing an assessment of the HC's current capacity along todays and tomorrow's patient journeys, and by estimating some incremental structural, human, and organizational resources that the HC is likely to need in the coming future to strengthen its preparedness.

Methods: Data collection is based on public sources, supplemented by a survey conducted on centers (public and private) involved in the diagnosis and management of AD (280 answers. A mathematical model was developed to estimate the incremental capacity of some resources, according to current and future patient population. A Scientific Committee validated the process.

Results: The report assesses crucial steps along the patient journey, through the measurement of indicators: a) in over 60% of the respondent centers, patients arrive at the center having consulted other center and/or specialists highlighting a fragmented patient journey ;b)for 70% of the respondent centers, the time available for the execution of neuropsychological tests is insufficient; c) in over 50% of the respondent centers, neuroradiological training and improvement in standardization in the execution of MRI are necessary; d) according to the model, increase of 57% of lumbar punctures and 23% of PET scans would be required to improve the biological diagnosis of early AD; e) over 60% of the respondent centers believe that increasing staff is necessary to meet current demand; f) a limited number of CME courses (about 60) in AD (33% on early AD) were accessible to General Practitioners and healthcare professionals.

Discussion: The report provides some initial elements of evaluation, to be further enriched and refined in the future, which captures some turning points in the current AD journey. Investment in personnel and multidisciplinary teams, optimization of diagnostic pathway, awareness and information on AD early stages and dedicated infrastructures are identified by the report as key focus area.

Conclusions: This report wants to stimulate some reflections for potential area of investments for the management of AD patients, as the debate on implication of a possible paradigm shift in AD is going forward. It provides decision-makers with an understanding of possible actions and future steps for the optimization of processes and healthcare organizations that can increase efficiency and ensure the benefits of potential pharmacological innovations to patients.

SUNDOWNING IN DEMENTIA: PREVALENCE, CLINICAL AND NEUROPSYCHOLOGICAL FEATURES

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Background and aims: Sundowning, or sundown syndrome, is the emergence or worsening of neuropsychiatric symptoms in the late afternoon or early evening in people with dementia. Despite being well known among caregivers and healthcare providers, this condition has triggered limited scientific interest so far. We aimed to evaluate the prevalence and clinical manifestations of sundowning among patients with dementia and to investigate its association with socio-demographic and clinical features.

Methods: We consecutively enrolled patients with dementia attending the memory clinic of the Department of Human Neurosciences of the Sapienza University of Rome between June 2019 and April 2020. The presence of sundowning was investigated through a specifically designed questionnaire administered to caregivers. We compared the socio-demographic and clinical features of sundowners vs. non-sundowners and performed a logistic regression analysis to identify the variables associated with the syndrome. A subset of patients underwent a complete neuropsychological evaluation to explore differences in cognitive profiles.

Results: Among 184 recruited patients, 39 (21.2%) exhibited sundowning. The most common manifestations were agitation (56.4%), irritability (53.8%), anxiety (46.2%), and delusions (38.5%). In the univariate analyses, sundowners were significantly older, had a later onset of dementia and exhibited more severe cognitive and functional impairment. Moreover, they were more likely to experience nocturnal awakenings and hearing impairment and to use medications with an anticholinergic profile and antipsychotics, while less often they used Memantine. The logistic regression analysis showed an association between severity of cognitive decline and sundowning; while the use of Memantine was inversely correlated with the occurrence of the syndrome. The neuropsychological profiles of sundowners and non-sundowners appeared to be similar, with the only exception of a worse performance of patients exhibiting sundowning in a memory evaluation test.

Conclusions: Sundowning represents a common neuropsychiatric manifestation among patients with dementia and it appears as a multiply determined condition. Its presence should always be evaluated in routine practice and a multidimensional approach should be adopted to identify its predictors.

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FROM RETINA TO VISUAL CORTEX: CHANGES OF VISUAL PATHWAY IN LEWY BODY DEMENTIA

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Background: The visual system may be involved in several core clinical features of dementia with Lewy bodies (DLB), such as visual hallucinations (VHs), visuospatial/visuoperceptive impairment and circadian dysfunction. However, very few data on retinal layers abnormalities in patients with DLB are available. Moreover, studies that try to connect retinal data with brain structural and metabolic imaging are lacking.

Aim: To identify structural and metabolic features along the visual pathway (i.e. from retina to primary visual cortex) that are specific for DLB.

Methods: 1) 35 DLB patients and 30 healthy subjects (HS) underwent a full Spectral Domain retinal Optical Coherence Tomography (OCT) scan and peripapillary RNFL (pRNFL) thickness, macular layers thicknesses and volumes were compared. Moreover scans were acquired for all DLB patients. We analyzed the relationships between different structures of visual system acquired with OCT and 18F-FDG-PET/MRI. Exclusion criteria for all subjects were presence of retinopathy, severe glaucoma and age-related macular degeneration. All DLB patients underwent clinical interview and neurological examination: presence of VHs, parkinsonism, cognitive fluctuations and REM-sleep Behavior Disorder (RBD) was recorded using appropriate clinical scales. Each DLB patient underwent a comprehensive neuropsychological evaluation.

Results: As for the OCT the inner temporal and inferior sectors of the GCIPL layer was thinner in DLB patients when compared to control subjects (84.41 ± 9.56 μm and 88.37 ± 7.30 μm, F = 4.06, pcorr = 0.04; 87.44±9.01 μm and 92.08±7.51 μm, F = 4.02, p = 0.04). Significant lower values of retinal thickness of the inner nasal and superior quadrants in DLB did not survive correction for multiple comparisons. The mean thickness of the GCIPL whole disc was also thinner in DLB (86.93 ± 8.44 μm and 92.08 ± 7.05 μm, F =5.96, p = 0.01). We identified no other differences in considered retina layers and papillae volumes. The correlation analysis between PET-MRI data of primary visual pathway structures shows a significative positive correlation between the thickness of pRNFL and the volume of lateral geniculate nucleus (r = 0.65, p=0.01). We didn't find any significative correlation considering MRI/PET data with clinical and neuropsychological data.

Conclusion: in DLB patients parafoveal macular GCIPL is thinner than in control subjects. Moreover, thinner peripapillary RNFL correlated with atrophy thalamic primary visual pathway. Our work was the first that underlie in DLB group a link between a retina biomarker and an important key center of thalamus in primary visual pathway.

LATE-ONSET AFFECTIVE AND PSYCHOTIC DISORDERS: THE CHALLENGE OF DISENTANGLING NEURODEGENERATIVE DISEASES WITH PSYCHIATRIC ONSET FROM PRIMARY PSYCHIATRIC DISORDERS

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Background: Neurodegenerative diseases leading to dementia may present with behavioral changes typical of primary psychiatric disorders (PPD), such affective disorder or psychosis, and the differential diagnosis with neurodegenerative diseases with psychiatric-onset remains a challenge.

Aim: To investigate epidemiology, clinical and cognitive characteristics of patients with a diagnosis of neurodegenerative dementia (AD, DLB and FTD) with psychiatric onset referred to a psychiatric clinic and compared these characteristics to a group of patients with primary psychiatric disorders.

Methods: 78-subjects with late-onset psychiatric disorders were prospectively enrolled at Neurology Clinic of Padova Hospital and Casa-di-Cura-Parco-dei-Tigli. Inclusion criteria were late onset bipolar disorder over 50 years old or late onset depression over 50 years old, including patients with a single past depression episode (20yr before) or a late onset psychosis over 60 years old or late onset OCD over 50 years old. An epidemiological analysis was performed evaluating the prevalence of neurodegenerative diseases versus PPD at admission and after clinical evaluations and follow-up. A principal component analysis (PCA) was conducted in the whole group using the minimum complete cognitive dataset. We compared neuropsychological tests' results between the group of patients with neurological diseases and with PPD. We further investigated differences between types of neurodegenerative diseases and PPD. We validated the results of the analysis on a subsample of patients that received a biological diagnosis of neurodegenerative disease (n=32).

Results: 42 patients received a clinical diagnosis of neurological disorder, specifically 39 of 78 (50%) with a dementia diagnosis, and 36 a diagnosis of PPD (mean age 68±10 and 68±8, p=.9; gender 25F and 23F, p=1; disease duration 2±3 and 3±4, p=.2, respectively) Most of the patients with a final diagnosis of neurological disorder fell into the bvFTD group (19pt), followed by DLB (11pt) and AD (9pt). The majority of patients with a baseline diagnosis of BD-like symptoms was finally classified as PPD(10/13), on the contrary late-onset psychosis and OCD were more frequent presentation of dementia neurodegenerative disease group(9/10 and 5/6 respectively), while depression was equally distributed between neurodegenerative and primary psychiatric groups(25/49). Psychotic patients had the poorer performance at cognitive tests. Patients with FTD and PPD showed a similar pattern of cognitive deficits.

Conclusions: Late-onset psychiatric symptom could mask a diagnosis of neurodegenerative disease in about 50% of cases. We encourage a multidisciplinary evaluation in the assessment of late-onset psychiatric manifestations and suggest some clinical and cognitive red flags of help in the differential diagnosis.

VALIDITY AND RELIABILITY OF REMOTE ADMINISTRATION OF NEUROPSYCHOLOGICAL TESTS IN SUBJECTS AFFECTED BY COGNITIVE DISTURBANCES: PRELIMINARY DATA

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Objectives: Primary aim of the study was to evaluate the reliability and validity of the remote administration of neuropsychological screening and domain-specific tests compared to the face-to-face administration in patients with cognitive disorders. Secondary aim was to assess the feasibility and level of satisfaction of patients and caregivers about remote administration.

Materials and Methods: The study enrolled consecutive patients of the AOUI Verona - UOC Neurology A CDCD with subjective cognitive disorder or neurocognitive disorder (mild or major), regardless of etiology. All included patients were submitted (in presence or remotely) to a brief evaluation through MMSE, ADL and IADL. All patients with MMSE ≥ 18 were also submitted to a standardized neuropsychological battery (T = 0). After 15 days (T1) each participant repeated the evaluation in the mode of administration opposite to the previous one. Finally,

all patients and/or caregivers completed a satisfaction questionnaire about the remote administration.

Results: 55 patients were enrolled in the study [16M/35F, mean age 75.9±7.64 years, mean disease duration 25.07±26.89 months]; 33 performed the extended battery. MMSE score was significantly higher in remote administration modality (p = 0.002); this significance was not found in the subgroup of patients affected by dementia. Regarding the neuropsychological battery, significant differences were found at the Rey's 15 Words (immediate recall p = 0.002, delayed recall p = 0.03) and at the semantic verbal fluency (p = 0.005), in favour of the remote assessment; conversely SDMT mean score was higher in the presence modality (p = 0.03). No statistical difference was found in patients affected by dementia. According to the satisfaction questionnaire the main advantages of the remote evaluation were: reduction in waiting times (41.2%), avoiding travel (38.2%), feeling of safety and "protection" at home (38.2%). 91.2% of patients said that tele-assessments should be an additional evaluation modality to be used in the future.

Discussion: Remote administration of both screening and domain-specific neuropsychological tests seems to be equally reliable to face-to-face administration in patients with dementia, with good levels of feasibility and satisfaction. The enrollment of a larger sample and the balancing of the participants according to the order of the evaluation method will allow to verify these preliminary results in patients with milder cognitive disturbances, also evaluating the effect of possible bias (learning).

Conclusions: Confirmation of the results would increase the tools available for the evaluation of patients with cognitive disorders, making neuropsychological tele-assessments applicable in everyday clinical practice.

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CEREBROVASCULAR DISEASES

THE COLOSSEO STUDY, AN "INTENT-TO-ACT" OF NEUROLOGY AND NEUROLOGICAL REHABILITATION UNITS OF THE LAZIO REGION

M. C. Altavista[1], M. Marano[2], A. Suppa[3], D. Toni[4], on behalf of post-stroke spasticity and botulinum toxin study group[5]

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Objectives: Spasticity is a debilitating phenomenon, developing after a stroke with dynamic and progressive features (40-50%). There is an unmet need about the prediction of spasticity, to provide a better outcome of treatments such as botulinum toxin (BoNT). The latter, through peripheral-induced neuromodulation, improves rigidity. The project will study the post-stroke patient path, to investigate the post-stroke spasticity (PSS) predictors and the efficacy of BoNT.

Materials: "Comprehensive Observational & Longitudinal study on the Outbreak of Stroke related Spasticity focusing on the Early Onset management with BoNT" (COLOSSEO-BONT, NCT05379413) is a prospective observational study with BoNT according to the clinical practice. It aims at investigating the post-stroke (upper limb) patient path from the stroke-unit, to rehab and territorial facilities.

Methods: The study group (SG) will collect predictors at V0 (within 10 days after ischemic stroke) and the following information during a 24 month follow up (V1-V5): PSS development (Modified Ashworth Scale), BoNT patient selection and treatment features, patient sensory-motor function (Fugl-Meyer), upper functionality (ARM-A), quality of life, pain, and rehabilitation features. The project followed a survey of BoNT outpatient clinics (n=20) on their practice, which is also presented below.

Results: The large part of BoNT patients treated in the Lazio region are affected by PSS, 50% of the clinics has at least 30 cases, treated every 4 months. Only 60% declared a patient management in "equipe", frequently there is no structured and systematic use of scales/instruments/rehab tools. COLOSSEO involved all the Lazio stroke and rehab units. The design has been approved by the ethical committee and will recruit 960 patients. 40% (384) will develop spasticity, 50% (192) will be treated with BoNT. The latter will be stratified in quartiles according to the time-to-injection. Untreated patients will be natural controls. Such a design has an 80% statistical power and a 0.05 alpha.

Discussion: The survey identified the presence of a large heterogeneity in the PSS treatment – due to the absence of a structured network based on evidence. Since the stroke network is constantly improving, it is necessary to design a better post-stroke patient path. The SG believe that the ischemic stroke involving the upper limb is the best model (i.e., robust evidence) to test the PSS network.

Conclusions: The SG aims at improving the PSS practice, designing the paths, identifying the critical points and methods to optimize patient health and BoNT treatment with data by COLOSSEO and through robust research activity.

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RETINAL VASCULARIZATION CHANGES IN PATIENTS WITH TIA AND MINOR STROKE: PRELIMINARY RESULTS FROM THE REMARK TIA STUDY

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Objective: To investigate changes in retinal vascularization in TIA and minor ischemic strokes (MIS).

Materials and methods: Cross-sectional study assessing retinal vascularization qualitatively (dilated fundus photography - DFP) and quantitatively (optical coherence tomography angiography - OCTA). A population of patients with confirmed diagnosis of TIAs or MIS (NIHSS≤5) was prospectively enrolled. DFP and OCTA were performed ≤7 days from symptoms onset. Collected variables included the presence of microvasculature abnormalities, foveal avascular zone (FAZ) area, superficial and deep capillary plexus (SCP and DCP) whole image, foveal and parafoveal vessel density (VD). Clinicodemographic characteristics and retinal parameters were compared with controls without prior TIA/stroke.

Results: We enrolled a total of 47 patients (42.5% MIS, 57.5% TIAs) and 36 controls (mean age 70.2±12.4 vs. 67.1±11.6; p=0.102). Patients differed from controls for sex (72% vs. 38.8%; p<0.001) and risk factors (hypertension 80.9% vs. 58.3%; p<0.001, diabetes 31.9% vs. 13.8%; p=0.006, dyslipidemia 48.9% vs. 11.8%; p<0.001). Microvasculature abnormalities were more frequent in TIA/MIS (36/90 eyes, 40.0%) vs. controls (8/71 eyes, 11.3%; p<0.001), especially arteriolar narrowing, arteriovenous nicking/nipping and enhanced arteriolar reflex (all p<0.001). As compared to control eyes (N=71), TIA/MIS eyes (N=88) showed higher FAZ (0.270±0.08 vs. 0.207±0.08 mm3) and reduced SCP and DCP whole-image (45.0±4.0 vs. 42.8±4.8% and 47.7±5.1 vs. 51.0 ±4.4%, respectively), foveal (18.5±6.0 vs .21.17±5.4% 33.5±6.0 vs. 36,4 ±6.0%, respectively) and parafoveal (45.4±5.3 vs. 47.9±4.2% and 53.5 ±4.2 vs. 50.2±5.8%, respectively; all p<0.005) VDs. Adjusting for sex and risk factors, a significant difference in FAZ and DCP whole-image VD was confirmed (p<0.005). Small-vessel occlusion-related MIS (N=13) showed higher FAZ areas (0.306±0.06 mm3) and lower DCP whole-image VD (44.4±4.8%) vs. other etiologies (N=7; 0.209±0.07; p<0.001 and 48.4±4.1%; p=0.014, respectively).

Discussion and conclusions: TIA/MIS patients exhibit significant differences in retinal vascularization compared to subjects without prior cerebrovascular ischemic events. DFP and OCTA could provide valuable non-invasive in vivo biomarkers, especially in small vessel occlusion-related MIS.

STROKE-INDUCED IMMUNODEPRESSION: ROLE IN THE NEUROREHABILITATION SETTING

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Aims: Stroke-induced immunodepression is a well-known phenomenon characterized by the rapid suppression of cellular and humoral immune responses in peripheral blood, with a neutrophil/lymphocyte ratio (NLR) > 5. The aim of this study is to assess the role of stroke-induced immunodepression as a prognostic factor of rehabilitative outcome.

Materials: We enrolled 98 patients (54 males, age 70.6±14.3) with ischemic (88.7%) or hemorrhagic (11.3%) stroke.

Methods: Immunodepression was defined as a NLR > 5 at admission in the Rehabilitative Unit (NLR+, n=14, 14.3%). Clinical and disability scores were recorded at baseline and at hospital discharge (average duration of 48.9±18.6 days).

Results: When compared to patients without immunodepression (NLR-), NLR+ group showed worse baseline scores at the Functional Independence Measure (56.5±27.5 vs. 74.8±25.1, p=0.015), Barthel Index (23.2±22.3 vs. 43.4±25.4, p=0.006), Tinetti scale (5.7±8.4 vs. 12.7±9.8, p=0.014), and NIHSS (11.0±5.9 vs. 7.0±4.5, p=0.006), while gait indicators (Hauser index and speed of gait) did not differ between groups. All these parameters improved at hospital discharge, and the degree of improvement was comparable between NLR+ and NLR- groups. Despite this amelioration, NLR+ were still more disabled when compared to NLR- group at hospital discharge. Infectious complications were more prevalent in NLR+ group (84.6% vs 25.9% in NLR- group, p=0.001), as expected.

Discussion: Indeed, patients with a NLR above 5 showed poorer functional and motor independence, higher rate of infectious complication and a more severe clinical picture at hospital admission and discharge. Nonetheless, a significant clinical improvement was achieved in both groups.

Conclusion: Stroke-induced immunodepression is a negative prognostic factor in the neurorehabilitation setting.

SMARTPHONE APP IN STROKE MANAGEMENT: A NARRATIVE UPDATED REVIEW

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Background: Progressive digitalization of medicine has deeply changed clinical practice. Spread of smartphone and mobile-Health (m-health) has progressively changed clinical practice, implementing access to medical knowledge and communication between doctors and patients. Dedicated software called Applications (or Apps), assists the practitioners in the various phases of clinical practice, from diagnosis to follow-up and therapy management. The impact of this technology is even more important in diseases such as stroke, which are characterized by a complex management that includes several moments: primary prevention, acute phase management, rehabilitation, and secondary prevention. The aim of this review is to evaluate and summarize the available literature on apps for the clinical management of stroke. We described their potentials and weaknesses, discussing potential room for improvement.

Methods: Medline databases were interrogated for studies concerning guideline-based decision support apps for stroke management and other medical scenarios from 2007 (introduction of the first iPhone) until January 2022.

Results: We found 551 studies. 43 papers were included because they fitted the scope of the review. Based on their purpose, apps were then classified into three groups: primary prevention apps, acute stroke management apps, post-acute stroke apps. We described the aim of each app and, when available, the results of clinical studies.

Discussion: Each stage of stroke management shows peculiar features. In the pre-hospital stage, diagnosis and reduction of DNT are the main determinants of patient outcome. Some apps have been developed to assist the recognition of symptoms (iLAMA). Other apps like FAST-ED, SPSMS and ESN allow to share patients' data with the hospital neurologist, avoiding the loss of information during transport to hospital. In intrahospital management adherence to guidelines represents one of the major determinant of patient prognosis. Apps like JOIN, Stop Stroke and Act-fast allow video calls with experienced neurologists to assist with the therapeutic decision. Another important step in stroke recovery is neurorehabilitation. Telemedicine and use of smartphone embedded sensors (gyroscope and accelerometer), along with additional wearable technologies, provides a constant monitoring of the rehabilitation phases.

Conclusion: For acute stroke, some apps have been designed with the main purpose of helping communication and sharing of patients' clinical data among healthcare providers, but interactive systems apps aiming to assist the clinicians are still lacking and this field should be developed because it may improve stroke patients' management.

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ASSESSMENT OF CEREBRAL VASOMOTOR REACTIVITY IN PATIENTS WITH ACUTE MILD STROKE AND TRANSIENT ISCHEMIC ATTACK (TIA) WITH DIFFERENT ETIOPATHOGENESIS: RESULTS AT BASELINE

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Objectives: An impaired vasomotor reactivity (VMR) represents a negative prognostic factor for vascular and degenerative cognitive deterioration1,2. However, only few studies have addressed VMR in acute stroke phase3. We aim to investigate if VMR, calculated through the breath holding index (BHI), is a prognostic marker of clinical outcome in stroke/TIA patients.

Methods: In this longitudinal observational study (January 2020-2023) we enroll patients with acute stroke or TIA of anterior circulation with NIHSS<8. The study observation period of 12 months includes 4 assessments: T1 (48-72h from onset), T2 (1 month follow up [FU]), T3 (6 months FU) and T4 (12 months FU). Clinical scales and cognitive tests are performed at every time point. VMR is evaluated at T1 and T3.

Results: From January 2020 to May 2022, 116 patients (70% men) with a median age of 67 (56-75.5) years were enrolled. 70% had a stroke. The median NIHSS at onset was 2 [1-3]. The median pre-mRS was 0 (0), the median mRS at baseline was 1 (0-1). We found an inverse correlation between the adjusted MMSE and Pulsatility Index (PI) of Middle Cerebral Artery (MCA) ($p<0.001$) and between the adjusted MMSE and PI of Posterior Cerebral Artery (PCA) ($p=0.003$) at baseline. We also observed an inverse correlation between MOCA and PI of MCA ($p=0.003$) and between MOCA and PI of PCA ($p=0.006$) at baseline. An inverse correlation was also observed between age and adjusted MMSE ($p<0.001$) and MOCA ($p<0.001$) at baseline. We found a direct correlation between age and PI of MCA ($p<0.001$) and PI of PCA ($p<0.001$) at baseline. 103 patients were evaluated at T2, 79 at T3 and 53 at T4. 20 patients (17.24%) presented a reduced VMR (BHI<0.69) in acute phase independently from etiopathogenesis.

Conclusion: The results at baseline show an inverse correlation between cognitive tests and PI of MCA/PCA and between age and cognitive tests; and a direct correlation between age and PI of MCA/PCA. An impaired VMR could be observed in acute phase independently from etiopathogenesis.

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BLOOD UREA NITROGEN TO CREATININE RATIO AS A PROGNOSTIC BIOMARKER IN ISCHEMIC STROKE PATIENTS WITH NEW ONSET ATRIAL FIBRILLATION

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Objectives: Acute ischemic stroke (AIS) is the one of the leading causes of death and long-term disability in developed countries. Cardioembolic stroke accounts for 25-30% of the events, with non-valvular atrial fibrillation (NVAF) as the main source. Blood-urea-nitrogen (BUN) to creatinine ratio (BCR) has been shown as a prognostic biomarker in AIS. However, data about relationship between BCR and NVAF are lacking. This study was aimed to study a possible relationship between BCR and NVAF in AIS patients.

Materials and Methods: We recruited AIS patients admitted in two Stroke Units (Neurological Clinic, Ospedali Riuniti, Ancona and Internal Medicine, Ospedale Santa Croce, Fano) between July 2018 and December 2019. For each patient, we collected sex, age, stroke features, cardiac rhythm, serum urea and creatinine, BCR, NIHSS and mRS before and after AIS. The association between BCR, NVAF and NIHSS was studied using a generalized linear multivariate model for repeated variables.

Results: We obtained 411 subjects (45% females and mean age 71,8 ± 12,6 years), of whom 68 patients had pre-existing (pNVAF) and 69 subjects new-onset (nNVAF) non-valvular atrial fibrillation. Patients with NVAF had a significantly higher BCR ($p=0,001$). There was a significant difference in BCR value between nNVAF subjects ($p<0,001$) and the other part of the sample, while there was no significant difference in pNVAF subjects ($p=0,566$). In multivariate model, we observed a significant association between NIHSS, BCR, nNVAF and stroke class ($p=0,044$), which resulted more relevant in within subjects design ($p=0,010$).

Discussion: AIS can cause sympathetic hyperactivation, leading to a higher β-adrenergic stimulation which could be responsible of both higher BUN passive reabsorption in the kidney with increased BCR levels and atrial electrophysiology modification precipitating nNVAF. The same neurohormonal activation could determine worse blood pressure control, more extended infarct with insular lobe involvement and cardiac arrhythmia with major risk of sudden cardiac death. These elements can be converged in an autonomic cardiac disfunction caused by AIS, which we assume to be more pronounced in patients with nNVAF with a worse outcome.

Conclusion: A higher pathologic BCR can be a biomarker of nNVAF in AIS and could be associated to worse prognosis. Our observations should be validated in larger, prospective cohorts.

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ORGANIZING HEALTHCARE FOR BETTER ACUTE ISCHEMIC STROKE TREATMENT IN METROPOLITAN AREA OF BARI, ITALY

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Background and aims: Improving the number and reducing the delay of endovascular treatment (EVT) are actually mandatory for our regional sanitary service and mostly depend on the organization, which include the emergency medical service (EMS), the primary stroke centers (spoke) and the comprehensive stroke center (hub).

Methods: We have retrospectively analyzed our data from Italian Registry of Endovascular Treatment of Stroke. Between January to December 2021, 116 patients with ischemic stroke due to large vessel occlusion were treated: 61 patients were transported directly to the hub; meanwhile 55 firstly to a spoke.

Results: Mean age was similar on two groups (74 years). The "spoke strokes" (SS) were slightly more severe (median NIHSS 18 vs 16) but 23% of the "hub strokes (HS)" had a pre-existing mRS score ≥ 2 (vs 13% SS). Intravenous thrombolysis was administered in 46% of HS and 56% of SS. The median door-in-door-out time of our spoke centers was 180 minutes. The median door-to-groin time of our hub was 180 minutes. The median groin-to-reperfusion time was 70 minutes in HS and 75 in SS. A good reperfusion (TICI $\geq$2b) was reached in 72% of HS and in 83% of SS. 59% of HS had mRS $\leq$2 at 90 days and 47% of SS had mRS $\leq$2 at 90 days.

Conclusion: Our experience evidenced the better outcome when reducing the delay in starting EVT. In our region the mothership model need to be proposed to EMS protocol decision making as the best way to approach an acute stroke patient.

SEX-RELATED ELECTROCORTICAL DIFFERENCES TO TMS IN PATIENTS WITH MILD VASCULAR COGNITIVE IMPAIRMENT

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Background: Although research on vascular cognitive impairment (VCI) has recently identified a number of factors for disease development and progression, many aspects are still debatable, such as sex differences, which are basically lacking in comparison to those available for Alzheimer's Disease or Vascular Dementia (VaD). In VCI, transcranial magnetic stimulation (TMS) has been exploited as a non-invasive tool to evaluate in vivo the cortical excitability, the neuroplastic phenomena and the underlying transmission pathways. To date, however, a direct TMS comparison between males and female patients with mild VCI at risk for VaD or mixed dementia is lacking.

Methods: 60 patients (27 males and 33 females, mean age ± standard deviation 70.5 ± 6.3 and 66.8 ± 5.4 years, respectively) underwent clinical, psychopathological and functional assessment, as well as both single- and paired-pulse TMS, bilaterally. Measures of interest consisted of resting motor threshold, latency of the motor evoked potentials (MEPs), contralateral cortical silent period, amplitude ratio, central motor conduction time (CMCT), including the calculation through the F wave technique (CMCT-F), as well as short-interval intracortical inhibition (SICI), intracortical facilitation, and short-latency afferent inhibition (left hemisphere only), at different interstimulus intervals (ISIs).

Results: Males and females were comparable in terms of age, educational level, vascular burden and neuropsychiatric symptoms. Males scored significantly worse than females at global cognitive tests, executive functioning and independence scales. MEP latency was significantly longer in males than in females, from both sides, as well as the CMCT and CMCT-F from the left hemisphere; a lower SICI at ISI of 3 ms from the right hemisphere was also found. After correction for demographic (age, sex) and anthropometric features (height, weight), the effect of sex remained statistically significant for MEP latency, bilaterally, as well for as for the CMCT-F and SICI. The presence of diabetes, MEP latency bilaterally, and both CMCT and CMCT-F from the right hemisphere inversely correlated with executive functioning, whereas TMS measures did not correlate with vascular burden.

Conclusions: These findings confirm the worse cognitive profile and functional status of male patients with mild VCI compared to females and highlight that sex-specific changes in intracortical and cortico-spinal excitability exist in VCI. This points to some TMS measures as potential markers of cognitive impairment and altered neurophysiology, as well as new targets for customized neuromodulating approaches. Further studies and follow-up assessment are needed to confirm these results and clarify the role of TMS metrics in VCI process and progression in both sexes.
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TRANSIENT ISCHEMIC ATTACK AND MINOR STROKE AS "SURGERY STUFF": A REVIEW OF LITERATURE

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Objective: To review the subtypes of Transient ischemic attack (TIA) and minor stroke (mS) in which a surgical treatment is needed, discussing the importance and the timing of a multidisciplinary approach.
Methods: Case series and review of literature of TIA and mS due to conditions at high risk of early recurrence with potential surgical approach, even in urgency.

Results: Cases of patients suffering from symptomatic carotid stenosis, hemodynamic stroke, bacterial endocarditis, atrial myxoma, and Bow-Hunter disease.

Discussion: Symptomatic carotid stenosis, or particular cases of hemodynamic cerebrovascular events, should be promptly referred to vascular surgeon, since increasing evidences highlighted a benefit from an early artery revascularization. In addition, beyond arrhythmic causes, cardioembolic events due to bacterial endocarditis and atrial myxoma should be quickly diagnosed, possibly in emergency department, because they are, as well as a concern of standard acute and prophylactic treatments, a presumptive urgency for heart surgery. In addition to the above mentioned conditions, in patients suffering from vertebrobasilar TIA or mS, clinicians should keep in mind Bow-Hunter disease (rotational vertebral artery occlusion), because surgical artery decompression can represent the only suitable treatment in selected cases.

Conclusion: When a surgical treatment is needed, it is fundamental the timing of a multidisciplinary approach, in order to achieve an optimized management and prevent major strokes or other critical complications.

TENECTEPLASE VERSUS ALTEPLASE IN THROMBOLYSIS FOR ISCHEMIC STROKE: A META-ANALYSIS OF RCTS

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Background and Purpose: Alteplase (ALT) is indicated in acute ischemic stroke treatment. Tenecteplase (TNK) is a fibrinolytic agent that would make it a useful therapy. The most recent US American Heart Association/American Stroke Association acute ischemic stroke guidelines recognized TNK as an alternative to ALT. Aim of this study was to compare the efficacy and safety of TNK with ALT.

Methods: Systematic literature search and meta-analysis were conducted according to PRISMA guidelines, including only randomized controlled trial. The primary endpoint was a very good outcome at 3 month follow up (mRS 0 – 1), while secondary endpoints were safety and imaging findings. Statistical analysis was performed using the Maentel-of freedom from disability (modified Rankin Scale score, 0–1) outcome at 3 m, and additional efficacy and safety outcomes, were analyzed. Odds ratios for endpoints were pooled with meta-analysis and compared between reperfusion strategies.

Results: Systematic search identified 9 trials enrolling 3792 patients (1906 TNK and 1886 ALT). Mean age was 70.3 years, with 59% male. The mean score of the baseline National Institutes of Health Stroke Scale was 8.5. All ALT patients received standard dose, while TNK dosing was 0.1 mg/kg in 6%, 0.25 mg/kg in 59%, and 0.4 mg/kg in 35%. Primary endpoint was achieved by 902 and 869 TNK and ALT patients, respectively (OR: 1.05; 95%CI: 0.87 – 1.27). The higher OR was observed in the subgroup of patients treated with TNK dose of 0.25 mg/Kg (OR: 1.16;95%CI: 0.98 – 1.39). For secondary endpoint, symptomatic intracranial hemorrhages occurred in 35 and 30 TNK and ALT treated patients, respectively (OR: 1.17; 95%CI: 0.69 – 1.98).

Conclusions: Results coming from this study provides evidence that TNK is effective in acute stroke treatment, as well as ALT, with better findings for primary endpoint considering 0.25 mg/Kg dosing. Safety appeared to be similar in the two treatments.
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TIME FROM IMAGING TO ENDOVASCULAR TREATMENT IS NEGATIVELY RELATED TO GOOD FUNCTIONAL OUTCOME IN ANTERIOR CIRCULATION LARGE VESSEL OCCLUSION STROKE WITHIN THE EARLY THERAPEUTIC WINDOW

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Background: Among patients with acute ischemic stroke (AIS) due to large vessel occlusion (LVO), a shorter time to endovascular-reperfusion therapy (EVT) is associated with better outcome. Nevertheless, patients treated in the late window have a no time-dependent response [1], but the largest absolute increase in functional independence due to favourable collateral circulation and substantial slow infarction growth. In the early stage the rate of infarct progression is unclear and any delay in treatment may result in progressive decrease in the odds of favorable long-term outcome. Imaging time is particular relevant in the stroke workflow because represents when the treatment decision is made based on parenchyma and collaterals status [2-3].

Aim: To evaluate the effect of time and specific imaging-related workflow metrics on functional outcome in patients treated in the early stroke stage.

Methods: We included patients admitted to our Stroke Unit with anterior circulation AIS and LVO who underwent EVT and achieved a good final reperfusion (mTICI 2b-3). We analyzed out-of-hospital and intra-hospital workflow metrics: time from symptom onset-to-door (OTD), onset-to-imaging (OTI), onset-to-groin (OTG), imaging-to-groin (ITG), imaging-to-reperfusion (ITR), onset-to-reperfusion (OTR). The effect of time on outcome at 3-months was described via odds ratio for every 15-minutes delay in all subjects and in subgroups divided by OTG, NIHSS, ASPECTS, and collaterals status.

Results: Of 208 patients, EVT was started within 6 hours from symptom onset in 131 patients. Mean age was 69 years, median admission

NIHSS 14 (8-18), median ASPECTS 9 (8-10). At 3-months 62% of patients achieved a functional independence outcome (mRS 0-2). Among patients treated within 6h, median workflow times (minutes) were as follows: OTG 206 (168-248), OTD 73 (54-116), OTI 118 (89-157), ITG 86 (61-104), ITR 133 (89-154), GTR 31 (21-62) and OTR 260. The ITR time showed a significant negative association with favourable outcome (OR, 0.77; 95%CI, 0.65-0.91), ITG was negatively associated only with excellent outcome (mRS 0-1; OR 0.77; 95%CI, 0.60-0.99). Considering different time intervals within 6h, a significant association for imaging-related intervals was found in patients with OTG 3-4.5h, rather than in the very early (OTG<3h) and early late therapeutic window (OTG 4.5-6h), and in patients with NIHSS>5, poor collaterals and ASPECTS<9 (OTG<6h). No significant association was found for pre-imaging workflow metrics (OTD, OTI).

Conclusion: In patients with anterior circulation LVO stroke in the early therapeutic window(<6h) any time delay between imaging and EVT is strongly associated with the risk of poor functional outcome at 3-months.

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THE ROLE OF BETA-AMYLOID, TAU, AND ALFA-SYNUCLEIN PROTEINS AS PUTATIVE BLOOD BIOMARKERS IN PATIENTS WITH CEREBRAL AMYLOID ANGIOPATHY

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Background: Cerebral amyloid angiopathy (CAA) is a cerebrovascular disorder characterized by the deposition of beta-amyloid protein (Abeta) within brain blood vessels that develops in elderly people and Alzheimer's Disease (AD) patients. A definite CAA diagnosis is determined by post-mortem autopsy only, while just a Probable or Possible diagnosis can be done in vivo with the Boston Criteria. Therefore, the investigation of biomarkers able to differentiate CAA patients from healthy controls (HC) and AD patients is of great interest, in particular in peripheral fluids.

Objective: The current study aimed to detect the concentration of serological biomarkers (i.e, Abeta1-40, Abeta1-42, t-tau, and alfa-synuclein) levels in both red blood cells (RBCs) and plasma of CAA patients and healthy controls, evaluating their role as putative peripheral biomarkers for CAA.

Methods: To this purpose, the proteins' concentration was quantified in RBCs and plasma by home-made immunoenzymatic assays in an exploratory cohort of 20 CAA patients, which were enrolled at the Neurology Unit in the Pisa's Hospital, and 20 HC enrolled from volunteers. Patients and HC were matched for age and sex.

Results: The results highlighted a significant increase of Abeta1-40 and alfa-syn concentrations in both RBCs and plasma of CAA patients, while higher Abeta1-42 and t-tau levels were detected only in RBCs of CAA individuals compared to HC. Moreover, Abeta1-42/Abeta1-40 ratio increased in RBCs and decreased in plasma of CAA patients. The role of these proteins as candidate peripheral biomarkers easily measurable with a blood sample in CAA needs to be confirmed in larger studies.

Conclusion: In conclusion, we provide evidence concerning the possible use of blood biomarkers for contributing to CAA diagnosis and differentiation from other NDs.

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COGNITIVE IMPAIRMENT AFTER MECHANICAL THROMBECTOMY: A CONSEQUENCE NOT TO BE UNDERESTIMATED

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Objectives: After successful mechanical thrombectomy for middle cerebral artery occlusion, basal ganglia infarction is commonly detectable, due to their selective vulnerability to ischaemic insults. While the functional outcome of these patients is often good, less knowledge is available about cognitive outcome. The aim of our study is to investigate the presence of cognitive impairment within 1 week after thrombectomy.

Materials: One week after thrombectomy, 43 subjects underwent a general cognitive assessment using Montreal Cognitive Assessment (MoCA) and an extensive neuropsychological battery evaluating memory, visual praxis, attention, executive functions, and language.

Methods: Patients were classified as cognitively impaired (CImp) or not (noCImp) according to a MoCA score below 18. RESULTS. CImp amounted to 60.5%. CImp and noCImp differed neither in their NIH-Stroke Scale (NIHSS) at admittance and in ASPECT score, but they did in age ($p<0.028$), modified Rankin Scale (mRS) at the admittance ($p=0.037$) and in Fazekas scale ($p=0.020$). At discharge, CImp showed higher scores than noCImp on NIHSS ($p<0.001$) and mRS ($p<0.001$). Compared to noCImp, CImp showed worse performances in all neuropsychological tests, with higher impairment in ratings of executive and attention functions.

Discussion: Mechanical thrombectomy has proven to be particularly important in specific categories of patients, to save extensive brain areas from ischemia. Despite this, in our study almost the entire sample showed on CT/MRI lesions involving the basal ganglia after successful procedure, confirming the particular susceptibility of the basal ganglia to ischaemic damage. Furthermore, older age correlated with worse neurological outcome, and, although no patients enrolled had cognitive impairment prior to ischemia, higher mRS at admittance predisposed to a greater

likelihood of developing it after stroke. The same applies to chronic vascular leukoencephalopathy.

Conclusions: Some patients who underwent thrombectomy experienced a detectable cognitive impairment, that probably lead to worse NIHSS and mRS at discharge. Interestingly, the profile of such cognitive impairment resembles the defects that are observed in other conditions involving basal ganglia, such as Parkinson's Disease and Vascular Dementia.

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MECHANICAL THROMBECTOMY IN MINOR STROKE DUE TO ISOLATED M2 OCCLUSION: A MULTICENTER RETROSPECTIVE MATCHED ANALYSIS

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Background and objectives: The benefit of mechanical thrombectomy (MT) in patients with ischemic stroke due to isolated occlusion of the M2 segment of the middle cerebral artery and baseline minor symptoms remains unclear. The purpose of this study was to evaluate the effectiveness of MT in this subgroup of patients.

Materials and Methods: The databases of 16 high-volume Stroke centers were retrospectively screened for consecutive patients with isolated M2 occlusion and a baseline National Institute of Health Stroke Scale (NIHSS) score ≤ 5 that received either early MT (eMT) or best medical management (including intravenous thrombolysis - BMM) with the possibility of rescue MT (rMT) upon early neurological worsening. We used propensity score matching (PSM) to estimate the treatment effect of eMT compared to the BMM/rMT, accounting for differences in baseline variables. Primary outcome measure was a 90-days modified Rankin Scale score 0-1.

Results: 388 patients were initially selected and, after PSM, 100 pairs of patients receiving eMT or BMM/rMT respectively were available for analysis. Univariate analysis on the matched cohort showed a non-significant benefit of eMT over BMM/rMT on excellent neurological outcome, that remained instead associated with baseline NIHSS score and successful reperfusion (mTICI 2b-3) after MT, moreover there was no significant difference regarding cerebral bleedings and 90-day mortality. The involvement of M2 superior branch was instead associated with an unfavorable outcome. Similar results were observed also after comparison between patients receiving eMT with those receiving rMT.

Discussion: The appropriateness of MT in this subgroup of patients is debated due to uneven and contradictory data. Some studies showed a

higher rate of asymptomatic intracranial hemorrhage and no better outcome in patients who underwent MT, compared to BMM. [1,2] More recently, MT has been associated with better results, possibly due to last-generation thrombectomy devices. [3] Our study has shown a non-significant benefit of early MT over BMM/rMT, in spite of a minimal and non-significant benefit of early MT over rMT. Overall, the great majority of patients in our study achieved a favorable outcome regardless the type of acute treatment.

Conclusion: Our multicenter retrospective analysis has shown non-significant benefit of early MT in patients with minor stroke due to isolated occlusion of M2 over a more conservative therapeutic approach. Although our results must be viewed with caution, in this subgroup of patients it appears reasonable to consider a BMM as first option and rMT in presence of an early neurological deterioration.

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THE UNMET NEEDS IN THE ACUTE PHASE TREATMENT OF INTRACEREBRAL HEMORRHAGE: DATA FROM A POPULATION-BASED STUDY

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Aims: Intracerebral hemorrhage (ICH) represents only 10-20% of all strokes but is responsible of high mortality. There are no specific treatments for ICH; however, an acute bundle of care based on blood pressure reduction, rapid administration of procoagulants to anticoagulants-related ICH, and rapid neurosurgical referral for selected patients, can substantially decrease short-term ICH mortality. We aimed at evaluating the practice of acute phase care of ICH in a population-based cohort.

Materials and Methods: We recruited patients from a prospective population-based stroke registry, admitted from 2018 to 2020 to the hospitals of the district of L'Aquila due to ICH. We obtained data relevant to the acute bundle of care (blood pressure at the Emergency Room and on admission to the ward, neurosurgical referrals, and use of procoagulants in patients with ICH related to anticoagulants). Thirty-day mortality was also assessed.

Results: During the study period, we identified 212 patients with ICH, of whom 186 (87.7%) had complete information on the acute bundle of care; 108 (58.1%) of those 186 patients were male, while the mean age was 76.2±13.7 years; 140 (75.3%) patients had arterial hypertension, while 31 (16.7%) were on anticoagulant treatments; 130 (69.9%) patients had systolic blood pressure values ≥140 mmHg on admission. Median duration of Emergency Room stay was 147 (interquartile range 84-266) minutes. Among patients with systolic blood pressure values above 140mmHg at onset, reduction under 140mmHg was achieved in 76 (58.5%); procoagulants were not administered to any patient; neurosurgical referral was asked for 161 (86.6%) patients, while only 20 patients (12.4%) underwent ICH evacuation. In-hospital mortality was significantly lower in patients achieving systolic blood pressure values <140mmHg than in those not achieving that value (23.5% vs 44.0%; P=0.030).

Discussion: We found that, in patients with ICH, management of BP was suboptimal in the emergency setting. Additionally, none of the patients on anticoagulants underwent anticoagulant-reversal therapy. On the other hand, many patients underwent neurosurgical referrals but the final number of patients who actually underwent surgery was low.

Conclusions: In our population there is room to improve ICH management in the emergency setting and training of the emergency staff is on the agenda. It is important to explore if sub-optimal management of ICH occur is limited to our area of if it is more broadly generalizable to Italy.

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HIGH FREQUENCY OF MULTIPLE LESIONS AT NEUROIMAGING IN PATIENTS WITH MINOR ISCHEMIC STROKE OR TIA: THE READAPT STUDY

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Background: Short-term dual antiplatelet treatment (DAPT) is recommended for secondary prevention of non-cardioembolic minor ischemic stroke or high-risk TIA. Despite treatment, some patients have recurrent ischemic events, which may be due to multiple factors including an occult cardioembolic source requiring anticoagulation. In some cases, multiple acute lesions represent a radiological hallmark of cardioembolism. We aim at addressing frequency and mechanisms of multiple acute ischemic lesions in patients receiving DAPT for minor stroke and TIA.

Methods: The Real-life study on short-term dual antiplatelet treatment in patients with ischemic stroke or transient ischemic attack (READAPT) is a prospective, nationwide, multicentre, observational study started in February 2021, which includes patients with non-cardioembolic minor-to-moderate ischemic stroke or high-risk TIA receiving short-term DAPT in clinical practice. The recruitment and 90-day follow-up are still ongoing.

Results: As of 22nd May 2022, out of 774 patients included from 52 Italian Centres, 752 (97%) underwent a brain CT scan and 578 (74.4%) a brain MRI scan. Overall, 239 patients had a duration of symptoms <24 hours. Among patients with a MRI brain scan, 120 (20%) had no acute lesions, 271 (47%) single and 187 (33%) multiple acute lesions. In this latter group, the event was mostly of undetermined or large vessel cause (96, 52% and 56, 30% respectively), and more rarely of other defined cause such as dissection, vasculitis or hypercoagulable state (35, 18%); 139 (74%) were investigated with >24 hours cardiac monitoring. Out of 56 patients with large vessel strokes, 23 (41%) had intracranial stenosis consistent with acute ischemic lesion, 20 (36%) had >50% and 12 (21%) <50% symptomatic carotid stenosis, and 1 (2%) vertebrobasilar stenosis. The multiple acute lesions were in the same vascular territory in 154 (82%) patients and in different vascular territories in 33 (18%). In the 33 patients with multiple lesions in different vascular territories, 22 (67%) had undetermined stroke, of whom 12 (54%) met criteria for ESUS definition, 6 (18%) had stroke due to other defined cause and 5 (15%) a large vessel stroke.

Discussion and conclusions: We found that around 1/3 of patients receiving DAPT for minor stroke and TIA have multiple acute ischemic lesions, which were mostly associated with arterial stenosis or of undetermined origin. The ongoing follow-up of the READAPT study will reveal if patients with multiple acute lesions are at higher risk of 90-day stroke recurrence.

THE "SALPARE STUDY" OF SPONTANEOUS INTRACEREBRAL HEMORRHAGE

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Background and aims: Spontaneous intracerebral hemorrhage (ICH) is a devastating type of stroke with a huge impact on patients and families [1]. The lack of an incisive treatment, together with an expanded use of oral anticoagulants and an ageing population might contribute to an epidemiological change [2]. In view of these trends, we planned a study to obtain a contemporary picture and identify early prognostic factors to improve secondary prevention.

Materials and methods: This multicenter prospective cohort study recruited consecutive adult patients with non-traumatic ICH admitted to three Italian university hospitals (Salerno, Padova, Reggio Emilia) over a 2-year period. Demographic characteristics, vascular risk profile, clinical data, and radiological characteristics including early non-contrast CT markers of hematoma expansion were correlated to 90-day clinical outcome.

Results: Out of 682 patients [mean age: 73±14 years; 316 (46.3%) females] enrolled in this study, 40% died [86/180 (47.8%) in Salerno, 120/320 (37.5%) in Padova, 67/182 (36.8%) in Reggio Emilia; $p<0.05$)] and 36% were severely disabled at 90 days. The following characteristics were associated with a higher risk of poor functional outcome (mRS>2): premorbid mRS score ≥1, antithrombotic drug use, hyperglycemia, previous cerebrovascular accident, low platelet count, GCS score at onset ≤14, NIHSS score at onset ≥9, pontine/intraventricular hemorrhage, baseline hematoma volume >15 mL, blend sign, swirl sign, margin irregularity ≥4, density heterogeneity ≥3, hypodensity ≥1, island sign, satellite sign, black hole sign, and hematoma expansion. However, at multivariate analysis, only pre-ICH mRS score (OR 30.84), GCS score at presentation (OR 11.88), NIHSS score at presentation (OR 25.89), and baseline hematoma volume (OR 29.71) were independent predictors of death and poor functional outcome.

Discussion: This study shows that the 3-month outcome after ICH is still poor even though mortality and disability rates are slightly better than previously reported. However, prognosis differs among centers and likely reflects a different management in the acute phase, suggesting that further therapeutic improvement is possible. In this context, the identification of early reliable outcome predictors might aid in the selection of ICH patients significantly benefiting from a more intensive care. In our population, GCS/NIHSS at admission, pre-ICH mRS scores and baseline hematoma volume were able to independently predict patients outcome, while early NCCT markers of hematoma expansion did not seem to add any clinically significant information.

Conclusion: Despite the heterogeneity among centers, this study on ICH has identified four simple prognostic factors that can independently predict patients outcome, stratify their risk, and guide their management.

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SHORT-TERM DUAL ANTIPLATELET TREATMENT FOR MINOR STROKE OR TIA IN THE REAL LIFE: DO PATIENTS MATCH INCLUSION CRITERIA AND PROCEDURES OF CLINICAL TRIALS? INSIGHTS FROM THE READAPT STUDY

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Background and aims: Short-term dual antiplatelet treatment (DAPT) is recommended by international guidelines1, for the secondary prevention of minor ischemic stroke (NIHSS score ≤3 or ≤5) or high risk-TIA (ABCD2 score ≥4 or ≥6). In randomized controlled trials (RCTs) of DAPT2,3, patients undergoing acute revascularization procedures were excluded, while two out of three RCTs included only subjects ≥40 years; DAPT had to be started within 12-24 from symptom onset, and all patients received a variable initial dose of aspirin (50-325 mg) and a loading dose of clopidogrel or ticagrelor. In clinical practice, RCTs inclusion/exclusion criteria and procedures might not be strictly followed. We aim to describe the characteristics of patients with minor stroke or TIA treated with DAPT in clinical practice in order to understand if inclusion/exclusion criteria and procedures of RCTs are followed.

Materials and Methods: READAPT is a prospective, multicenter, real-world observational study including patients receiving short-term DAPT, that are followed-up to 90 days. For this analysis, we refer to baseline data of patients included up to May 22nd, 2022.

Results: Overall, 774 patients from 55 centers were included. Most patients were male (511, 65.8%); mean age was 70.0±13.1 years; 239 (30.9%) received DAPT after TIA and 535 (69.1%) after stroke. Only 211 (27.2%) patients matched RCTs inclusion/exclusion criteria and followed RCTs procedures. In detail, 373 (48%) of patients did not match at least one inclusion criterion of RCTs and 526 (67.9%) did not exactly follow RCTs procedures. In patients with stroke, 157 (29.0%) patients had NIHSS >3 and 40 (7.4%) had NIHSS >5. In patients with TIA, 45 (18.0%) had ABCD2 <4 and 192 (80.0%) had ABCD2 <6. Additionally, 106 (13.6%) patients underwent intravenous thrombolysis and 6 (0.8%) endovascular treatment; 17 (2.2%) were treated with urgent carotid endarterectomy. DAPT was started within 25-48 hours in 134 cases (17.3%) and after 48 hours in 121 cases (15.6%). Only 206 (26.6%) received a loading dose of aspirin, while 291 (37.6%) received a loading dose of clopidogrel.

Discussion and conclusions: Our data show that short-term DAPT in clinical practice does not strictly follow RCTs inclusion/exclusion criteria and procedures. READAPT aims to establish effectiveness of DAPT in a real life setting and particularly in subgroups of patients which were not addressed in RCTs but who in real-life are considered suitable to receive DAPT.

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INSIGHT ON ENDOCARDITIC THROMBI: COMPOSITION AND IMMUNE HALLMARK

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Objectives: Infective endocarditis (IE) is a rare but relevant cause of embolic ischemic stroke. IE is a serious disease, and the pathophysiologic mechanisms underlying the formation and the embolization of endocarditic vegetation are not clearly understood. For this reason, the analysis of cerebral thrombi retrieved by endovascular thrombectomy in patients with large vessel occlusion stroke and IE could be a vehicle to better understand the underlying immune-thrombotic mechanisms and a complement to diagnostic investigation.

Materials and Methods: We performed a systematic multimodal analysis on cerebral thrombi retrieved by endovascular thrombectomy in patients with ischemic stroke from IE (n=7) and control patients with cardioembolic stroke (CEE, n=23) or stroke with concomitant sepsis and/or other infections (n=8). We conducted a histological and microbiological analysis, searching for the presence of microorganisms within the thrombus, and examining the structural and immune composition of cerebral thrombi.

Results: Performing histochemical stainings, thrombus culture and/or PCR amplification, we observed the presence of invading pathogens in all cerebral thrombi with IE. In 5 out of 7 IE patients hemocultures were positive for the same microorganism, while 2 patients had negative hemocultures. Moreover, IE thrombi showed a unique composition, compared to controls, characterized by lower levels of red blood cells (represented by the yellow area of MSB/Lendrum staining), and higher amounts of monocytes/macrophages (CD68+ cells), while no differences were found in terms of fibrin (the pink area of MSB/Lendrum staining), platelets (CD61+ areas), T and B lymphocytes (CD3+ and CD20+ cells) and neutrophil counts (MPO+ cells). Interestingly, IE thrombi presented a higher prevalence of Neutrophil Extracellular Traps (NETs) (CitH3+ area) characterized by cell- and filopodia- dominant morphology.

Discussion and Conclusions: The analysis of cerebral thrombi represents a unique adjunctive possibility in the diagnostic process of patients with suspected IE. The presence of higher amount of macrophage and of a peculiar NETs pattern highlights the primary role of immunity in the pathogenesis of IE thrombi and in the disease course. The finding of a typical composition of these thrombi could be a useful tool to recognize patients with IE. Especially in those cases with negative hemocultures, the identification of the pathogen into the thrombotic material might be of primary importance for a target therapy.

DYNAMIC BRAIN STATES IN SPATIAL NEGLECT AFTER STROKE

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Introduction: Previous studies have shown that spatial neglect is characterized by widespread alteration of static resting-state functional connectivity 1 as well as by changes of functional topology 2 of large-scale brain systems. However, it is unknown whether such network modulations exhibit temporal fluctuations which are related to spatial neglect. Here we investigated the association between dynamic functional connectivity (dFC) and spatial neglect after stroke.

Methods: A cohort of right hemisphere damaged patients (n=20) underwent a neuropsychological assessment of neglect as well as structural and resting-state functional MRI sessions within two weeks since stroke onset. We employed the sliding window approach and the clustering method3 on a set of higher-order associative and sensory-processing brain networks.

Results: We identified two distinct dFC-based brain states, characterized by different degree of brain modularity. Crucially, we detected a double dissociation such that patients having neglect exhibited higher occurrence of low modularity state as compared to those without neglect, whereas an opposite pattern was observed for the high modularity state (i.e., larger occurrence for non-neglect vs. neglect patients).

Discussion: Current findings indicate that stroke leading to spatial attention deficits affects the temporal properties of functional interactions among large-scale networks, hence, providing potential insight for the treatment of spatial neglect.

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ARTIFICIAL INTELLIGENCE FOR THE STUDY OF CEREBRAL HAEMODYNAMICS: CURRENT STATE OF THE ART

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Transcranial Color Doppler (TCD) is an effective, cheap and bedside tool for prolonged monitoring of intracerebral circulation and microembolic signals detection; however, its applicability in daily practice has been limited, mostly due to the need of trained personnel during the examination. Therefore, we assessed the potential application of artificial intelligence driven TCD (AI-TCD) in different clinical settings. Experienced sonographers of two large university centers used AI-TCD (NovaGuide™ Intelligent Ultrasound, NovaSignal Corp., USA) to detect and then automatically track the middle cerebral artery flow bilaterally. Monitorings were performed in several settings, including stroke unit, intensive care unit, neuroradiological and cardiological interventional suites and operation theater. Exam duration, technical aspects and safety issues were collected. We performed 66 prolonged monitorings on 57 patients (30 in Padua and 27 in Linz). AI-TCD examinations were safe in all patients. Yet, the examination was feasible in 5 of 7 settings. Infact, the exam was not possible during carotid endarterectomy, since the device was interfering with the surgical field, and during endovascular intracranial procedure, as the system was not radiotransparent and did not allow radiological intra-procedural control. Furthermore, the exam was stopped earlier than expected in 14 cases (21%) due to patient's poor compliance or discomfort. AI-TCD proved to be effective and safe for continuous blood flow monitoring in most intensive and acute clinical settings. Therefore, it might represent a pivotal tool to expand neurosonological monitoring application in daily practice. However, further developments are needed to extend the range of settings in which this new technology might be applied.

THROMBECTOMY IN CERVICAL ARTERY DISSECTION RELATED STROKE: A CHALLENGE OR AN OPPORTUNITY?

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Background and aims of the study: Spontaneous cervical artery dissection (sCAD) is a major cause of acute ischemic stroke (AIS) in young and middle-aged adults, accounting for up to 25% of all cases. Concerning acute stroke treatment on sCAD patients, thrombolytic therapy has been shown to be safe and effective. However, data on mechanical thrombectomy (MT) in large vessel occlusion (LVO) are scant. For this reason, we decided to analyze safety and efficacy of MT in a series of sCAD patients and compare these results with data from our general stroke registry.

Materials and methods: Data on 375 consecutive patients who underwent MT for LVO AIS from January 2015 to June 2021 were analyzed. The following variables were obtained: baseline characteristics (demographic, clinical, neuroradiological, etiological and treatment variables), procedural characteristics, time intervals, recanalization rates, adverse events, and functional outcome.

Results and discussion: Out of 375 patients, 20 (5.3%) were diagnosed with sCAD. SCAD patients were younger ($p < 0.001$), showed lower rates of cardiovascular burden (hypertension, $p = 0.003$; diabetes mellitus, $p = 0.05$; cardiopathy, $p < 0.001$; dyslipidemia, $p = 0.04$; atrial fibrillation, $p < 0001$) and were less often on antithrombotic therapy at the time of stroke onset (antiplatelets, $p = 0.01$; anticoagulation $p = 0.05$). Tandem occlusions were more often detected in sCAD patients ($p < 0.001$), while there was a trend towards lower ASPECTS score in sCAD. Onset to admission time interval was shorter in dissected patients ($p = 0.004$), while endovascular treatment duration was longer as compared to the non-sCAD group ($p = 0.01$). While undergoing MT, general anesthesia was the method of choice in sCAD ($p < 0.001$) and intra-procedural antithrombotics were used more frequently ($p = 0.01$). MT-related adverse events and recanalization rates did not differ between the two groups. In unadjusted analysis, functional outcome was better in dissected patients (50% or more percentage improvement of NIHSS at discharge, $p = 0.01$; mRS at discharge, $p = 0.01$; mRS at 3 months, $p = 0.01$; mRS 0-2 at 3 months, 85.0% vs 62.0%, $p = 0.049$). As expected, after adjusting for possible confounders (age, cardiovascular risk factors and pre-stroke mRS) statistical significance was lost.

Conclusions: According to our study, although MT represents a procedural challenge, it constitutes a safe and effective treatment for sCAD patients with LVO stroke.

FROM TIME TO TISSUE IN THE ACUTE ISCHEMIC STROKE TREATMENT. TIME FROM ONSET VERSUS CT PERFUSION SELECTED PATIENTS IN A REAL-WORLD SETTING

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Background: The current guidelines for acute ischemic stroke management recommend intravenous thrombolysis (IVT) or endovascular treatment (EVT) on the basis of the temporal criterion (time from onset to treatment) or on the basis of specific CT perfusion criteria. The aim of our study is to evaluate the outcome and safety in a group of CT perfusion selected patients compared to onset time selected patients.

Methods: We included in the study a group of patients with stroke onset < 4.5 hours for systemic thrombolysis and < 6 hours for thrombectomy (Time selected group, TSG) and a group of CT perfusion selected patients with wake-up stroke, unknown onset and onset between 4.5 and 9 hours for IVT and between 6 and 24 h for EVT selected by CT perfusion criteria mismatch ratio: 1.2 for IVT and 1.8 for EVT (CT perfusion group, CTPG). The patients included in our study underwent IVT, EVT or both according with national guidelines.

Results: We included 51 patients in the time selected group (TSG) and 44 patients in the CT perfusion selected group (CTPG). No significant differences were detected between TSG and CPG regarding features at inclusion: mean age (74.68 vs 72.29), NIHSS score (12.86 vs 13.37) and pre-stroke mRS (0.45 vs 0.90). Stable mRS at discharge compared to pre-stroke mRS was detected in 37.3 % in TSG vs 19.0% in CTPG (p: 0.07). NIHSS improvement at 24 h was detected in 80.8 % in TSG vs 72.4% in CTPG (p:0.07), and NIHSS improvement at 7 days was detected in 86.3% in TSG vs 81.8 CTPG (p:0.5). However, mRS improvement, NIHSS improvement after treatment (at 24 h and 7 day) were significantly higher in TSG compared to CTPG (p:0.001). No significant difference was detected in sICH between TSG e CPG (p:0.4)

Conclusion: Our data support the use of CT perfusion criteria for the selection of patients in the treatment of acute ischemic stroke during the late therapeutic window. Further investigation and clinical trial are needed to investigate the possible role of CT perfusion in the early treatment window.

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CEREBRAL SMALL VESSEL DISEASE MARKERS ARE ASSOCIATED WITH LESS TISSUE SALVAGE IN ACUTE ISCHEMIC STROKE TREATED WITH INTRAVENOUS THROMBOLYSIS

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Introduction: Cerebral Small Vessel Disease (SVD) exerts modifications in cerebral tissue, but the consequences on acutely ischemic brain tissue have been poorly elucidated. We investigated the associations between SVD features and evolution of the ischemic tissue from ischemic core to final infarct in patients treated with intravenous thrombolysis.

Methods: On pre-treatment Magnetic Resonance scans of patients from an International anonymised dataset we rated number of pre-existing lacunes, white matter changes (WMCs), brain atrophy and global SVD burden. Two independent radiologists rated acute ischemic core and final infarct volumes. We investigated the association between SVD signs

and ischemic core, final infarct, infarct growth (IG) (final infarct-ischemic core) and relative tissue loss (rTL) [(final infarct-ischemic core)/ischemic core]. We used linear regression adjusted for main confounders to investigate independent associations.

Results: We included 165 patients, mean(±SD) age 69.5(±15.7) years, 74(45%) males. Mean (±SD) ischemic core volume was 25.48(±42.22) ml, final infarct volume was 52.06(±72.88) ml, rTL 7.22(±38.12). A total of 70 (42%) patients had large vessel occlusion, 18 (11%) had lacunar stroke, 16 (10%) had infratentorial stroke. Frequency of pre-existing SVD features was as follows: WMCs 79%, lacunes 37%, brain atrophy 78%. There were no differences in final infarct volumes between patients with or without SVD. In linear regression analysis WMCs and brain atrophy were associated with less rTL (β=-0.30; p=0.004; β=-0.31; p<0.001, respectively); lacunes and brain atrophy with less IG (β=-0.17; p=0.024; β=-0.27; p=0.004, respectively). We did not find associations with global SVD burden.

Conclusions: In stroke patients treated with intravenous thrombolysis, single SVD features were associated with fewer volume loss of ischemic tissue and infarct growth despite similar final infarct volumes, suggesting less salvageable tissue at time of administration of reperfusion therapy.

COGNITIVE PROFILE IN CEREBRAL AMYLOID ANGIOPATHY IN COMPARISON WITH HYPERTENSION-RELATED CEREBRAL SMALL VESSEL DISEASE

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Aims: Cerebral small vessel disease (cSVD) represents a cluster of vascular disorders with different pathological backgrounds. Hypertension-related cSVD and cerebral amyloid angiopathy (CAA) are the most common forms. CAA is increasingly recognized as a cause of cognitive impairment, but its cognitive profile needs to be further characterized. The present study aimed at comparing cognitive profile between CAA and hypertension-related cSVD patients, and at identifying factors associated with cognitive performance.

Material and Methods: The study population was composed of patients with CAA diagnosis (CAA) and patients with cognitive impairment and hypertensive cSVD (vMCI). All participants underwent an extensive clinical, neuropsychological, and neuroimaging protocol. Cognitive impairment was defined by the presence of ≥1 impaired neuropsychological test, and further classified according to MCI subtypes (amnestic/non-amnestic and single/multi-domain) and cognitive profiles (amnestic, dysexecutive, mixed).

Results: Thirty-two CAA patients (mean age 76±5.8 years) and thirty-nine vMCI patients (mean age 74.1±7.2 years) were included in the analyses. There were not significant differences between the CAA and vMCI groups for demographics, except for sex (males 47% vs 74% respectively, p=.018). Compared to vMCI patients, CAA ones presented a worse performance at MoCA (mean score 21.5±4.1 vs 17.6±5.4 respectively, p<.001) and at semantic fluency (mean score 35.2±6 vs 30.7±10.7 respectively, p=.023). The amnestic MCI subtype was more frequent in CAA patients compared to vMCI ones (68% vs 46% respectively, p=.087), while there were no differences for cognitive profiles. Univariate correlation analyses, conducted separately for CAA or vMCI patients, showed that the multi-domain MCI subtype was associated with a worse performance at MoCA (rpb=-.431, p=.036), immediate (rpb=-.544, p=.007) and delayed (rpb=-.549, p=.007) Rey Auditory Verbal Learning Test (RAVLT), and semantic fluency (rpb=-.430, p=.036) in CAA patients and with a worse performance at Symbol Digit Modalities Test (SDMT) (rpb=-.364, p=.023) and phonemic fluency (rpb=-.351, p=.029) in vMCI ones. In multivariate models, the presence of a multi-domain deficit was confirmed as the only factor associated with performance at immediate RAVLT (β=-.574, p=.032) in CAA group and with performance at SDMT (β=-.364, p=.023) and phonemic fluency (β=-.351, p=.029) in vMCI group.

Discussion: Our results confirmed the existence of two potentially distinct patterns of cognitive deficits in CAA or vMCI patients. Specifically, while the cognitive profile of vMCI patients was confirmed as mainly attentional/executive, CAA patients seem to have a more complex cognitive profile, characterized by a reduced global cognitive efficiency and a deficit in semantic memory.

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PINK TRIAGE

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Introduction: Our recent study showed higher rate of Paroxysmal Atrial Tachyarrhythmias (PAT: P preserved tachyarrhythmias, atrial fibrillation and flutter) and Non-Paroxysmal Atrial Fibrillation (NPAF) in females compared to males, admitted for Acute Cerebro-Vascular (ACV) events [1]. The aim of our study was to identify possible negative haemodynamic factors accounting for higher risk of ACV in females.

Materials and Methods: We recruited 83 Other Neuropsychiatric Diseases (OND), 92 Chronic Cerebrovascular Diseases (CCVD), 552 Acute Strokes (AS) patients. They were subgrouped in no-hysterectomized (A: 81 OND, 88 CCVD, 519 AS) and hysterectomized (B: 2 OND 2, 4 CCVD, 33 AS).

Results: Our preliminary results showed a rate of 9/33 (11%) PAT vs 1/33 (3%) NPAF in OND-A, 1/2 (50%) PAT in OND-B, 22/89 (25%) PAT vs 5/89 (6%) NPAF in CCVD-A, 1/4 (25%) PAT in CCVD-B, 90/519 (17%) PAT vs 94/519 (18%) NPAF in AS-A, 2/33 (6%) PAT vs 6/33 (18%) NPAF in AS-B. Clinical, haematological, urinary and echocardiographic data were not significantly different in A vs B.

Discussion: PAT may evolve to NPAF, especially if risk factors are present. The unexpected finding of similar rate of NPAF in no-hysterectomized vs hysterectomized AS patients suggest that atrial disarrangement may be related to concomitant conditions, as thyreopathies, constipation, diverticulosis, dysbiosis, inflammatory reactions, accounting for increased cerebro-cardio-vascular risk. Complications of conservative approach in gynaecological diseases are well known, as anemia. Those related to surgical choice are poorly considered, as bleeding, hormonal deficiencies and damage to pelvic autonomic nerves. The most appropriate care in emergency should be performed independently on body neglecting or camouflaging appearance and relational attitude, while any no-urgent treatment should be discussed with the patient, according to her preferences, expectations and beliefs. PAT, also in OND, highlights that haemodynamic factors may contribute to worst conditions, requiring careful management, which may be realized by pink triage and dedicated care.

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SEASONAL INCIDENCE OF ISCHEMIC STROKE IN A SICILIAN POPULATION RELATED TO HUB STROKE CENTER

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Aims: To describe the seasonal trend of Ischemic Stroke (IS) incidence in a Hub Stroke Center in Sicily where there is a characteristic Mediterranean climate.

Materials & Methods: We retrospectively collected data about patients who were admitted to the Stroke Unit (SU) of Policlinic G. Martino in Messina for Ischemic Stroke (IS) between January 2015 and December 2021. Messina Hub Stroke Center admits patients from territory of province of Messina (626.876 inhabitants). The diagnosis of IS was confirmed by neuroimaging (brain CT or MRI).

Results: We included 2265 patients, 1141 (50,3%) females, admitted in SU. The range of age was between 16 and 103 years. The average of hospitalization for years was 189 (range: 161-215) for IS. The highest number of IS ever was recorded in December 2019 (n=45). The lowest was in March 2015 (n=14) and February 2016 (n=14). During the entire period of observation, the highest rate of IS for years was observed in July 2015 (n=33), January 2016 (n=32), June 2017 (n=34), December 2018 (n=36), December 2019 (n=45), October 2020 (n=41), and May 2021(n=40). The lowest was in March 2015 (n=14), February 2016 (n=14), September 2017 (n=19), July 2018 (n=20), June 2019 (n=19), April 2020 (n=18) and November 2021 (n=20).

Discussion: Many studies describe hypothetical associations between seasonal effect and incidence of cerebrovascular disease including IS and ICH [1]. However, even if most studies have reported a peak of IS incidence in colder months of winter and springs, others describe opposite data [2]. These differences could be due to the different microclimate including temperature, humidity and atmospheric pressure which can have an impact on blood pressure regulation mechanisms and consequently on the vascular risk [3].

Conclusions: Our study does not indicate seasonal differences in terms of IS incidence and no peaks have been observed in 7 years. However, IS data reflecting the reality of a population living in an island with a characteristic microclimate and it could be useful for new comprehensive analyzes including patients with transient ischemic attack.

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PREDICTORS OF MOBILITY IMPAIRMENT IN ELDERLY PATIENTS WITH ATRIAL FIBRILLATION: STRAT-AF STUDY

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Aims: Atrial Fibrillation (AF) presents significant associations with many other comorbidities. Our aim was to evaluate in elderly AF subjects' longitudinal determinants and predictors of motor impairment.

Materials and Methods: The Strat-AF study (Stratification of cerebral bleeding risk in AF) is an observational, prospective study, conducted in 2017-2020 on AF patients ≥65 years referring to Thrombosis Center of Careggi University Hospital. All participants underwent clinical visit and brain MRI at baseline and after 18-months. Mobility assessment included Short Physical Performance Battery (SPPB) and falls in last year.

Results: 194 patients (mean age 78.1±6.7 years) were enrolled, 133 completed follow-up. Mean SPPB score (9.4±2.1 at baseline and 9.5 ±2.2 at follow-up) was abnormal (<=10) in 124 (64%) patients at baseline and 80 (60%) at follow up. Sixty-nine (36%) patients reported ≥1 fall during previous year. Baseline characteristics associated with SPPB score (correlation analyses, r and p values for baseline and follow-up respectively) included: higher thromboembolic risk (r=-.292, p=001; r=-.367, p=001), lower global cognitive efficiency (r=.319, p=001; r=.267, p=002), higher depressive symptoms (r=-.185, p=010; r=-.237, p=006), and worse functional performance (basic preserved (r=.316, p=001; r=.377, p=001) and instrumental lost (r=-.386, p=001; r=-.425, p=001) ADL). Many of these factors were also associated with history of falls. Among neuroimaging variables, non-lacunar infarcts (r=-.153, p=.047; r=-.177, p=.049) and severe medial temporal lobe atrophy (r=-.157, p=.042) were associated with SPPB scores.

Discussion: In our cohort, motor impairment and history of falls were frequent findings, resulting associated with many clinical factors, including cognitive performance. Both vascular and neurodegenerative lesions seem to influence mobility.

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ACUTE STROKE-LIKE DEFICITS ASSOCIATED WITH NONKETOTIC HYPERGLYCEMIC HYPEROSMOLAR STATE: AN ILLUSTRATIVE CASE AND SYSTEMATIC REVIEW OF LITERATURE

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Introduction: Nonketotic hyperglycemic hyperosmolar state (NKHHS) is associated with a wide spectrum of neurological syndromes [1] including acute neurological deficits. [2] Clinical features and etiology have not been established yet.

Methods: Here we provide a case illustration and systematic review on non epileptic focal deficits in NKHSS. The systematic literature search followed PRISMA guidelines and a predefined protocol, including cases of NKHSS with acute neurological deficits.

Results: The database search yielded 18 cases. Hemianopia was the most common clinical presentation (73%), followed by partial or total anterior circulation syndrome (26%). Patients with symptoms of acute anterior circulation infarct were significantly older (69.5 ± 5.1 vs. 52.2 ± 13.9 years; p=0.03) and showed higher mean glucose levels at the admission vs. those with hemianopia (674.8 ± 197.2 vs. 529.4 ± 190.8 mg/dL; p=0.16). Brain MRI was performed in 89% of patients, resulting abnormal in 71% of them, especially hemianopic (91%). Subcortical hypointensities in T2-FLAIR MR sequences were present in all the analyzed cases. Cortical DWI hyperintensities were also common (64%). EEG showed diffuse or focal slow waves activity in 68% of patients, especially with visual hallucinations (85%). Neurological symptoms completely resolved in 78% of patients within 6 (IQR 3 – 10) days, following aggressive treatment and glucose normalization.

Conclusions: Our results suggest neuronal dysfunction on a metabolic basis as the leading cause of non epileptic acute deficits in NKHHS. Despite the generally favourable prognosis, prompt identification and aggressive treatment are crucial to avoid irreversible damage. Larger cohort studies are needed to confirm our findings.

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CAPSULAR WARNING SYNDROME: FEATURES, RISK PROFILE AND PROGNOSIS IN A LARGE PROSPECTIVE TIA COHORT

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Introduction: Features and prognosis of capsular warning syndrome (CWS) have been poorly investigated prospectively.

Aims: To characterize CWS clinical features, risk profile, short- and long-term prognosis, among a large TIA cohort.

Methods: Prospective cohort study of consecutive TIAs from 1/8/2010 to 31/12/2017. Demographic and clinical characteristics, risk profile, primary (stroke and composite outcome) and secondary (TIA recurrence, cerebral hemorrhage, new onset atrial fibrillation) outcomes were compared between CWS, lacunar (L) and non-lacunar (NL) TIAs.

Results: 1035 patients (33 CWS, 189 L-TIAs, 813 NL-TIAs). Newly diagnosed (ND) hypertension, hypercholesterolemia, cigarette smoking and leukoaraiosis were independent risk factors of CWS ($p<0.05$). CWS showed the highest stroke (30.3% vs. 0.5% and 1.5% for L-TIAs and NL-TIAs, respectively) and composite outcome risk at follow-up ($p<0.001$), but better 3-month post-stroke prognosis (mRS 0-2 90.0%vs. 36.8%; p=0.002). CWS related-stroke mostly occurred <48 hours (80.0%) and had a small-vessel occlusion etiology (100%), affecting more often the internal capsule (60.0%). Dual (DAPT) vs. single antiplatelet therapy was associated with lower 3-month cumulative stroke incidence (12.5% vs. 57.1%; p=0.010). Intravenous thrombolysis (IVT) showed similar 3-month efficacy and safety in strokes after TIAs groups (median mRS 0, IQR 0-1; p=0.323).

Conclusions: CWS is associated with higher stroke risk and better functional prognosis than lacunar and non-lacunar TIAs. CWS risk profile is consistent with severe small vessel disease and ND hypertension could represent a major risk factor. DAPT and IVT seem effective and safe in preventing and treating stroke following CWS.

THE PRESTO STUDY: A PUBLIC AWARENESS CAMPAIGN FOR RAPID RECOGNITION OF STROKE SYMPTOMS

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Background: The best medical treatments of ischemic stroke are rapid admission to a stroke unit, intravenous thrombolysis and thrombectomy. The time from symptoms onset to medical intervention is the best predictor of the clinical outcome. Thus, rapid recognition of stroke symptoms is the first step to achieving timely access to medical assistance. All over the world, many educational campaigns have been organized with the purpose of informing people about what a stroke is and what is necessary to do after clinical onset.

Material and Methods: The PRESTO campaign was organized in Genoa to spread easy and clear messages about the management of the acute phase of a stroke. Educational material (leaflets, videos, radio messages, newspaper articles, social media messages, etc.) was diffused to educate people to call emergency medical services (EMS) as soon as stroke symptoms appear. In the PRESTO study, were enrolled patients with ischemic stroke who accessed hospital within 24 hours after symptoms onset. The data collected from the three main city hospitals (E.O. Ospedali Galliera, Policlinico San Martino and Ospedale Villa Scassi) were: epidemiological characteristics of the patients, time from onset of symptoms to hospital admission. The study was divided into three phases: pre-PRESTO campaign (from February 2018 to May 2018), during (from June 2018 to January 2019) and post-campaign (from February 2019 to May 2019).

Results: We enrolled 1,132 patients: 235 (20,8%) in the "pre" phase, 563 (49.7%) in the "during" phase, and 334 (29.5%) in the "post" phase. Our data showed a mild reduction in onset-to-door time (24 minutes) during the months following the end of the campaign and a slight increase in number of patients who arrived at hospitals, in particular with milder symptoms and transient ischemic attack, as opposed to the same period before the campaign. In the months after the end of the campaign, we observed a slight reduction of the percentage of patients who accessed hospitals after 4.5 hours from symptoms onset. There was no difference in the way of arrival to hospital; indeed, the majority of patients called EMS in all the three periods of observation (78.7% before, 77.6% during, and 78.1% after the campaign).

Conclusions: Our results may suggest that an informative campaign can be successful in making people rapidly aware of stroke onset, with the consequent rapid access to hospital. Therefore, we believe that further effort must be made to improve informative campaigns targeted on the at-risk population.

CEREBRAL VENOUS THROMBOSIS DURING SARS-COV-2 INFECTION

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Background, purpose: The SARS-COV-2 infection seems to trigger a pro-thrombotic state with the involvement of both venous and arterial vessels. When it causes cerebral venous thrombosis (CVT), in-hospital mortality is very high (about 40%). Several authors have tried to explain how the SARS-COV-2 infection could determine the CVT and which therapeutic approach could be the most appropriate. Herein, we report two CVT cases with concomitant SARS-COV-2 infection.

Methods, materials: Two patients were admitted to our hospital between February and March 2022, presenting with CVT and a positive nasal swab test for SARS-COV-2. We describe the clinical, laboratory and radiological features, and the related therapeutic aspects.

Results: Patient 1 was a 57-years-old female presenting with right upper limb weakness, expressive dysphasia and a confusional state. Patient 2 was a 38-years-old male complaining of headache, left upper limb weakness and subsequently a status epilepticus. Both patients were previously vaccinated against SARS-COV-2. The cerebral MRIs highlighted the involvement of multiple venous sinuses and cortical and deep venous vessels. The laboratory tests showed elevated D-dimer and inflammatory indexes. Both patients were treated with low-weight molecular heparin (LWMH). Patient 2 also underwent venous mechanical thrombectomy (MT), then was admitted to the intensive care unit because of the worsening neurological condition. In both cases, the patients finally improved and were discharged respectively 17 and 30 days after admission.

Discussion: To our knowledge, more than 50 cases of CVT related to SARS-COV-2 infection have been reported. Among them, only three patients underwent MT and two of them died respectively 1 and 6 days after surgery. Several factors have been proposed to explain the pathogenesis of CVT. When we examined the possible causes of CVT in our two patients, we excluded platelet dysfunction, coagulation alteration, or the presence of anti-phospholipid antibodies. Compared with the CVTs due to the SARS-COV-2 vaccine, the herein described CVTs show some different laboratory, radiological and therapeutic elements, similarly to other SARS-COV-2 infection-related CVTs reported in the literature. The European guidelines for the management of CVT suggest the use of LWMH as the main therapeutic approach, whereas MT has controversial indications. However, the herein reported patients survived after treatment with LWMH or MT.

Conclusion: CVT could be a life-threatening disease and patients with SARS-COV-2 infection are particularly exposed to this risk. According to our patients' outcomes, it is reasonable to suggest that in patients with severe CVT, clinicians should also consider the endovascular approach.

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ACUTE PSEUDOBULBAR PALSY IN A PATIENT WITH COVID-19 AND UNKNOWN CADASIL

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Objective: To describe a case of multiple acute cerebral infarcts precipitated by COVID-19 in unknown CADASIL.

Material, Method and Result: A 32 years old man presented with acute mild dysphagia and dysarthria on wake up; he had a prodrome 4-5 days earlier of fever and throat pain. A nasal swap was positive for COVID-19 and at first his symptoms were referred to pharyngolaringitis. His past medical history was unremarkable. As a personal choice he didn't receive COVID-19 vaccine. On day 2 he suddenly became anartric with severe dysphagia and a neurologist was consulted. On examination the patient was alert and walking but unable to talk, to close his jaw or handle his secretions, arms and legs had normal strenght, meningism was absent. Urgent CT brain scan was performed to find out the etiology of the acute pseudobulbar palsy and showed white matter hypoattenation within both corona radiata. ADEM was the first suspicion, CSF examination was normal and negative for viral PCR; e.v. metilprednisolone was started. On day 3 a brain MRI was obtained and demonstrated multiple acute infarcts bilaterally within an internal border zone distribution; steroid was stopped and antiaggregation introduced. Only on day 5 his mother revealed a genetic confirmed asymptomatic CADASIL (c.397C>T); genetic analysis confirmed the same patogenetic variant in his son; screening for other causes of stroke in young was performed and negative. He was fed through nasogastric tube for 2 weeks, then he slowly improved. On day 21 he was discharged with persistent moderate dysartria whilst dysphagia and jaw drop resolved.

Discussion: Inflammatory, demyelinating and stroke are possible etiologies of acute pseudobulbar palsy. Few cases of COVID-related acute stroke in CADASIL patients are described in literature. Proposed mechanisms are endothelial injury with microvascular thrombosis and cerebral dysautoregulation. Patients with CADASIL should be considered a vulnerable group during the pandemic.

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OUTCOME AND MORTALITY IN PATIENTS WITH HEART FAILURE AND ISCHEMIC STROKE TREATED WITH MECHANICAL THROMBECTOMY: AN ANALYSIS OF THE ITALIAN REGISTRY OF ENDOVASCULAR TREATMENT IN ACUTE STROKE (IRETAS)

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Aims: Heart Failure (HF) is the second most important risk factor for stroke after atrial fibrillation (AF). Few data are available on mechanical thrombectomy (MT) in acute ischemic stroke (AIS) patients with HF.

Materials: The source of data is the multicenter Italian Registry of Endovascular Treatment in Acute Stroke (IRETAS).

Methods: All patients≥ 18years with AIS treated with MT from 2011 to 2019 were categorised in two groups according to the presence/absence of HF. Baseline clinical and neuroradiological findings on admission were analysed. Left Ventricular Ejection Fraction (LVEF)for HF patients was calculated through transthoracic echocardiography (TTE).

Results: Of 8924 patients, 642(7.2%) had HF. Compared to the no-HF group, HF patients were older and had higher prevalence of cardiovascular risk factors. 219 (34.1%) of HF patients and 4052(48.9%) of no-HF patients received combined treatment (MT plus intravenous thrombolysis). The rates of complete recanalization (TICI 2b-3) was comparable between HF and no-HF group (76.9% versus 78.1% respectively, p=0.481). Good clinical response to MT was similar in HF (46.6%) and no-HF (50.5%) patients(p=0.084). No difference in terms of symptomatic intracerebral hemorrhage at 24-hours CT between the two groups (7.6% vs 8.3%, respectively, p=0.520). At 3 months, a 0-2 mRS was present in 36.4% of HF patients and 48.2% of no-HF patients (p <0.001) and mortality was higher in HF group (30.7% versus 18.5%, respectively, p <0.001). Quantitative LVEF data were available for 364(56.69%) of 642 HF patients. No statistically significant differences were found among LVEF groups in terms of 90-days good outcome or mortality. General anaesthesia(GA) was associated with a good outcome(mRS 0-2) in only 32.2%, versus 41.0% of no-GA group(p=0.034). In multivariate logistic regression HF was independently associated with mortality at 3 months (OR 1.53, 1.24-1.88 95% CI, p<0.001). In multivariate ordinal regression, HF patients had a probability of transitioning to a higher mRS level of 1.23 (1.05-1.44 95% CI, p= 0.012). The propensity score analysis of two groups matched for age, sex and NIHSS at admission, yielded the same results.

Discussion: This is the largest real-word cohort of unselected AIS patients with HF who underwent to MT. The relationship between unfavourable 3-months functional outcome and HF in our cohort may not be related to acute reperfusive stroke therapies, but to several intrinsic HF-related mechanisms and characteristics leading to long term complications in HF patients.

Conclusion: MT is safe and efficacy in HF patients with AIS. Patients with HF and AIS suffered from higher 3-months mortality and unfavourable outcome regardless of acute treatments

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STROKE CHAMELEON: ABDOMINAL PAIN AND VOMITING DUE TO VERTEBRAL ARTERY DISSECTION

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Background and Aims: Intractable nausea and vomiting is a commonly encountered problem in any general medicine or gastroenterology service. Several causes from infection to chronic medical conditions can

be listed. Rarely, also neurological causes can induce this clinical pattern when brainstem is involved [1], for instance in stroke by occlusions of the anterior spinal artery or small vessel branches of the vertebral artery [2].

Methods: A 46-year-old male had a sudden onset of cold sweating and syncope, with subsequent appearance of headache, dizziness, vomiting and severe abdominal pain. Laboratory tests didn't show significant pathological findings suggesting inflammation. Abdominal investigation didn't show gastrointestinal anomalies. A non-contrast CT of the brain was normal and he was subsequently admitted for the management of dehydration, secondary to suspected gastroenteritis.

Results: Nausea, vomiting and headache improved shortly after admission and the next day the patient developed right Bernard-Horner syndrome. So extracranial duplex sonography was performed with evidence of right vertebral artery dissection (VAD), confirmed by TC-Angiography. Furthermore, patient reported also repeated cervical stress (carrying heavy leather on the shoulder and pruning of olive trees). Brain MRI pointed out restricted diffusion small lesions in right cerebellar hemisphere and dorsolateral region of bulb, including visceral sensitive afferents and tractus solitarius nucleus. Therefore patient started high-dose acetylsalicylic acid, prophylactic enoxaparin and atorvastatin 80 mg. An extensive hypercoagulability workup was initiated, which included protein C, protein S, antithrombin III, factor V Leiden, prothrombin, anticardiolipin and beta-2-glycoprotein without pathological findings. The patient improved clinically and neurological evaluation was normal at discharged. He performed a six-months follow up MRI-angiography which still showed occlusion of intra and extracranial right vertebral artery, without wall hematoma or pseudoaneurysm.

Conclusions: VAD is a rare cause of stroke, with an estimated annual incidence of 1 per 100,000 individuals. Events most commonly occur in young individuals who typically present nonspecific symptoms such as vertigo, headache, and neck pain. VAD is classically associated with trauma or connective tissue disorders. However, one recent meta-analysis demonstrated that nearly 50% of cases occur in the absence of such risk factors [2]. Anyway, recognizing that intractable nausea and vomiting may be attributable to stroke is valuable in mitigating extraneous and ineffective medical management and direct the right diagnostic and therapeutic process [3].

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COVID-19-ASSCOIATED STROKE: A CASE-CONTROL STUDY

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Objectives: To assess whether COVID-19 could be a concurrent factor in the genesis and/or worsening of stroke and to provide data on COVID-19–associated stroke patients during the first pandemic wave and comparative data on COVID-19 negative stroke patients in the same period.

Materials and Methods: This is a retrospective, observational, case-control, single centre study, carried out in a General Hospital in Northern Italy. Sixty-three consecutive stroke patients were included, COVID-19-associated stroke was classified as cases and non COVID-19-associated stroke as controls.

Results: A total of 19/63 (28.8%) had a COVID-19-associated stroke, 11 /63 (17.5%) were haemorrhagic and 52/63 (82.5%) ischaemic. The average age of our study group was 76.05 +/- 8.8 for cases and 73.2 +/- 12.61 for controls (p-value n.s.). There was no statistically significant difference between cases and controls for haemorrhagic stroke frequency (10.5% and 20.5% respectively, p-value n.s.), rtPA treatment (15.5% and 20.5% respectively, p-value n.s.), in-hospital mortality (15.8% and 6.8% respectively, p-value n.s.) or stroke etiologies, such as large vessel disease (21.1% and 11.4% respectively, p-value n.s.). Cases had a higher: median NIHSS (9, IQR 4-15 versus 4, IQR 2-8, p-value 0.019), risk of death or serious disability (mRS 4-5) (OR 3.79, CI 95%: 1.21-11.93, p-value 0.19), median LDH value (314, IQR 203-504 versus 232, IQR 194-271, p-value < 0.001), median D-dimer level (6600, IQR 1448.8-27068 versus 839-5, IQR 324.5-1235.8, p-value 0.001). A multivariate logistic regression analysis confirmed an association only for the LDH level (p-value 0.003). The COVID-19-associated stroke patients with onset during hospitalization for COVID-19 had a more severe stroke than patients with COVID-19 onset during hospitalization for stroke (p-value 0.019).

Discussion: In literature, COVID-associated stroke had a higher rate of large vessel occlusion, a lower rate of small vessel disease and lacunar stroke, atypical stroke presentation, multi-territory involvement, stroke in territory of distribution of uncommonly affected vessels and a worse outcome [1]. A proinflammatory-prothrombotic state, CIC and endothelial injury, associated with SARS-CoV-2 infection, also supports the hypothesis of COVID-19-associated stroke [2]. We observed an excess of large-artery disease in cases (20.5%), compared to controls (10.4%), furthermore stroke with onset during hospitalization for SARS-CoV-2 infection seems to lead to a particularly severe disability.

Conclusion: Although no relationship was observed between the stroke aetiology and COVID-19, intriguingly, COVID-associated stroke turned out to be more severe and disabling. Hopefully, further studies will provide more data and help in the management of this emerging population.

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HYPERDENSE MIDDLE CEREBRAL ARTERY SIGN AS A PREDICTOR OF GOOD OUTCOME AFTER MECHANICAL THROMBECTOMY: A RETROSPECTIVE STUDY

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Objectives: This study aimed to evaluate prognostic implications of the HMCAS on treatment outcomes after MT for acute MCA occlusions.

Materials: We conducted a single-center retrospective observational study of 191 consecutive patients presenting with acute MCA occlusions

who underwent MT at Udine University Hospital from June 2015 to August 2021.

Methods: Patients were stratified into two groups based on the presence of HMCAS visually assessed on CT by a board-certified neuroradiologist. The outcomes of interests were presence of symptomatic intracranial hemorrhage, major neurological improvement at discharge (improvement of 8 points on the NIHSS from baseline or a NIHSS score of 0 or 1 at discharge), in-hospital mortality and 3-months-good-outcome measured by the ordinal Modified Rankin (mRS).

Results: Of 191 patients, presence of HMCAS was identified in 140 patients (73.3%). There was no significant difference between the two groups in age, baseline mRS, NIHSS, and time to reperfusion. The presence of HMCAS was related with lower rate of symptomatic intracranial hemorrhage (OR:0.14, CI:0.04-0.48, p = 0.002) and in-hospital mortality (OR 0.36, CI: 0.14-0,91, p=0,03). Moreover, HMCAS was associated with 3 months-good-outcome (OR 2.3, CI: 1.1-4.6, p = 0.02) and major neurological improvement at discharge (OR 2.68, CI: 1,36-5,30, p=0,004) after adjusting for other significant predictors, including age, anamnestic mRS and NIHSS at the time of admission.

Discussion: Hyperdense middle cerebral artery sign (HMCAS) on non-contrast head computed tomography (CT) scan is one of the early ischemic radiological findings in patients with acute MCA occlusion. HMCAS represents an intraluminal clot from a thrombus or an embolus, which contains an accumulation of components of the blood system, including platelets, cellular debris, fibrin, and erythrocytes. The prognostic value of the CT hyperdense artery sign has yet to be defined in the setting of mechanical thrombectomy (MT). Recent studies have deemed HMCAS as an indicator of good prognosis while other researchers have not found a significantly association with the outcome [1-3].

Conclusions: Our results show that HMCAS is associated with better outcome in patients presenting with MCA occlusions undergoing MT. These patients are also more likely to have rapid neurological recovery than those without the sign. Whether this result is due to the underlying etiologies responsible for the composition of the intraluminal clot, remains to be investigated.

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PROPRANOLOL FOR THE TREATMENT OF FAMILIAL CAVERNOUS MALFORMATIONS: THE TREAT_CCM STUDY

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Objectives: Propranolol was found effective in cutaneous haemangiomas and reported as beneficial for the treatment of cerebral cavernous malformations (CCM) not suitable for surgery. Our aim was to evaluate the safety and efficacy of propranolol in familial CCM (FCCM).

Methods: Treat_CCM was a randomized, open-label, phase 2 multicentre trial. Patients were randomly assigned centrally (2:1) to receive either propranolol 20-320 mg daily or standard care for 24 months. Follow-up with clinical evaluation and 3T brain MRI was performed at baseline, 12 and 24 months. The primary outcome was new occurrence of symptomatic intra-cerebral haemorrhage (ICH) or focal neurological deficit (FND) attributable to CCM. Analyses for safety and primary endpoints were performed in the intention-to-treat population. Treat_CCM was registered with EudraCT (2017-003595-30, 21/02/2018) and ClinicalTrials.gov (NCT03589014, 17/07/2018).

Results: 83 patients were enrolled between April 2018 and November 2019: 57 patients were assigned to receive propranolol and 26 standard care. Mean age was 46±15 years and 57.8% were women. All participants but one presented symptomatic CCM. Based on baseline MRI and genetic testing, 12 patients were not confirmed as FCCM. Propranolol was safe, without excess of hospitalizations, and well tolerated, 3 patients discontinued for self-reported fatigue. Four patients experienced primary endpoint events. The incidence rate per 100 person-years was 1.7[1.4-2.0] in the propranolol group and 3.9[3.1-4.7] in standard care. Patients assigned to propranolol showed a non-significant reduction in the occurrence of ≥5 or ≥10 de-novo lesions, however, no effect on lesions' size was observed. This trial was not powered to assess differences in efficacy outcomes between groups.

Conclusion: Propranolol was safe and well tolerated. The direction and magnitude of the effects of propranolol on clinical and imaging outcomes, which were not statistically significant, justify definitive main phase 3 trials.

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EXPLAINED AND UNEXPLAINED EARLY NEUROLOGICAL DETERIORATION AFTER REPERFUSION THERAPY FOR LARGE VESSEL OCCLUSION STROKE

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Early neurological deterioration (END) after ischemic stroke is a relevant clinical issue that could be related to worse outcome. END could be due

to explained (exEND) or unexplained (unEND) causes. We aimed to evaluate the incidence and outcome of END, exEND and unEND in stroke patients with large vessel occlusion (LVO) who underwent thrombolysis and/or thrombectomy. Also, relation with recanalization was explored. We retrospectively collected data from 134 eligible patients admitted to our department from January 2019 to December 2020 with ischemic stroke and LVO of the anterior circulation. All patients underwent reperfusion therapy. END was defined as NIHSS worsening ≥4 points 24 hours after ischemic stroke; it was considered to be "explained" (exEND) if epileptic crisis, early recurrent ischemic stroke, PH2 hemorrhage or severe cerebral edema developed 24 hours after the ischemic reperfusion treatment. Otherwise, it was considered to be "unexplained" (unEND). Two measures of poor 3-month outcome were considered: a) modified Rankin Scale (mRS) score ≥ 3; b) mRS shift from baseline (mRS>1 if baseline mRS 0-2 and mRS shift ≥1 if baseline mRS≥3). Recanalization was judged to be satisfying in the case of mTICI≥2b and/or TIBI≥4. Eighteen patients (13,4%) developed END (7 exEND and 11 unEND). A satisfying recanalization was achieved in 4 patients with exEND and in 3 patients with unEND. None of the patients who developed END had favorable outcome three months after the ischemic stroke considering both measures of poor 3-month outcome. There was a significant high rate of unsatisfactory recanalization in patients with END compared to patients without END (p = 0.00013). Not significant difference between exEND and unEND patients was found in terms of satisfying recanalization using a Fisher's exact test (p = 0.33). In conclusion, the observed incidence of END is similar to what has been reported in literature. Our population sample confirms that END is associated with poor outcome after stroke, regardless of whether it was "explained" or "unexplained". The first 24 hours after a stroke have significant prognostic value and require careful patient monitoring. Why some patients develop exEND or unEND is not understood, even in the case of satisfying recanalization. This may be due to other neurological issues currently not properly evaluated, such as the patency of microcirculation. Further studies are needed to clarify the factors causing early neurological deterioration.

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PREDICTIVE FACTORS OF EARLY NEUROLOGICAL DETERIORATION AND POOR OUTCOME AFTER ACUTE ISCHEMIC STROKE TREATMENT

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Early neurological deterioration (END) after acute stroke treatment is associated with poor outcomes. We aimed to evaluate predictive factors of END in stroke patients who underwent thrombolysis and/or thrombectomy for large vessel occlusion of the anterior circulation. We retrospectively collected common clinical and laboratory data about the pre-treatment period, the treatment itself, and the 24 hours post-treatment of 134 eligible patients admitted to our department from January 2019 to December 2020. END was defined as NIHSS worsening ≥4 points 24 hours after ischemic stroke. To assess the clinical outcome as favorable or poor, we considered the three-month mRS itself and its shift from baseline (favorable if baseline mRS 0-2 and three-month mRS<2 or if baseline mRS≥3 and three-month mRS shift ≤1). Recanalization was judged to be satisfying in the case of mTICI≥2b and/or TIBI≥4. If the clinical and laboratory variables were found to be significant (p<0,05) in the binary univariate logistic regression, they were included in backward binary multivariate logistic regression models to identify independent predictors of END and poor outcome in the whole sample and in patients with and without satisfying recanalization. The best cut-off for continuous variables was estimated using ROC curves and Youden's index. 18 patients (13,4%) developed END and 65 (48,5%) had poor outcome after three months. Mean systolic blood pressure >153 mmHg in the 24-hours after treatment was an independent predictor of neurological deterioration in the whole sample and among patients without satisfying recanalization. High leukocyte count (>13335/mm3), high neutrophil/lymphocyte ratio (>5,29) and low platelet/neutrophil ratio (<0,026) measured within 24-hours after treatment were independent predictors of END and poor outcome considering the whole sample and among patients with satisfying recanalization. S100B >0,24 ug/L measured within 24-hours after treatment strongly predicted poor outcome despite satisfying recanalization. Previous antiplatelet treatment was an independent predictor of END when a satisfying recanalization was not achieved. Apart from previous antiplatelet treatment, no clinical or laboratory parameters of the pre-treatment period were an independent predictor of END or poor outcome. In conclusion common clinical and laboratory parameters may help predict END and poor outcome. Our results strengthen the widely accepted notion that the first 24 hours after acute stroke treatment may be crucial in determining clinical outcomes in the short and long term.

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FIBROMUSCULAR DYSPLASIA, MULTIVASCULAR DISSECTION AND NEUROLOGIC MANIFESTATIONS: A CASE REPORT

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Background: Fibromuscular Dysplasia (cFMD) is an idiopathic disease involving the wall of medium-caliber arteries. It is associated, especially in young woman, with spontaneous vascular dissection, severe stenosis or intracranial aneurysm, ischemic stroke and subarachnoid hemorrhage. We propose a peculiar case of cFMD in a patient presenting with headache to share our experience and highlight the mounting complexity of the diagnostic and therapeutic process.

Materials: Brain computed tomography (CT), supra-aortic trunks echocolordoppler, thoracic, supra-aortic, abdomen and coronary CT-angiography (CTA), neck MRI-angiography (MRA), diagnostic angiography and genetic analysis were performed.

Methods: We report the case of a 39 year-old woman, with a history of pre-eclampsia, premature birth, diastolic hypertension and smoking, admitted to the Emergency Department due to general malaise, nausea and pulsating hemispheric and retroauricolar headache, radiating to the right side of the neck and exacerbated by the Valslava maneuver. She was discharged with diagnosis of virosis due to the finding of neuthrofilic leucocytosis in laboratory tests. She returned to hospital 24 hours later due to persistence of symptoms.

Results: Brain CT was negative. Supra-aortic trunk echocolordoppler showed soft bilateral plaques in the carotid bulb and mild circumferential myointimal thickening of the right subclavian artery. CTA showed a non-stenotic sleeve of solid tissue surrounding the subclavian artery and the origin of the right vertebral artery; diagnostic angiography confirmed dissection of the right vertebral artery in the V2 tract. Neck MRA revealed a right subclavian wall hematoma and abdomen CTA also showed a right superior mesenteric wall hematoma. Coronary CTA was normal.

Discussion: The diagnostic work-up revealed a multivasal cFMD, involving the right subclavian, vertebral and mesenteric arteries. The involvement of the mesentric artery is infrequent and a multivascular desease is rare. In agreement with literature, percutaneous angiography, with or without stenting, is the best therapeutic approach in patients with cFMD, recurrent symptoms and severe hemodynamic involvement. In our case, endovascular procedure had only a diagnostic value. The patient complained only of headache and was well responsive to symptomatic therapy with paracetamol. With respect to secondary prevention, we started double anti-platelet therapy (ASA 100 mg and clopidogrel 75 mg) and required a genetic examination.

Conclusions: In light of our experience, we think that the integration between clinical-instrumental data and the use of endovascular procedures represents the best diagnostic and therapeutical approach. Prevention of complications depends on the use of antiplatelet and anticoagulant agents.

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POTENTIAL EMBOLIC SOURCES IN PATIENTS WITH EMBOLIC STROKE OF UNDETERMINED SOURCE: A RETROSPECTIVE ANALYSIS

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Objectives: Embolic Stroke of Undetermined Source (ESUS) identifies nonlacunar ischemic strokes whose source of embolism remains unknown despite adequate diagnostic workup, according to ESUS International Working Group definition. A recent study suggests that follow up can reveal potential embolic sources (PES) covert during acute phase.

Materials: We retrospectively collected data about patients discharged from our Stroke Unit as ESUS from 2016 to 2021.

Methods: We investigate new medical findings occurred after discharge and suggestive of PES such as atrial fibrillation (AF), atrial cardiopathy, myocardial infarction, patent foramen ovale (PFO) and new diagnosis of cancer.

Results: We collected 90 patients of whom 46 were men (51%) and median age at time of event was 70 years old (IQR 55 – 78). Acute ischemic stroke was the most common clinical picture (88 pts, 97%), while transitory ischemic attack was the index event in only three patients (3%). Median NIHSS score at onset was 3 (IQR 1.25-6) and median mRS at 90 days was 0.5 (IQR 0 - 2). Median time from discharge to follow-up was 15 months (IQR 7-34). Thirteen patients referred loop recorder implantation of whom 8 revealed AF after a mean time of 1 month. Twenty patients had PFO, 6 atrial cardiopathy, 5 left ventricular dysfunction, 2 cardiac valvulopathy, 3 patients discovered neoplastic lesions and 2 thrombophilic disorders. Forty patients remain unknown for any PES.

Discussion: Our data showed result similar to the literature, regarding sex prevalence of ESUS and good recovery at 90 days. We did not find any PES in 44% of patients although wide time of follow-up (median 535 days). 43% of patients had at least one, whereas 5% of patients had at least two PES; only 2.2% of patients had four PES. PFO was the most prevalent PES among younger patients (median age of 49, IQR 38-55) while new-onset AF and atrial cardiopathy were more prevalent on older (median age 74, IQR 66 -79). About one third of patients with loop recorder discovered occult AF confirming its diagnostic value.

Conclusion: PFO is an important cause of ESUS in younger patients. Covert AF is also a frequent PES especially in patients older than 60 years. ESUS diagnostic work-up remain a challenge, suggesting that additional effort could be important, and, in our experience, a selection criterion based on age could be useful to direct further investigation.

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META-ANALYSIS OF THE EFFICACY/EFFECTIVENESS AND SAFETY OF REPERFUSION/RECANALIZATION TREATMENTS IN YOUNG PATIENTS WITH ACUTE ISCHEMIC STROKE: COULD STROKE VOLUME THRESHOLDS AND TIME INTERVALS BE RELATED AND ADJUSTED TO PATIENT AGE CLASS?

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Background and Objectives: Stroke in young people has a major socio-economic impact. Since young stroke patients have longer expected survival than older patients, effective acute treatment may produce substantial more quality-weighted life-years in young stroke victims. In general, guidelines on IV thrombolysis (IVT) and endovascular treatment (EVT) for the young are the same as those for the old patients. Indeed, there are no specific recommendations on young patients. The subgroup analyses by age of most published randomized controlled trials or observational studies only refers to elderly using an age cutoff of 70/80years. The objective of this study was to make a systematic literature review to evaluate the number of studies assessing the efficacy/effectiveness and safety of IVT and/or EVT in young stroke patients and to perform a meta-analysis in order to obtain a quantitative synthesis of this information.

Methods: By using predefined keywords, we screened 257 and 752 articles for IVT and EVT, respectively, assessed them for eligibility, and eventually included 8 specific studies for IVT and 5 for EVT. For the

meta-analysis, we used Fixed effect model as the main method with Random Effect model used as for sensitivity analysis when study heterogeneity was high.

Results: The age range was 18-64years in the young groups and from 41years and above for the older groups. Median baseline NIH Stroke Scale score was mostly lower in the young groups. Compared with older counterpart, young patients had a higher rate of protocol violations, a trend towards larger baseline infarct and higher symptom onset-to-treatment time intervals. For both IVT and EVT, functional independence as per modified Rankin Scale (mRS) 0-2 at 90 days were significantly more frequently achieved by young than the older patients (IVT: Odds Ratio [OR] 2.16, 95% Confidence Intervals [CI] 1.98-2.36, p<0.0001, I2=0%; EVT:2.82 [2.50-3.17], p<0.0001, I2=84%). Findings were similar for excellent outcome in terms of mRS0-1. Young patients had a significantly lower in-hospital mortality as well as 90-day mortality (0.31 [0.26-0.37], p<0.0001, I2=0%; EVT:0.24 [0.20-0.29], p<0.0001, I2=61%). Regarding symptomatic intracerebral hemorrhage (any definition), the risk resulted lower in young compared with the older patients (IVT:0.36 [0.30-0.45], p<0.0001, I2=0%; EVT:0.66 [0.47-0.94], p=0.02, I2=50%), also when the studies were grouped by the same definition. In EVT studies, no significant between-age group difference was found in terms of successful recanalization.

Discussion and Conclusions: Young patients may still benefit from acute recanalization despite large necrotic cores. Therefore, specific studies are needed to evaluate whether stroke volume thresholds and time intervals could be related and adjusted to the patient age class.

ADEQUACY OF CLINICAL DEMENTIA RATING SCALE (CDR) IN IDENTIFYING COGNITIVE DECLINE IN POST-STROKE PATIENTS

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Aim: The Clinical Dementia Rating Scale (CDR) is a global rating tool originally designed to stage elderly patients with Alzheimer's disease (AD) according to their cognitive functioning. It is often used as an inclusion criterion or a primary outcome measure in AD clinical trials. The aim of our study is to verify the adequacy of CDR in measuring cognitive decline and to examine its possible use for clinical trials in post-stroke patients.

Materials: One-hundred-twenty-four patients were assessed 6 months after stroke with two different methods: a) a neuropsychological evaluation coupled with scales assessing autonomy in everyday functioning (NPS); b) the total score obtained on CDR.

Methods: On both assessment methods, patients were classified according to the severity of cognitive impairment in cognitively unimpaired (0), mild cognitive impairment (MCI; 0.5), and dementia (1). The degree of concordance between these two measures was then analyzed (Cohen's kappa coefficient), and cognitive profiling and comparison analyses were performed across patient groups classified in the 3 severity categories with the 2 methods.

Results: The two diagnostic methods identified cognitive impairment with moderate agreement (k = 0.475). Compared with patients who were found to be cognitively unimpaired on CDR (CDR=0) and defined MCI using the neuropsychological evaluation (NPS=0.5), patients who were identified as MCI by both instruments (CDR and NPS=0.5) were more likely to have more than one neuropsychological test score below cutoff and more than one cognitive domain impaired. Importantly, these patients had a substantially overlapping cognitive profile (e.g., executive deficits and difficulties in some time-dependent tasks), differing significantly only in memory and verbal fluency tasks. Compared with patients who were found to be MCI according to CDR but demented at neuropsychological evaluation (CDR=0.5; NPS=1), patients who are identified as demented by both tools (CDR and NPS=1) have, numerically, more test scores below cutoff and are more likely to have global impairment.

Discussion: CDR seems adequate to detect MCI and dementia in the post-stroke population only when the deficit is more severe and involves multiple domains, among which memory and verbal fluency seem to be necessary. This is not surprising since memory is a primary item in determining CDR total score. On the other hand, executive functions and some time-dependent abilities seem to influence less CDR total score determination.

Conclusion: We recommend caution when using CDR to identify cognitive decline in post-stroke patients, as the intrinsic structure of this scale largely privileges memory, at the expense of other more frequently compromised domains.

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CLINICAL AND SUBCLINICAL ATHEROSCLEROSIS IN PATIENTS WITH MIGRAINE WITH AURA IN A COHORT OF YOUNG PATIENTS WITH STROKE

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Background: Migraine with Aura (MA) is associated with an increased stroke risk through different mechanisms which are not fully understood. The aim of our study is to evaluate the clinical and subclinical atherosclerosis in MA patients having a stroke.

Methods: We retrospectively searched the Hospital's electronic dossiers for patients younger than 60-year-old with the diagnosis of "acute stroke" from 2007 to 2022. We defined two groups: young stroke without MA history (S+MA-) and young stroke with MA history (S+MA+). We collected demographic characteristics, vascular risk factors, the results of PFO detection tests, neck vessels ultrasound, and MR brain angiography. Stroke severity, etiology and vascular territory were also defined. In MA patients, aura characteristics were also recorded (onset age, type, attack frequency, duration).

Results: We found 338 stroke patients (mean age: 50.3 (7.9) yrs, male: 68.0%). Of these, 32 patients (9.5%) had a history of MA. S+MA+ patients resulted younger than S+MA- (46.3 (10.2) ys 50.7 (7.6), p=-038), more frequently female (56.3% vs 43.8%; p=.004) and on contraceptive pill (33.3% vs 12.4%, p=.038), less frequently hypertensive (15.6% vs 44.1%, p=.002). Besides, S+MA+ patients presented less frequently a plaque on the contralateral (12.9% vs 43.3% p = 001) and ipsilateral side (29.0% vs 47.4%, p=.059) to stroke and lower values of mean intima-media thickness (.65 vs .73, p=013). No other differences were observed in vascular risk factors profiles or stroke severity (NIHSS). Moreover, S+MA+ patients presented a higher prevalence of PFO (p=.005), although not of high-risk PFO. Time from MA onset age to stroke was 17.0 ys (SD 13.4).

Conclusions: MA patients having a stroke present lower clinical and subclinical atherosclerotic burden compared to young stroke patients without aura. Besides, MA patients were younger and less frequently

hypertensive. Interestingly, high-risk PFO was not prevalent in MA+ compared to the MA- group. These findings suggest that the migraine brain is particularly vulnerable to hypoxic insults, as it faces ischemic damage despite a lower atherosclerosis burden.

THERAPEUTIC STRATEGIES IN VASCULAR COGNITIVE IMPAIRMENT: A SYSTEMATIC REVIEW

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Vascular cognitive impairment (VCI) is a common condition, encompassing heterogeneous clinical and pathophysiological conditions. Currently, no approved treatment exists for VCI. We aimed to perform a systematic review of therapeutic strategies in this high-burden condition. 1756 unique medical entries indexed by two widely employed search engines, PubMed® and Embase®, on clinical interventional studies published from inception to December 31, 2021. We initially searched the two databases with a composite research string assessing the presence in title or abstract of the following keywords (and derivatives, truncations or synonyms thereof) alone or in combination: "vascular", "small vessel", "post-stroke", "subcortical vascular", "multi-infarctual", "cognitive impairment", "dementia", "MCI", "therapy", "management". We then conducted a cooperative 3-person review of matching entries using Covidence systematic review software. Abstracts and then full texts were randomly screened for adherence to inclusion criteria by at least two reviewers. Any conflict was resolved by consensus and eventually by a fourth reviewer. Data from included studies were extracted, focusing on study characteristics, design and population, employed interventions and any relevant outcome. Across VCI subtypes, data were available from 126 selected trials including 20,287 participants with a mean duration of follow-up of 5.79 months (SD 5.71, range 1 day - 36.50 months). Seventy-five different interventions have been investigated (55 pharmacologic, 9 employing physical agent application, 11 rehabilitation strategies). The most frequently reported for each category were respectively: donepezil (11.1% of studies), ginkgo-biloba extracts (7.9%) and citicoline (7.1%); classic acupuncture (10.3%), remote ischemic conditioning (2.4%) and electroacupuncture (1.6%); cognitive rehabilitation (17.5%), therapeutic instrumental music performances (2.4%) and aerobic exercise (1.6%). Treatment efficacy was assessed by means of 125 outcome measures: 49 cognitive-behavioral (MMSE 51.9%, memory 28.3% and executive tests 22.0%); 29 instrumental (evoked potentials and P300 4.7%, transcranial ultrasounds measures 3.9 % and hemorheological values 3.9%), and 47 functional outcomes (Activities of Daily Living 18.3%, Barthel Index 7.9% and CIBIC-plus 7.9%). Our review outlined that the therapeutic strategies in VCI have been heterogeneous, the duration of clinical trials has been on average short, and the outcomes not standardized. Together with the clinical heterogeneity of VCI, these aspects likely contributed to the lack of evidence of beneficial therapeutic effects. To tackle more effectively this complex scenario, a change in strategy is needed. Future studies should focus on evaluating treatments with plausible clinical efficacy, employing reproducible outcomes, throughout an adequate timespan to observe possible effects.

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INTRACRANIAL CAROTID ARTERY CALCIFICATION PATTERNS IN DIVERSE ETIOLOGICAL SUBTYPES OF ISCHEMIC STROKE

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Aims: Intracranial carotid artery calcifications (ICAC) are a common finding on non-contrast head CT scans. ICAC have been associated with an increased risk of developing ischemic stroke and with higher risk of stroke recurrence. However, there is limited evidence on the association between different ICAC patterns and stroke etiology. The aim of our study was to investigate the association between ICAC pattern and etiological subtypes of ischemic stroke.

Materials: Retrospective analysis of a single center prospective cohort of patients with ischemic stroke with known etiology. Stroke etiology was classified into lacunar, cardioembolic or atherothrombotic large artery atherosclerosis (LAA) etiology, according to the TOAST classification. Admission CT scans were rated to define the calcification pattern (intimal, medial, mixed). Each carotid artery was rated separately.

Method: The association between ICAC patterns and stroke etiology was investigated using a binary logistic regression model adjusting for main confounders.

Results: A total of 300 patients were included in the analysis (mean age 78 years, 47% male). Stroke etiology was LAA in 80(27%), cardioembolic in 161(54%) and lacunar in 59(20%) patients. Intimal pattern was more frequent in lacunar subtype (LAA 17%, cardioembolic 25%, lacunar 44%, $p<0.001$), whereas medial pattern was more frequent in cardioembolic (73%) and LAA (66%) etiology compared with lacunar (37%). After adjustment for confounders, intimal pattern (OR 2.14;95%CI=1.07 - 4.30) was associated with increased odds and medial pattern (OR 0.33;95%CI=0.16-0.67) with reduced odds of lacunar etiology respectively.

Discussion: The frequency of ICAC pattern differs according to stroke etiology in patients with acute ischemic stroke, and intimal pattern was associated with lacunar etiology, whereas medial pattern reduced the odds of lacunar stroke subtype. This association might be explained by the high burden of cardiovascular risk factors in this subgroup of patients, but a direct contribution of atherosclerotic disease to lacunar stroke may be considered. If confirmed, ICAC pattern may serve as a useful marker to help classification of stroke etiology in clinical practice.

Conclusions: Intimal ICAC pattern is independently associated with lacunar stroke. Further studies are needed to confirm our findings and to characterize the underlying pathophysiological mechanisms.

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NON CONTRAST COMPUTED TOMOGRAPHY PREDICTORS OF INTRACEREBRAL HEMORRHAGE EXPANSION: THE EFFECT OF ONSET-TO-SCAN TIME

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Objective: Non Contrast Computed Tomography (NCCT) density and shape features can identify intracerebral hemorrhage (ICH) patients at high risk of hematoma expansion (HE) [1]. We investigated whether onset-to-scan time influences the diagnostic performance of these imaging markers.

Materials: Retrospective analysis of patients admitted for primary spontaneous ICH at 7 academic sites in Europe and China. The presence of the following imaging markers was rated on baseline NCCT, according to standardized diagnostic criteria: hypodensity, heterogenous density, irregular shape and blend sign [2]. ICH volume was calculated with semi-automated planimetric softwares.

Method: HE was the main outcome of interest, defined as >33% and/or > 6 mL growth. The study population was stratified into three groups based on NCCT timing: <2 h; 2-4 h; > 4 h. We calculated sensitivity, specificity, positive and negative Predictive Values (PPV and NPV) of NCCT markers for HE.

Results: A total of 1027 patients were included (mean age 69, 56.2% males) of whom 301 (29.3%) had HE. Onset to NCCT time was < 2 hours in 298 (29.0%) patients, 2-4 hours in 364 (35.4%) and over 4 hours in 365 (35.5%) patients. The frequency of HE was lower in late presenters (31.5% - 32.4% - 24.4% in the three groups respectively, p=0.035). Prevalence of hypodensity and heterogeneous density was higher in early presenters. Hypodensity performed better in patients presenting within 2 h and its diagnostic performance declined over time from ICH onset to imaging (sensitivity 0.78; 0.59; 0.63; and PPV 0.46; 0.45; 0.37). Similar findings were observed for heterogeneous density, whereas the diagnostic performance of irregular shape and blend sign was not influenced by NCCT timing.

Discussion: HE is more common in early presenters and some density-related imaging features have higher sensitivity in this subgroup of patients. These findings are consistent with the biological hypothesis that density features may identify more immature, bleeding-prone hemorrhages.

Conclusion: Hypodensity and heterogenous density have a better diagnostic performance within 2 h from ICH onset. Our findings may help risk stratification in future studies focusing on HE prediction and prevention.

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IMPLANTABLE CARDIAC MONITORING IN PATIENTS WITH CRYPTOGENIC STROKE: A REAL-WORLD EXPERIENCE

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Introduction: The use of implantable cardiac monitoring (ICM) is currently recommended by European stroke guidelines1 in patients with a cryptogenic stroke and, in clinical trials, leads to the detection of atrial fibrillation (AF) in up to 30% of patients after a 3-year follow-up. Aim of this study was to evaluate the use of ICM in a large cohort of cryptogenic stroke patients in a real-world setting.

Methods: Among patients admitted for an acute ischemic stroke to the Luigi Sacco Hospital stroke unit in Milano, from January 2018 to May 2022, those with a cryptogenic stroke were proposed an ICM. Patients who received the ICM were followed on an outpatient basis by the referring neurologist and cardiologist, who reviewed all ICM transmissions and diagnosed AF in case of an appropriate tracing lasting □2 minutes. Demographic and clinical features of patients who developed AF were compared with those of patients who did not. The start of anticoagulant therapy after AF diagnosis was also registered.

Results: 680 patients were admitted to the Stroke Unit during the enrolment period, 196 patients (29%) were diagnosed with a cryptogenic stroke, and 130 patients of them (66%) received an ICM. In this group, median age was 74 years, 82 patients (62%) were males, median NIHSS score at baseline was 3, hypertension was present in 91 patients (70%), coronary artery disease in 20 (15%), diabetes mellitus in 28 (22%),

dyslipidemia in 72 (55%). Over a median time of follow-up of 21 months, 33 patients (25%) were diagnosed with AF, with a median time of 4 months from ICM implanting to diagnosis. Compared to patients who did not develop AF, those who did were significantly older (OR 1.06, p=0.007). Among the 33 patients with AF, 30 patients (91%) started a direct oral anticoagulant and 2 patients (6%) started warfarin, while one patient (3%) refused anticoagulant therapy.

Discussion: Using an ICM, AF can be detected in 25% of highly selected patients with a CS over a median time of follow-up of 21 months. Our results are similar to those derived from clinical trials, such as CRYSTAL-AF, 2 showing the applicability of this approach to routine clinical practice and outlining the ensuing indication for anticoagulation after an ICM-based AF diagnosis in a real-world setting although the effectiveness of anticoagulation in these patients remains to be further proven.

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ACTIGRAPHIC SENSORS DESCRIBE STROKE SEVERITY IN THE ACUTE PHASE: A NEW PERSPECTIVE ON IMPLEMENTING MULTI-PARAMETRIC MONITORING IN STROKE UNIT

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Objectives: Stroke patients in the acute phase are often unstable and their clinical condition can change suddenly. For this reason, vital parameters, such as heart rate, blood pressure and oxyhemoglobin saturation, are continuously monitored in the setting of a Stroke Unit. Patients are also frequently clinically examined, but it is very challenging constantly observe the evolving clinical picture. In this context, an automatic system able to monitor the patient's motor activity, such as actigraphic sensors, could be particularly useful. Specifically, Motor Activity (MA) and Asimmetry Index (AR) are two well-established actigraphic parameters that describe the motor activity of the arms and that have been previously found to correlate with the neurological condition of stroke patients.

Materials: We conducted a multicenter prospective observational study enrolling patients with ischemic stroke of the middle cerebral artery during their stay in a sub-intensive Stroke Unit. NIHSS was performed every hour since admission and motor activity of both arms was continuously recorded using a wearable accelerometer-based actigraphic system positioned on each wrist.

Methods: In order to verify whether actigraphic parameters were able to identify clinical conditions of different severity, we calculated the mean values of MA and AR in the first hour after admission and in the first hour following a significant clinical change (at least 4 points of NIHSS) or at the end of hospitalization. We identified the best actigraphic parameters to describe NIHSS with a regression model and calculated the Receiver Operating Characteristic (ROC) curve in order to find a cut-off value to discriminate minor (NIHSS <5) from major stroke (NIHSS ≥5) and NIHSS 5-9 from NIHSS≥10.

Results: We recruited a total of 69 patients. We found that the combination of AR and MA of the non-paretic arm is the best model to properly predict NIHSS score, with a sensitivity=89%, specificity=82%, PPV=92% and NPV=75% in discriminating minor (NIHSS<5) from major stroke (NIHSS≥5). We also identified an AR cut-off value able to identify severe stroke patients (NIHSS≥10) with sensitivity=82% specificity=74% (AUC 0.86 p<0.001) PPV=73% NPP=82%.

Discussion: We identified actigraphic parameters able to distinguish minor from major stroke. Actigraphic system can reliably describe the overall severity of stroke patients with motor symptoms. Long-lasting actigraphic monitoring of upper limbs' motor activity could be useful to detect clinical fluctuations in the first days after stroke.

Conclusions: These data support the addition of a wearable actigraphic system to the standard multi-parametric monitoring in stroke unit.

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THE POTENTIAL OF SMART DEVICES FOR SECONDARY PREVENTION OF CEREBROVASCULAR DISEASE: A PROOF-OF-PRINCIPLE STUDY

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Background and aims: Stroke is one of the leading causes of death and disability in the western world. Despite the recent advances in secondary prevention, the rate of stroke recurrence at five years ranges from 10 to 20% of patients and it has not substantially changed in the last decade. Commercially available health devices are gaining momentum and represent a great opportunity for monitoring patients for prolonged periods. This study aims at testing the feasibility of a smart devices-based secondary prevention program in a cohort of patients with undetermined aetiology cerebrovascular disease.

Methods: We recruited patients with transient ischemic attack (TIA) or mild ischemic stroke (NIHSS < 3) - in which no specific aetiology had been identified with the usual diagnostic work-up. Patients were provided with a smartwatch and smart devices to monitor several vital parameters for a 4-week period (Watch group). This group was compared with a standard-of-care group. The compliance with the use of smart devices was evaluated as the number of measures performed during the observation period.

Results: In total, 161 patients were recruited, 87 in the Watch group and 74 in the control group. In the watch group, more than 90% of patients recorded the ECG at least once a day. In total, 5335 ECGs were recorded during the study. The median value of blood pressure measurements was 132 over 78 mmHg. The median oxygen saturation value was 97 %. From a clinical standpoint, nine AF episodes (10.3%) in the Watch group – vs 3 (4%) in the control group - were detected.

Conclusions: Our study suggests that prevention programs for cerebrovascular disease may benefit from the implementation of new technologies. In particular, new generation smartwatches might be useful to detect covert atrial fibrillation and could represent a valid aid in the diagnostic work-up of undetermined aetiology stroke. This pilot study demonstrated that available technologies could be readily implemented even with the current population's technical and intellectual resources.

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MECHANICAL THROMBECTOMY FOR TREATMENT OF PEDIATRIC CEREBRAL VENOUS THROMBOSIS. CASE REPORT AND LITERATURE REVIEW

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Background: Mechanical thrombectomy in Cerebral Venous Thrombosis (CVT) aims to achieve a rapid recanalization of the sinuses restoring the cerebral venous drainage. In adult it should be considered in patients with a high risk of poor outcome. In pediatric CVT it has been reported in rare case and small series, typically in the most critically ill patients.

Case report and literature review: At age of 12-year a girl had left transverse sinus thrombosis with left temporo-parietal haemorrhagic infarction without disability. The diagnostic workup showed only the presence of the G20210A prothrombin gene mutation in heterozygosis. She was treated with anticoagulation for two years. At age of 16-year she experienced headache, vomiting, and decrease of consciousness. Brain CT scan did not show acute lesions. CT angiography demonstrated thrombosis of superior sagittal sinus (SSS), right transverse and sigmoid sinus, hyplopasia and irregular transverse sinus due to past CVT. Due to extensive thrombosis, involvement of multiple sinuses, and mental status disturbances, a mechanical thrombectomy was performed. thrombus aspiration was performed in SSS and right transverse sinus. Almost complete recanalization of the occluded sinuses was achieved. No complications were observed. Anticoaugulation was restarted. Brain MRI and MR-venography after 7 days showed almost complete sinuses recanalization; no parenchymal lesions were detected. The girl was discharged after 10 days without neurological deficits with anticoagulant therapy for long life. At 2-year follow-up she did not complain any symptoms. A literature review identified 28 other cases of mechanical thrombectomy. It demonstrated that mechanical thrombectomy with modern devices such as large-bore aspiration catheters and stent retrievers in experienced centers may be safe and effective in severe pediatric cases of CVT.

Discussion and Conclusions: Thrombectomy could be a therapeutic option in carefully selected pediatric patients with CVT and risk of poor outcome. A multicenter registry of all pediatric patients treated with thrombectomy is desirable to provide data on safety and efficacy of this treatment.

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CLINICAL-CT MISMATCH PREDICTS EARLY NEUROLOGICAL DETERIORATION IN STROKE PATIENTS UNDERGOING MECHANICAL THROMBECTOMY

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A clinical-CT mismatch between stroke severity and baseline lesion volume at tomography imaging appears to identify acute ischemic stroke (AIS) patients with penumbra. We hypothesized that clinical-CT mismatch could predict the clinical benefit obtained with mechanical thrombectomy (MT). We included patients with AIS of the anterior circulation undergoing MT who were admitted at the Stroke Unit of the Marche Polytechnic University General Hospital. The Alberta Stroke Program Early CT Score (ASPECTS) was used to assess brain CT lesions at baseline. The clinical-CT mismatch was defined as an admission National Institutes of Health Stroke Scale (NIHSS) score ≥8 and a baseline-CT-ASPECT score ≥9. The outcome measure was the Early Neurological Deterioration (END), defined as a 4-point worsening of the NIHSS score at 24 hours assessment. Patients included were 214 and 81 (37.9%) presented a clinical-CT mismatch. In univariate and multivariate analysis, the clinical-CT mismatch was associated with a lower risk of END at 24 hours from stroke (odds ratio 0.185, p=0.030). Clinical-CT mismatch may be able to predict early outcome of patients with AIS undergoing MT.

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"DOACS FAILURE" IN PATIENTS WITH ACUTE ISCHEMIC STROKE: EXPERIENCE FROM UDINE STROKE REGISTRY

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Aims: This study aimed to evaluate the frequency and causes of "anticoagulation failure" in consecutive patients suffering of acute ischemic strokes (IS) treated with direct oral anticoagulants (DOACs).

Materials and Methods: We conducted a single-center retrospective observational study of consecutive patients recovered in Stroke-Unit at Udine University Hospital. Adult patients with non-valvular atrial fibrillation (NVAF) receiving treatment with DOACs and admitted for acute IS were included. We considered as "true DOACs failure" patients who took the drug with the correct dosage and adequate adherence.

Results: During the study period, 674 patients with IS were admitted. Among these patients 52 patients with NVAF were treated with DOACs and 26 with Vitamin-K antagonists. Of 52 patients receiving DOACs, 35 had adequate adherence and dose to DOACs. Inadequate compliance was greater in single-dose-DOACs. Patients with adequate therapy to DOACs, compared with other patients with IS, were older (77.1+/-8.8anni vs.72.6 +/-12.9anni, p=0.005) and had more frequently a previous IS (32.4% vs.9.3%, p<0.001). No significant differences were identified between the two groups in terms of stroke severity and functional impairment scores at admission. One of the 35-patients had intravenous thrombolysis and 13-patients had thrombectomy. The DOAC plasma-levels were determined in emergency in 15/35 patients: a total of 43.8% of patients had low DOAC levels, 25.0%intermediate and 31.2% high.

Discussion: Use of DOACs has increased over the years, because they represent a safe and effective alternative to the Vitamin-K antagonists for the prevention of IS in patients with NVAF. With their increased use, an increasing proportion of IS is emerging to be related to anticoagulation failure. Different factors have been considered to explain an anticoagulation failure: drugs interference, coexisting stroke mechanisms, incidental stroke-triggers. Recently, the availability of the plasmatic dosage of these drugs, both in the emergency and follow-up setting, allows a greater clarity on the etiology of possible failures. Our study showed an increase of IS in patients treated with DOACs, in parallel with greater prescription of DOACs. Only a small proportion of these patients did benefit from reperfusion therapies, although a low plasma level of DOACs was found in most cases. In most of them stroke etiopathogenesis was not clear after diagnostic work-up.

Conclusions: Plasmatic dosages of DOACs should become part of routine management of patients treated with DOACs, both in emergency services and in patients' follow-up. This seems extremely important to include patients in reperfusion treatments and to reveal undertreated or resistant patients, or patients in which stroke might be related to other mechanisms.

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PREDICTORS AND PROGNOSTIC IMPACT OF HEMATOMA EXPANSION IN INFRATENTORIAL CEREBRAL HEMORRHAGE

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Objective: To evaluate the predictors and prognostic impact of hematoma expansion (HE) in infratentorial cerebral hemorrhage (ICH).

Materials: Retrospective analysis of patients with infratentorial ICH admitted at 5 European academic sites. Non contrast computed tomography (NCCT) images were analyzed for the presence of the following features, according to validated criteria: hypodensities, irregular shape, heterogeneous density, blend sign, fluid level.

Methods: Mortality at 90 days and occurrence of HE (defined as > 33% and/or > 6 mL growth) were the outcomes of interest, whose predictors were investigated with binary logistic regression with backward elimination at p<0.1. The logistic regression model for mortality accounted for the ICH score and for variables with p<0.1 in univariate analysis. ICH volume, antithrombotic treatment, onset-to-CT time and NCCT features were included in logistic regression for HE.

Results: A total of 139 patients were included (median age 76 years, 45.3% males), of whom 34 (24.5%) died within 90 days and 34 (24.5%) had HE. Subjects with HE had higher mortality (41.2% vs 19.0%, p=0.009). The association between HE and mortality remained significant in logistic regression when accounting for confounders (odds ratio (OR) 5.08, 95% confidence interval (CI) 1.81-14.28, p=0.002). Secondary analyses with a more inclusive model and stratified by ICH location (brainstem vs cerebellar) confirmed this finding. Hypodensities were significantly more frequent in patients with HE (41.2% vs 23.8, p=0.050). Shorter onset-to-CT time (within 3 h from onset) and hypodensities were independently associated with higher odds of HE (OR 2.53, 95% CI 1.06-6.07, p=0.037 and OR 2.46, 95% CI 1.01-5.94, p=0.046 respectively).

Discussion: Similar to previous studies on supratentorial ICH, HE was associated with increased risk of death also in patients with infratentorial ICH. Shorter time from onset to baseline imaging and NCCT hypodensities predicted HE.

Conclusions: HE is an appealing therapeutic target in infratentorial ICH and NCCT features can identify patients at high risk of HE. Our findings may inform future studies and improve selection for randomized trials targeting HE.

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CEREBRAL VENOUS THROMBECTOMY: A SINGLE CENTRE EXPERIENCE

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Objectives: Aim of this work is to analyze and present our retrospective, single-centre, observational study reporting the mechanical thrombectomies (MT) procedures for dural sinus thrombosis performed between 2016 and 2021.

Materials and Methods: In the 5-year study period, a total of 51 patients were referred to our Stroke Unit Department for cerebral venous thrombosis (CVT). Among these, 18 patients underwent endovascular therapy for a total of 20 procedures. Patients characteristics, including risk factors, neurological signs and symptoms, procedural timing, technical and clinical outcomes are reported.

Results: There were 15 females (83%) and 3 males (17%), median age was 47 years (range 16-84 years). Most common symptoms were headache (88,8%), nausea or vomiting (50%); neurological deficits were present in 16 out of 18 patients (88,8%), with hemiparesis (44,4%) and aphasia (38,8%) being the most common. Seizures were observed in 4 patients (27,7%); 2 patients (12,5%) had consciousness impairment. In 13 cases (72,2%) two or more sinuses were involved. 78% of patients had an intracranial hemorrhage (considering intraparenchymal hematoma, subarachnoid hemorrhage, or both). The etiology/risk factors for CVT were identified in 11 patients, with oral contraceptive pill usage being the most common within female patients (5 out of 13). One young patient underwent MT during her 12th week of pregnancy. Median time from CVT to groin puncture was 3,5 hours. Median procedural time was 118 minutes. In 2 cases there was no recanalization. Aspiration alone was the first strategy in 17 out of 20 procedures; in 6 of these cases, thrombectomy was shifted to combined technique with stent-retriever, while combined technique was adopted as first-line strategy in 3 out of 20 procedures. At last follow-up, a favorable performance status (mRS 0-2) was observed in 16 out of 18 patients; two of them had an mRS of 1 due to a residual slight motor deficit at their right hand. Periprocedural complications were seen in 2 cases, consisting in sinus perforation and subsequent subdural hemorrhage, which required a decompressive craniotomy in 1 case.

Discussion: CVT is a condition with a potentially fatal outcome. Standard treatment consists in systemic anticoagulation with heparin at therapeutic dosage, even in hemorrhagic patients at baseline. MT should be considered in patients with clinical deterioration despite anticoagulation or with severe neurological deficit or coma. The TO-ACT trial demonstrated no improvement in functional outcome at 12 months in patients with severe CVT undergoing MT compared to those treated with medical therapy alone.

Conclusions: Our series has shown the safety and efficacy of both aspiration and combined technique with several devices for CVT; moreover, it underlines the potential benefit of an early intervention in selected patients at high risk of morbidity or mortality.

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NEUROSURGICAL TREATMENT IN ICH PATIENTS: A SINGLE CENTER EXPERIENCE FROM PERUGIA (ITALY)

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Introduction and Aims: The effect of surgical treatment for spontaneous intracerebral hemorrhage (ICH) remains uncertain. We conducted an observational retrospective cohort study on supra-centimeter spontaneous ICH treated with neurosurgical or conservative management. The baseline demographics and risk factors were correlated with in-hospital mortality and 3 and 6-month survival rates stratified by management.

Materials and Methods: We included all patients with evidence of spontaneous ICH > 1 cm on CT between August 2020- March 2021 and admitted to the "SMM" Hospital in Perugia.

Results: Onehundredtwentytwo patients were included in the study, and 45% (n.55) were surgically treated. The mean age was 71,9±15.3, and 61% (n.75) were males. Intra-hospital mortality resulted being 31% (n.38), 3 months-survival was 63% (n.77) and 6 months-survival was 60% (n.73). From the multivariate analysis of the surgical patients versus medical patient, we observed the surgical patients were younger (67,5±14,9 vs 75,5 ±14,7 y; OR 0.87; CI 95% 0,85-0,94; p 0,001), with greater ICH volume at the onset (61±39,4 vs 51± 64 cc; OR 1,03; CI 95% 1,005-1,07; p 0,05), more midline shift (7,61 ±5,54 mm vs 4,09 ±5,88 mm; OR 1,37; CI 95% 1,045-1,79; p 0,023), and a higher ICH score (3 vs 2 mean ICH score; OR 21,12; CI 95% 2,6-170,6; p 0,004). Intra-hospital mortality was respectively 33% vs 30%, 3 month-survival was 64% vs 63% and 6 month- survival were 60% in both groups.

Conclusion: Our patient cohort shows no overall benefit from surgery over conservative treatment, but surgical patients were younger and had larger ICH volume.

CARDIAC INJURY AFTER STROKE, A COMPARISON BETWEEN POSTERIOR AND ANTERIOR CIRCULATION

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Purpose: Stroke-heart syndrome is a documented complication of acute stroke. It consists in the cardiac injury following an acute stroke. The

etiopathogenesis underlying this process is partly unknown, however the main hypothesis is the cytokines storm involving the sympathetic system [1,2]. The aim of this study is to compare the heart injury markers following a stroke due to anterior (ACS) or posterior circulation (PCS).
Materials: We included 76 consecutive patients treated with thrombolysis during 2021 in our Stroke Unit with an anterior (61) or posterior (15) circulation stroke.

Methods: We compared demographic clinical features (sex, age, weight, cardiovascular risk factors, blood pressure, glycaemia, platelets, former treatment) and markers of cardiac injury (TnI, NT pro BNP, ECG). The statistical analysis was performed with Microsoft Excel using X^2 test/Fisher-Yates test/Mann Whitney U test as needed.

Results: We observed no statistical differences between the clinical/laboratory features of the two cohorts; moreover there were no significant differences of cardiac injury biomarkers. In particular, by comparing values of NT pro BNP in posterior circulation stroke and in the anterior strokes we found a median and IQR respectively of [1090; 268-3798] and [604; 251-1695], between the first value of TnI in PCS [10; IQR 6 - 21,75] and in ACS [12,5; IQR 7-28], similarly for the maximum value of TnI reached.

Discussion: This study suggests there are no differences in TnI or BNP levels between PCS and ACS. Maybe a common stress like vessel occlusion, regardless of location, induces a cytokine storm.
Conclusions: More studies are suggested to better investigate the role of stroke location on heart-stroke syndrome.
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INCIDENCE AND MANAGEMENT OF TIAS: A 5-YEAR RETROSPECTIVE STUDY IN TRIESTE

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Purpose: TIA is defined as a brief episode of neurological dysfunction caused by a focal disturbance of brain or retinal ischemia lasting less than 24 hours. [1]. Previous data suggest TIA precedes 15% of ischemic strokes, with a higher risk in the first week [2]. We provide data on TIA incidence in Trieste and the management of patients with TIA including the incidence of relapses.

Materials and Methods: This study is part of a 5-year prospective community-based registry of all transient cerebrovascular events admitted in the ED in the district of Trieste (230000 inhabitants), between January 1, 2017 and December 31, 2021. Statistical analysis was performed by calculating TIA rates on the total accesses, the relapse and mortality rates and prevalence of TIA in general population of Trieste district.

Results: Approximately, 180 patients per year referred to the ED for a focal neurological deficit and 8-10%/year of them reside in Gorizia area. Among the 890 patients diagnosed as TIA in the ED 477 were admitted to our department on a day hospital management. Patients were admitted to our unit between 24 and 96 hours from access to the ED. The recurrence rate of cerebrovascular disease was 1.9% within 90 days from the TIA (0,9% TIA, 0,6% ischemic stroke, 0.4% hemorrhagic stroke), and 6 % beyond 90 days (4,1% TIA, 1,7% ischemic stroke, 0.2% hemorrhagic stroke). At the end of the diagnostic tests a diagnosis of TIA/minor stroke (MS) was made in 330 patients (70%). The prevalence of confirmed TIA in the Trieste district is 1.11%. The mortality rate in TIA/MS was 5.6% with a median timing of 18.5 months [IQR 7,5-27,5].

Discussion and Conclusions: Previous data showed that a fast treatment of TIA significantly decreases the early risk of subsequent stroke. This study improves new data on TIA incidence and prognosis in Trieste and Friuli Venezia Giulia Region. We believe that the prompt recognition of patients at high risk for cerebrovascular events and specialist follow-up may reduce the incidence of major vascular event and death.
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CHARACTERISTICS AND OUTCOMES IN NON-ANEURYSMAL COMPARED WITH ANEURYSMAL SUBARACHNOID HEMORRHAGE IN A POPULATION-BASED STUDY

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Objectives: The vast majority of subarachnoid hemorrhages (SAHs) is aneurysmal (aSAH) – i.e., caused by the rupture of intracranial aneurysms –; non-aneurysmal SAH (naSAH) represents a rare and understudied condition. We aimed to evaluate the differences in characteristics and early case-fatality of naSAH versus aSAH in a population-based setting.

Materials and Methods: We included all patients with a first-ever SAH occurring in the resident population in the district of L'Aquila from 2011 to 2020. To identify SAH subtypes we applied the International Classification of Diseases, 10th Revision (ICD-10). naSAH was classified into three subgroups, namely perimesencephalic, non-perimesencephalic, and convexal SAH. We compared clinical characteristics and 30-day case-fatality between aSAH and naSAH and across naSAH subgroups.

Results: Over ten years, 161 patients with SAHs were included, 130 (79.5%) with aSAH and 31 (20.5%) with naSAH. The only significant difference between the two groups was a higher median age in those with naSAH compared with those with aSAH (76 years, interquartile range [IQR] 58-86, vs 62 years, IQR 51-71; P=0.005), while 30-day case fatality was not different between the two groups. All patients with aSAH had non-perimesencephalic SAH. Among the 31 patients with naSAH, 10 (32.3%, 95% confidence interval [CI]) had a perimesencephalic SAH, 16 (51.6%) a non-perimesencephalic SAH, and 7 (22.6%) a convexal SAH. The three subgroups differed by median age (55 years, IQR 46-73; 83 years, IQR 72-91; 69 years, IQR 39-85, respectively; p=0.009) and

by the prevalence of arterial hypertension (40.0%, 81.3%, and 28.6%, respectively; p=0.011); 30-day case-fatality was also different across the three subgroups (10.0%, 50.0%, and 0%, respectively; p=0.016).

Discussion: Basing on our registry, patients with perimesencephalic naSAH were younger than patients with other forms of SAH. This finding is in line with a previous study [1]. We found a different prevalence of arterial hypertension across the different naSAH subgroups that was not found by a previous study [1]. The favorable short-term outcome after perimesencephalic naSAH was in line with literature [2]; however, the most favorable short-term outcome belonged to convexal SAH.

Conclusion: According to our data, naSAH includes heterogeneous variants which differ in etiology and outcomes; perimesencephalic and convexal SAH carry a favorable prognosis, while non-perimesencephalic naSAH is associated with the highest short-term case-fatality and is influenced by arterial hypertension.

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"DE NOVO" COL4A1 MUTATION: CASE REPORT AND REVIEW OF THE LITERATURE

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Background: Mutations in COL4A1 and COL4A2 genes have been recently identified as a cause of autosomal dominant hereditary multisystemic disease. COL4A1 and COL4A2-related disorders are highly variable including cerebrovascular events, migraine, epilepsy, nephropathy, muscle cramps, arterial aneurysms, and ocular anterior segment diseases.

Purpose: We report on a patient affected by COL4A1-related disease and we review literature data in order to describe clinical and neuroimaging features related to COL4A1 and COL4A2 mutations in young and adults.

Results: A judo player 17-years-old girl was admitted for right hemiparesis due to subcortical hemorrhage. On neuroimaging, subcortical subacute small infarcts, calcifications, previous small hemorrhages, and subcortical leukoencephalopathy were also present. In her childhood, she was diagnosed with congenital bilateral subcapsular cataract, microhematuria, and raised creatine kinase. COL4A1 and COL4A2 analysis revealed a heterozygous novel pathogenic variant in the COL4A1 gene. The variant was not detected in her parents' and brother's samples, suggesting a de novo origin. We reviewed English-written case reports, series, and reviews that reported on subjects >= 16 years of age with mutations in COL4A1 or COL4A2 genes. In each eligible article (69 papers) we focused on the description of the clinical picture, as well as instrumental and laboratory data.

Conclusions: We present a novel COL4A1 mutation expanding the genotypic spectrum of COL4A1-related disorders. Moreover, we confirm the frequent occurrence of de novo pathogenic variants as causative of this disease, supporting the indication to perform genetic analysis in patients with familial or sporadic cerebral small vessel disease associated with multiorgan involvement.

CLINICAL PRESENTATION OF STROKE MIMICS AND CHAMELEONS: A HOSPITAL-BASED STUDY

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Background and Aims: Stroke mimics are clinical presentations that may resemble acute stroke but are caused by other diseases. Conversely, stroke chameleons are conditions in which symptoms suggesting other diagnoses are later recognized as stroke. Most of mimics include seizures, migraine aura, systemic infections, metabolic disorders, while common chameleon's presentations are altered mental status, syncope or headache disorders. Isolated sensory symptoms or brief episodes of dizziness are associated with high likelihood of a stroke mimic while abulia, confusion, non-focal weakness can underly a stroke chameleon. [1,2,3]. Our study aimed at identifying clinical signs associated to stroke mimics and chameleons in a hospital setting.

Materials and Methods: We prospectively identified all patients admitted to the emergency department (ED) with a suspect diagnosis of stroke from January to August 2021 in a single hospital of the district of L'Aquila. We collected demographics (age and sex), signs and symptoms of presentation, and symptom duration. We compared ED diagnoses with diagnoses at discharge from hospital. We defined cases as "actual strokes" when both ED and discharge diagnoses were of stroke, "mimics" when the ED diagnosis was stroke while the discharge diagnosis was of other diseases, and "chameleons" when the ED diagnosis was of other diseases while the discharge diagnosis was of stroke. Patients' clinical symptoms and signs were compared across the three groups.

Results: A total of 204 patients were identified (52.7% males, mean age 75±12 years); 155 (75.6%) were actual strokes, 32 (15.6%) stroke mimics, and 17 (8.3%) chameleons. Actual strokes were more likely to present with hemiparesis than mimics and chameleons (71.6%, 46.9%, 47.1%, respectively; p=0.007); the same applied to hemisensory impairment (29.0%, 25.0%, 0%, respectively; p=0.035) and speech disturbances (62.6%, 34.4%, 41.2%, respectively; p=0.006). Meningeal signs (21.9% vs 9.0% vs 0%, respectively; p=0.032) and headache (18.8% vs 5.2% vs 0%; p=0.011) were more common in stroke mimics compared with actual strokes and chameleons, while seizures were more common in chameleons than in mimics and actual strokes (5.9%, 3.1%, 0%, respectively; p=0.027).

Discussion and conclusions: The prevalence of stroke mimics and chameleons in our study was lower than that of similar studies (30-43% of mimics, 2-26% of chameleons) [2]. Meningeal signs and headache could lead to suspecting the occurrence of a stroke mimic, while the absence of sensory or motor symptoms and of language impairment, or the occurrence of seizures, should not always lead to immediately exclude the presence of a stroke.

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PREDICTORS OF CORRECT ANTIPLATELET RESPONSE IN STROKE PREVENTION MEASURED WITH ELECTRICAL IMPEDANCE AGGREGOMETRY

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Background and aims: Platelet function tests could allow a guided selection of the appropriate treatment in secondary stroke prevention. We aimed to detect clinical and laboratory factors influencing the platelet inhibition in patient on antiplatelet therapy.

Materials and methods: We retrospectively enrolled 300 patients hospitalized for acute cerebrovascular disease from 2017 to 2021, taking antiplatelet therapy and undergoing electrical impedance aggregometry. Demographic, clinical and laboratory data were collected and analyzed to detect predictors of high on-treatment platelet reactivity (HPR). Four parameters were analyzed: ASPI or ASPI/TRAP for aspirin and ADP or ADP/TRAP for P2Y12 inhibitors.

Results: Platelet count was an independent predictor of HPR with ASPI (OR 0.990, 95% CI 0.982–0.998, p = 0.01), ADP (OR 0.98, 95% CI 0.97-0.99, p=0.001) and ADP/TRAP (OR 0.993, 95% CI 0.988-0.999, p =0.02) tests; PTT was a predictor of correct response to aspirin measured by ASPI test (OR 1.06, 95% CI 1.01-1.11, p =0.02); glomerular filtration rate was an independent factor of HPR with ADP test (OR 0.97, 95% CI 0.95-0.99, p =0.02); as to ADP/TRAP ratio, smoking was an independent predictor of HPR (OR 0.23, 95% CI 0.06-0.91, p =0.04), while dyslipidaemia was associated with an effective antiplatelet response (OR 3.98, 95% CI 1.04-15.24, p =0.04). Discussion. We found some clinical and laboratory variables affecting the antiplatelet response measured by aggregometry.

Conclusions: If confirmed, our findings can help to better tailorize the antiplatelet therapy in secondary stroke prevention.

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CLINICAL AND RADIOLOGIC FEATURES OF TREATED PATIENTS WITH ACUTE ISCHEMIC STROKE DUE TO MEDIUM VESSELS OCCLUSIONS

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Background and aim: MeVOs account for 25–40% of all AIS. There is limited but promising evidence for the safety and efficacy of EVT in MeVOs. Our study aims to collect clinical and radiological features of MeVOs AIS patients admitted to our CSC treated with IVT, EVT, or both and to compare their clinical outcomes.

Methods: We retrospective collected clinical and radiological data of patients with MeVOs AIS admitted at "Maggiore" Hospital of Bologna between January 2019 and July 2021. The primary outcome was mRS ≤ 2 at three months. To identify potential predictors for mRS ≤ 2, we performed univariate analysis, including demographic, clinical, and treatment-related variables. All candidate variables were entered into binary logistic regression analysis, with a backward stepwise elimination approach set to simplify the model.

Results: We identified 180 patients with MeVOs AIS (IVT=59, EVT=38, IVT+EVT=83). mRS score ≤ 2 at 3 months was obtained for 61% of patients in the IVT, 31.6% in the EVT group and 63.9% in the IVT+EVT group. Overall rate of sICH was very low (1,1%). Procedural complications were vasospasm (4,2%) and subarachnoid haemorrhage (1,7%), no neurological deterioration due to the complications was reported. In the backward stepwise multivariable logistic regression IVT+EVT was found to positively and significantly impact the primary outcome (OR 2,33; CI 95% 0,88-6,14; p=0.05).

Conclusions: Combined treatment doubled the chance of good functional outcome compared to EVT only. EVT in MeVOs AIS seems feasible and safe. To establish the efficacy and safety of EVT in MeVOs patients RCTs are warranted.

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FOCAL SLOWING OF EEG PREDICTS DELIRIUM OCCURRENCE IN ACUTE STROKE: A PROSPECTIVE, OBSERVATIONAL STUDY

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Background: Delirium is an acute, fluctuating neuropsychiatric disorder which often complicates acute stroke. The aim of the present study is to

evaluate the baseline resting-state EEG predictors of delirium in patients with acute stroke.

Materials and Methods: The design of the study is prospective, cross-sectional, observational. Patients were consecutively enrolled among patients admitted to the Stroke Unit of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome. Inclusion criteria were: age ≥18 years, diagnosis of acute stroke, a National Institute of Health Stroke Scale (NIHSS) score ≥1 at the time of first clinical evaluation, that is when the first assessment of delirium was performed. Exclusion criteria were: stroke mimics, extreme severity of clinical condition, sedation as defined by a Richmond Agitation Sedation Scale (RASS) <-3 [1]. All patients were clinically assessed for delirium occurrence by means of RASS and Confusion Assessment Method-Intensive Care Unit (CAM-ICU) [2]. Evaluations for delirium were performed at baseline and repeated at least once daily. After enrolment to study, all patients underwent 10 minutes eyes-closed resting state 19-electrods EEG recordings. EEG registrations were performed at baseline evaluation within 24 hours from admission. If a patient scored CAM-ICU positive at baseline evaluation, the EEG recording was excluded from analysis. The exact low-resolution brain electromagnetic tomography (eLORETA) [3] software was used for EEG power spectral density (PSD) analyses.

Results: A total of 90 patients were enrolled to study, 54 (60%) males. Mean age was 71.4±12.3, mean NIHSS score was7.6±6.1. A total of 21 (23.3%) patients developed delirium during the study period. The two subgroups (patients with delirium and patients without delirium) were not different regarding age, sex, side, and localization of the stroke lesion. Patients with delirium had higher NIHSS score (p=0.003), higher mRS pre-stroke (p=0.005), and had higher need for physical restraints prior to delirium development (p=0.04). The baseline resting state EEG in the delirium group revealed increased PSD of the delta band in the left middle frontal gyrus and left anterior cingulate cortex ($p<0.05$). Moreover, the delirium group had increased PSD of the theta band in the left middle and inferior frontal gyrus, left precentral gyrus, and left cingulate gyrus ($p< 0.01$).

Conclusions: The standard resting state EEG has a potential predictive role for delirium occurrence after acute stroke. Slowing of the background EEG in the left frontal and limbic lobes is a risk factor for delirium occurrence in patients with acute stroke.

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THROMBOLYSIS AFTER DABIGATRAN REVERSAL: A NATION-WIDE ITALIAN MULTICENTRE STUDY AND META-ANALYSIS

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Objectives: People with recent intake of direct oral anticoagulants (DOACs) are not eligible for thrombolysis in case of acute ischemic stroke. Idarucizumab can be used for prompt reversal of dabigatran, a commonly used DOAC, in order to regain eligibility for thrombolysis. This nation-wide study, systematic review and meta-analysis aimed at assessing efficacy and safety of dabigatran reversal before thrombolysis, providing updated estimates for treatment effect.

Materials and Methods: We recruited people undergoing dabigatran-reversal before thrombolysis at 17 stroke centers in Italy, and age, sex, NIHSS and modified Rankin scale (mRS)-matched acute ischemic stroke patients receiving reperfusion treatment (no reversal) in 1:5 ratio. Demographic, clinical and treatment data were collected in a predefined dataframe. We compared reversal and control group for (i) any brain hemorrhage, (ii) sICH (ECASS II), (iii) mRS 0-2 at 3 months and (iv) death. Systematic review followed predefined protocol (CRD42017060274) and aimed at collecting all studies comparing the outcomes of interest in thrombolysis after reversal vs controls. Meta-analysis of odds ratios was implemented with conservative estimates through random effect modelling.

Results: Overall, 256 people were included, 40 in reversal group and 216 matched controls. Beside previous stroke, more common in reversal group, the remaining cardiovascular risk factors seemed well-balanced. All but one patient in reversal group underwent thrombolysis, vs 79.6% in controls, which had marginally higher rates of endovascular thrombectomy. No significant differences were found in mRS, intracranial bleeding and sICH. The systematic review retrieved 316 records, of which 2 reached quantitative synthesis being large nation-wide case series conducted in Germany and New Zealand (n=1795, n=112 with reversal). No significant differences emerged for sICH, death and mRS 0-2, with a marginal increase in the latter with dabigatran reversal (OR=2.55, 95%CI=0.96-6.75).

Discussion and Conclusions: People treated with reperfusion strategies after dabigatran reversal with idarucizumab seem not to differ from matched patients with stroke regarding functional outcomes and risk of bleeding. Larger studies are needed to define the efficacy and safety profile of dabigatran-reversal before thrombolysis.

CEREBRAL AMYLOID ANGIOPATHY-RELATED INFLAMMATION WITH LEPTOMENINGEAL INVOLVEMENT AND RIGHT HEMISPHERIC PREVALENCE STUDIED WITH BRAIN ANGIOGRAPHY: A CASE REPORT

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Objectives: Cerebral amyloid angiopathy related-inflammation (CAARI) is a subset of cerebral amyloid angiopathy (CAA) that can manifest inflammatory findings at MRI, usually bilateral and asymmetric. We report a case of CAARI with isolated right hemispheric involvement and angiographic evidence of right fronto-parietal-temporal blood flow slowing.
Case report: A 68-year old woman with a negative prior history presented with minute-long episodes of paraesthesias affecting the second, third and fourth left fingers, with progressive irradiation to the whole left superior limb, shoulder and left inferior face. Emergency CT was inconclusive, whereas EEG showed slow and sharp fronto-temporal waves with alternating side, thus lacosamide 100 mg twice/day was started, with resolution of symptoms. Brain MR showed right hemispheric cortical superficial sideroses, also involving the right central sulcus and the adjacent post-central gyrus, multiple cortico-subcortical microbleeds and right cortical thickening, associated with narrowing of sulci and diffuse leptomeningeal enhancement. MR venous angiography showed low flow signal of the left transverse sinus and anterior third of sagittal sinus. The patient was admitted to the Neurology Unit with the working diagnosis of cerebral venous thrombosis. Neurological examination was negative, except for one brief episode of left fingers' paraesthesia, blood tests showed mildly elevated anti-beta2 glicoprotein I IgG and anti-cardiolipin IgG. CSF analyses was normal except positive biomarkers of Alzheimer's disease. A brain angiography showed diffuse blood flow slowing in the arteriolar, parenchymal and venous phases within the right fronto-parietal-temporal vascular regions. We concluded for the co-presence of hypoplasia of left transverse sinus and leptomeningeal CAA, that had become clinically manifest with the occurrence of paraesthetic transient focal neurological episodes (TFNE). In particular, the ensemble of the clinical manifestations, MRI alterations and leptomeningeal enhancement were considered compatible with CAARI, despite the third criteria for probable CAARI from Auriel et al.'s (JAMA, 2016) [1], requiring the characteristic white-matter alterations, was not formally met. A brain PET-MRI with 18F-florbetaben was performed, with mild uptake of the tracer in the right parietal cortex. After 3 months, antiphospholipid antibodies were found negative, control MRI scan did not show leptomeningeal enhancement and the patient remained asymptomatic under the antiepileptic treatment.

Conclusions: The present case shows that CAA and CAARI can involve only one hemisphere and can severely alter the arterial and venous cortical blood flow in the acute phase. Such phenomenon might be linked to the pathophysiological factors underlying amyloid angiopathy and may be worth investigating further in future studies.
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THROMBOLYSIS IN STROKE-HEART SYNDROME: AN USEFUL TOOL FOR NEUROCARDIAC WELLNESS?

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Background and aims; Stroke-Heart Syndrome is a well-known physiopatological condition of cardiac suffering due to cerebral injury secondary to major vessel occlusion in anterior circulation. It can be detected by electrocardiogram alterations or increase of cardiac blood biomarkers like BNP or Troponin. Thrombolysis is one of the therapeutic strategies used in cardiac setting to achieve myocardial reperfusion in ischemic pathology. Our aim was to investigate a possible ancillary effect of thrombolysis in mitigating Stroke-Heart Syndrome after acute ischemic stroke.

Materials: We retrospectively collected ischemic stroke patients admitted to Trieste Stroke Unit and acutely treated between August 1st, 2018 and December 31st, 2021, with a comparable major cerebral vessel occlusion in anterior circulation and without anamnestic ischemic cardiopathy.

Methods: We divided patients into two groups. Group 1 included patients treated with both thrombolysis and thrombectomy; Group 2 included primary thrombectomy because of absolute contraindication to endovenous treatment. High-sensitivity Troponin I (with potential following curve of values) and BNP were measured in first 48 hours. We used Kolmogorov–Smirnov test to investigate normal distribution of variables and non-parametric Mann-Whitney U test to analyze data with SPSS Statistics 23 (IBM, Armonk/NY, USA).

Results: Group 1 was composed by 92 patients, Group 2 by 28 patients. The groups didn't differ in distribution of age (median 78 vs 74), baseline NIHSS (median 16 vs 14), discharge NIHSS (median 4 vs 6), cardiovascular risk-factors (atrial fibrillation, dyslipidemia, hypertension, diabetes) or TOAST etiology. We found significant (p=0.05) difference in Troponin peak between Group 1 (median 16.5, 25th percentile 9, 75th percentile 39.25) and Group 2 (median 38, 25th percentile 11.75, 75th percentile 115.25), while there wasn't significant difference in first Troponin value (median 13 vs 16.5, p=0.193), BNP (median 454.5 vs 784, p=0.200) or electrocardiographic alterations.

Discussion: Significant difference in Troponin peak could suggest usefulness of thrombolysis added to thrombectomy in mitigating Stroke-Heart Syndrome, possibly maintaining cardiac microcirculation free from obstructions during ischemic stroke acute phase. Only acute cardiac biomarker like Troponin differs between the groups. Classical chronic biomarker like BNP doesn't show significant differences. ECG alterations are aspecific, without exhibiting typical ischemic signs.
Conclusions: Bridge therapeutic approach in treating acute ischemic stroke could play an ancillary effect on heart wellness in the contest of Stroke-Heart Syndrome, compared to primary thrombectomy. More studies are suggested to confirm our findings.
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EFFICACY AND SAFETY OF REPERFUSION TREATMENTS IN DISABLING VERSUS NON-DISABLING MILD STROKE DUE TO ANTERIOR CIRCULATION VESSEL OCCLUSION: A PROPENSITY SCORE MATCHED ANALYSIS

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Background and Aim: The benefit of distinguishing between disabling vs non-disabling deficit in mild acute ischemic stroke (AIS) due to EVT-targetable vessel occlusion (EVT-tVO), including anterior circulation large (aLVO) and medium-vessel occlusion (aMeVO), is unknown. Despite mild initial presentation, EVT-tVO patients have high a priori risk of clinical deterioration. We compared safety and efficacy of acute reperfusion treatments in disabling vs non-disabling mild EVT-tVO.

Material and Methods: From the SITS-International Stroke Thrombolysis and Thrombectomy Register (SITS-ISTR), we included consecutive AIS patients treated within 4.5h, with full NIHSS items availability and score =<5, evidence of aLVO (intracranial internal carotid artery, M1 occlusion or T occlusion) or aMeVO (A1-2 or M2-3). After propensity score matching (PSM) and adopting an available definition, we compared disabling vs non-disabling groups.

Results: We included 1459 patients. PSM analysis of disabling vs non-disabling EVT-tVO (n=298 per group) found no significant differences in efficacy (3-month modified Rankin Scale [mRS] 0-1: 68.3% vs 71.3%, p = 0.501; 3-month mRS 0-2: 77.7% vs 80.2%, p = 0.538; early neurological improvement: 38.6% vs 38.2%, p=0.928) and safety (non-haemorrhagic early neurological deterioration: 8.1% vs 6.6%, p=0.500; any intracerebral [ICH] or sub-arachnoid haemorrhage: 10.2% vs 9.6%, p=0.796; symptomatic ICH: 2.2% vs 3.0%, p=0.574; 3-month death: 10.0% vs 5.9%; p=0.133) outcomes. Secondary and sensitivity analyses showed consistently similar results.

Conclusion: Our study suggests that in cases of high risk of neurological deterioration, decision whether to treat mild EVT-tVO should be taken irrespective to the disability related to the presenting deficit. Further studies are needed to clarify the best reperfusion treatment in mild EVT-tVO.

PERFUSION IMAGING IN ANTERIOR LARGE VESSEL OCCLUSION ACUTE ISCHEMIC STROKE WITHIN 6 HOURS FROM SYMPTOMS ONSET: FROM TIME-WINDOW TO TISSUE-WINDOW

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Background: Little is known on the role of perfusion imaging for patients treated within early (<6h) time window. We aimed to investigate whether pre-treatment perfusion parameters are associated with outcome in early-treated large vessel occlusion (LVO) acute ischemic stroke (AIS) patients.

Methods: Based on the ASTRAL registry, we retrospectively included consecutive anterior circulation LVO patients, treated within 6h and with available baseline perfusion data. We assessed the absence of perfusion-based mismatch according to EXTEND-IA, SWIFT-PRIME, DEFUSE 3 and DAWN trial, ischemic core and penumbra volumes, and perfusion/core ratio. We evaluated their association with 90-day modified Rankin Scale [mRS] >2) via univariate, multivariate and ordinal logistic regression analysis.

Results: 262 patients were included. Unmet EXTEND-IA criteria (29%) was independently associated (aOR 3.15 [95%CI 1.45-6.87]; p=0.004) with mRS>2, with aOR 2.77 (95%CI 1.53-5.04; p=0.001) for a shift in 90-day mRS. Unmet SWIFT-PRIME criteria (35.5%) was independently associated (aOR 3.62 [95%CI 1.71-7.65]; p=0.001) with mRS>2, with aOR 2.72 (95%CI 1.54-4.81; p=0.001) for a shift in 90-day mRS. Unmet DEFUSE 3 criteria (31.7%) was independently associated (aOR 2.86 [95%CI 1.34-6.10]; p=0.007) with mRS>2, with aOR 2.65 (95%CI 1.49-4.70; p=0.001) for a shift in 90-day mRS. Unmet DAWN criteria (64.1%) was independently associated (aOR 3.68 [95%CI 1.68-8.06]; p=0.001) with mRS>2, with aOR 3.26 (95%CI 1.87-5.67; p<0.001) for a shift in 90-day mRS. Ischemic penumbra volume (aOR 0.57 [95%CI 0.34-0.95]; p=0.032) and penumbra/core ratio (aOR 0.75 [95%CI 0.59-0.94], p=0.011) were also independently associated with mRS>2, with aOR 0.61 (95%CI 0.43-0.87; p=0.006) and 0.81 (95%CI 0.69-0.95; p=0.009) respectively for a shift in 90-day mRS.

Conclusion: The perfusion criteria for the early and extended time-window EVT-trial are not met in a substantial proportion of early arriving patients and are independently associated with poor outcome. If confirmed, our results may suggest a paradigm shift in acute stroke management: from time-window to tissue-window.

ETIOLOGIC RECLASSIFICATION OF CRYPTOGENIC STROKE AFTER IMPLANTABLE CARDIAC MONITOR AND COMPUTED TOMOGRAPHY ANGIOGRAPHY REASSESSMENT

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Introduction: Up to one third of all ischemic strokes do not receive a definite etiology and are defined cryptogenic. Over the last years, some studies have hypothesized different mechanisms possibly underlying cryptogenic stroke (CS), including subclinical atrial fibrillation (AF), nonstenotic carotid plaques (NCP), and aortic arch atherosclerosis (AAA). In a cohort of CS patients, we aimed to: 1) evaluate the prevalence of subclinical AF, NCP, and AAA, and to reclassify stroke etiology accordingly; 2) compare the clinical features of patients with reclassified stroke source with those with confirmed CS.

Methods: Data of patients hospitalized for CS in one hospital between January 2018 and February 2021 were retrospectively analyzed and re-assessed. CS patients were proposed implantable cardiac monitoring (ICM) to detect subclinical AF. Baseline computed tomography angiography (CTA) scans were re-evaluated to assess the presence of NCP and AAA. Since aortic plaques with ulceration or intraluminal thrombus were considered pathogenetic during initial work-up, only patients with milder AAA were included. Stroke etiology was reclassified as "cardioembolic" if subclinical AF was detected, "atherosclerotic" in case of ipsilateral NCP and/or AAA, "mixed" if both AF and NCP/AAA were detected, "true cryptogenic" if no AF, ipsilateral NCP, or AAA were detected. We compared baseline clinical, radiological, and echocardiographic characteristics of patients with "true cryptogenic" stroke and those with reclassified stroke etiology.

Results: Among 63 implanted CS patients, 21 (33%) were diagnosed with AF over a median follow-up time of 15 months, 12 (19%) had ipsilateral NCP, and 6 (10%) had AAA. Based on the pre-specified criteria, stroke etiology was reclassified in 30 patients (48%): cardioembolism was the most common possible etiology (n=14, 22%), followed by atherosclerosis (n=9, 14%) and mixed (n=7, 11%). Patients with true cryptogenic stroke had younger age compared to those with re-classified etiology (median age 67 vs. 76 years; p=0.001), with no differences in other baseline characteristics.

Discussion/Conclusion: A possible covert stroke source can be recognized in half of the patients with a diagnosis of CS through long-term cardiac monitoring and careful CTA re-assessment.

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INTERNAL CAROTID ARTERY PATENCY AFTER MECHANICAL THROMBECTOMY FOR STROKE DUE TO OCCLUSIVE DISSECTION: IMPACT ON OUTCOME

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Background: Internal carotid artery dissection (ICAD) is a rare cause of acute ischemic stroke with large vessel occlusion (AIS-LVO). The aim of this study was to investigate the impact on outcome of internal carotid artery (ICA) status (occlusion vs. patency) after mechanical thrombectomy (MT) for AIS-LVO due to occlusive ICAD.

Methods: We included consecutive patients with AIS-LVO due to occlusive ICAD treated with MT from January 2015 to December 2020 in three European stroke centers. We excluded patients with unsuccessful intracranial reperfusion after MT (modified Thrombolysis in Cerebral Infarction [mTICI] score <2b). We compared 3-month favorable clinical outcome rate, defined as a modified Rankin scale (mRS) score ≤2, according to ICA status (patency vs. occlusion) at the end of MT and at 24-hour follow-up imaging, using univariate and multivariable models.

Results: Among 70 included patients, ICA was patent in 54/70 (77%) at the end of MT, and in 36/66 (54.5%) patients with 24-hour follow-up imaging. Among patients with ICA patency at the end of MT, 32% presented ICA occlusion at 24-hour control imaging. Favorable 3-month outcome occurred in 41/54 (76%) patients with ICA patency post-MT and in 9/16 (56%) patients with occluded ICA (p=0.21). Rates of favorable outcome were significantly higher in patients with 24-hour ICA patency compared to patients with 24-hour ICA occlusion (32/36 [89%] vs. 15/30 [50%]), with an odds ratio (adjusted for baseline National Institutes of Health Stroke Scale [NIHSS] score, Alberta Stroke Program Early CT Score [ASPECTS], and time from symptoms recognition to MT) of 4.58 (95% CI, 1.25 to 16.72).

Conclusion: Obtaining a sustained (24-hours) ICA patency after MT could be a therapeutic target for improving functional outcome in patients with AIS-LVO due to ICAD.

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EPILEPSY IN CEREBRAL AMYLOID ANGIOPATHY: A MULTICENTRE OBSERVATIONAL RETROSPECTIVE STUDY OF A LARGE POPULATION

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Aims: Cerebral amyloid angiopathy (CAA) is a major cause of intracranial haemorrhage (ICH) in the elderly and epilepsy is a possible consequence. Currently there is a lack of studies on the role of epilepsy in CAA and the few available data mainly focus on the inflammatory form of the disease (CAA-ri). In this paper, we described the main features of epilepsy in a large cohort of CAA and identified predisposing factors for the development of seizures.

Methods: Retrospective, multicentre, observational study, with consecutive recruitment of CAA patients. Demographic, clinical, and instrumental data were collected. Radiological features (cerebral microbleeds, superficial cortical siderosis, perivascular spaces, white matter hyperintensity, small vessel disease score), presence of ICH and/or inflammation (CAA-ri), age at onset and gender were analysed as independent variables in separate models.

Results: 42.9% (84) of the 196 patients recruited developed epilepsy during prolonged follow-up. The most frequent type of seizure was focal (77.9%); 22.5% of the epilepsy patients developed a status epilepticus and 12.2% a drug-resistant form. The probability of developing epilepsy was significantly higher in patients with CAA-ri (OR 1.86, 95% CI: 1.04-3.32, p value=0.036) and in the presence of cSS at MRI scan (OR: 2.31, 95% CI: 1.05-5.06, p value=0.037).

Conclusion: Epilepsy is a common manifestation of CAA, although the pathogenetic mechanisms linking these two conditions are unknown. CAA-ri and cSS represent two predisposing factors for the development of seizures. These data confirm the importance of an accurate characterisation of patients with CAA in order to identify those at increased risk of epilepsy.

COGNITIVE IMPAIRMENT PREDICTS STROKE INCIDENCE AND MORTALITY: RESULTS FROM A POPULATION BASE STUDY IN AN ELDERLY SICILIAN POPULATION

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Background and Purpose: Despite improvements in treatment, stroke remains a leading cause of mortality and long-term disability. Several risk factors are known to increase mid- and long-term mortality of ischemic stroke patients. Information on predictors of early stroke mortality is scarce but often requested in clinical practice. Unfortunately, scanty population-based studies investigated predictors of cerebrovascular disease and mortality. Basing on a population-based study, we therefore aimed to identify predictors of stroke mortality.

Methods: A prospective population-based study has been performed in the elderly population of Bagheria, Sicily. Differences in patient characteristics, cognitive impairment, premorbid risk factors and hospital investigations were analyzed by t test or Chi square where appropriate. Relative risk, and Kaplan-Meier analyses were performed to investigate the effect of determinants on stroke occurrence and mortality. Statistical analyses were performed using SPSS software version 18.

Results: During the 9 year follow-up period 176 individuals out of a total population of 19800 developed a CVD. Risk for stroke was significantly higher among individuals affected by Cognitive Impairment (RR 1.7; 95% CI 1.3-2.1). BMI distribution showed a significantly different pattern between individuals who developed a CVD compared to the others (p for trend= 0.01). We also observed a significant association between male sex and a higher stroke related mortality compared to women (RR 1.22; 95% CI 1.1-1.4). K-M estimates showed a cumulative probability for stroke occurrence during follow-up higher among patients affected by cognitive impairment (log rank test p<0.0001). Survival estimates showed also a significant association for a lower survival among individuals with a stroke having a cognitive impairment compared to the others (p<0.0001).

Discussion: Obesity is widely accepted and known as a cardiocerebrovascular risk factor that increase mortality, especially for his cumulative risk with other high-risk factor (such as hypertension, hypercholesterolemia and high triglycerides). Cognitive impairment after ischaemic stroke injury is common in different populations. However, it has before described in other studies that if there are pre-existing MCI and pre-existing dementia, stroke worsens the cognitive impairment and increase death's risk. Such associations are not fully understood, nevertheless elder age may in part explain this correlation playing an important role in term of frailty, medical approach and hospitalization.

Conclusions: Findings of this study suggest that CI and BMI are associated with CVD occurrence and mortality displaying gender differences.

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ASSOCIATION BETWEEN CEREBRAL VASOREACTIVITY AND EXECUTIVE DYSFUNCTION IN ACUTE CEREBROVASCULAR DISORDERS

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An association between hemodynamics, cerebral vasoreactivity (CVR) and cognitive impairment in neurodegenerative and chronic cerebrovascular disorders (CVD) is reported. However this associations was not elucidated in the acute phase of CVD. Thus, the aim of this study was to evaluate cognitive functions, homodynamic parameters, CVR and their associations in acute and subacute CVD.

Methods: Patients with acute CVD, NIHSS score ≤ 10, no intracranial stenosis, no dementia or non-compensated cardiovascular diseases, who didn't undergo endovascular acute treatment were recruited. Patients were evaluated within 10 days of symptoms onset (T1) and after 3 months (T2). Clinical and demographic data were collected. NIHSS, MoCA, FAB and Stroop test (SCWI) were used to evaluate disease severity and cognitive functions. Hemodynamic parameters and Breath Holding Index (BHI) were measured with Transcranial Doppler (TCD).

Results: Sixty-eight patients were recruited [Age: 70 ± 11 years; M: 34 (50%)], 47 completed evaluation at T1 and 33 at T2. MoCA, FAB and SWCI improved between T1 and T2 and MCA max velocity, PI and BHI decreased. No significant correlation were found between the cognitive scores and clinical or TCD measurements at T1 while FAB and SCWI showed a negative correlation with MCA mean and minimum velocity at T2.

Conclusion: A mainly executive cognitive impairment in the acute phase of CVD was found with an improvement in the subacute phase and a role of altered blood flow regulation could be hypothesized. An increased CVR was observed in the acute phase but this seems to be an independent phenomenon.

VALIDATION OF COMBINED SCORE ASSESSING ASPECTS AND COLLATERAL VESSEL STATUS FOR OUTCOME PREDICTION IN LARGE-VESSEL OCCLUSION ACUTE ISCHEMIC STROKE

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Aims: To assess the accuracy of "tissue viability score" combining ASPECTS and collateral vessel status for prediction of functional outcome after acute ischemic stroke (AIS) with large-vessel occlusion (LVO).

Materials: Validation cohort comprising consecutive AIS patients admitted to our Comprehensive Stroke Center in 2019-2021 with anterior-circulation LVO, treated according to clinical guidelines within acute-phase treatment window.

Methods: Alberta Stroke Program Early CT Score (ASPECTS) and collateral vessel status (poor=0, intermediate=1, good=2) were rated on baseline non-contrast computed tomography (NCCT) and CT angiography scans and integrated into previously proposed "tissue viability score" (Vabanesi et al., Eur J Neurol 2019), calculated multiplying the three-level (0-to-2) collateral vessel score by 0-to-2 normalized ASPECTS

(ASPECTS ≤6 being 0; ASPECTS 10 being 2). Favourable stroke outcome was defined as mRS ≤ 2 at 90 days.

Results: 102 consecutive AIS patients were included, with median age 74 (IQR 65-84) and baseline NIHSS 15 (IQR 8-18). All subjects received acute-phase treatment: 92 mechanical thrombectomy (31 combined with thrombolysis), 10 intravenous thrombolysis. Tissue viability score assessing ASPECTS and collateral status predicted stroke outcome, controlling for onset-to-treatment time and treatment type ($p<0.001$). ROC curve was built (AUC 0.728); scores below the optimal threshold (1.5 units) displayed 53.1% (CI: 38.3–67.5) sensitivity and 79.3% (CI: 65.9–89.2) specificity for poor functional outcome at 90 days. Logistic regression model showed +16% odds for good outcome (OR 1.16, 95% CI: 1.08–1.26, $p<0.001$) for unitary increase of tissue viability score.

Discussion: Despite the recent focus on advanced stroke imaging techniques, in most clinical settings baseline assessment of AIS patients is performed with NCCT and CT angiography. In a recent multicenter work (Nguyen et al., JAMA Neurol 2022) in late-presenting LVO strokes, patient selection with NCCT alone showed comparable outcomes to advanced imaging protocols used in randomized trials. Our proposed score integrates collateral vessel status with NCCT-ASPECTS to predict sustained tissue viability and good functional outcome after acute treatment. The findings from this validation study suggest good replicability of our score within the same Institution. Analysis on multicenter cohorts may further support the validity of this approach.

Conclusions: Acute-phase decision making in acute ischemic stroke requires fast and reliable outcome prediction tools to optimize patient selection, resource usage and to prevent iatrogenic harm. Our proposed score combining ASPECTS and collateral vessel status showed promising accuracy in this validation cohort in predicting stroke functional outcome after acute treatment.

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BRANCH ATHEROMATOUS DISEASE: AN UNDERESTIMATED CAUSE OF EMBOLIC STROKE OF UNDETERMINED SOURCE

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Objectives: The term “branch atheromatous disease” (BAD) is used to describe a subcortical or pontine small infarct larger than lacunar stroke caused by an occlusion or stenosis at the origin of a deep penetrating artery of the brain, differently from small vessel disease in which lipohyalinosis changes are located distally. For their different follow-up, it is important to distinguish BAD from other causes of embolic stroke of undetermined source (ESUS).

Materials and Methods: We report the case of a 76-year-old woman with a history of arterial hypertension and hypercholesterolemia, admitted to the Emergency Department because of the acute onset of right hemihyposthenia and mild dysarthria (NIHSS 5).

Results: A CT scan of the brain showed no density alterations and a CT angiography showed no intracranial large vessel occlusion. The patient was not treated with intravenous thrombolysis. After 24 hours from acute onset, we observed a worsening of the motor deficit (NIHSS 11). A brain MRI showed an acute left paramedian pontine infarct with no hemosiderin deposition detected in GRE/SWI sequences. No intracranial stenoses were shown on transcranial doppler. A 24-hour Holter monitoring recorded sinus rhythm and no left atrial enlargement was found on echocardiogram.

Discussion: Our patient’s AF-ESUS score was 0, suggesting a noncardioembolic stroke. Early neurological deterioration (END) is reported to occur frequently in BAD. The site (paramedian), size (>15 mm) and shape (“wedge-shaped”) of the ischemic lesion were typical for BAD caused by occlusion of a deep penetrating artery which arises from basilar artery. We decided to start treatment with acetylsalicylic acid and high-dose statin and to set up a follow-up based on cardiovascular risk factor control.

Conclusions: A lot of patients with stroke due to BAD are discharged with the diagnosis of ESUS. Imaging (site, size and shape of the lesion), AF-ESUS score and the presence of END with no critical stenosis of the epiaortic and intracranial arteries can help us to make a correct diagnosis of BAD and thus to define appropriate diagnostic work-up and follow-up.

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CEREBRAL CALCIFIC EMBOLI: A CLINICAL AND RADIOLOGICAL STUDY

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Purpose: Cerebral calcific emboli (CCE) are quite rare and a relatively small number of cases is reported in literature [1]. The aim of our study was to identify CCE among our series of patients with stroke and to study radiological and clinical features, especially in terms of outcome and etiology.

Materials: We considered all patients diagnosed with ischaemic stroke or TIA admitted to the Neurology Department of Manzoni Hospital in Lecco in one year (August 2020 - August 2021). A Neuroradiologist selected all patients with CCE based on a brain CT scan performed in the Emergency Department.

Methods: Among 215 patients with acute ischaemic stroke/TIA, a total of 11 patients with CCE were identified. For these patients, we evaluated origin and number of emboli, their attenuation and localization, type of treatment and eventual subsequent fragmentation of emboli, whether stroke was iatrogenic, severity of initial stroke in terms of NIHSS and its outcome.

Results: Mean age of CCE patients (73% male) was 81 years. No event was "post-procedural" and presumed etiologies were atheroembolism with significant carotid stenosis (36%) and cardioembolism (27% AF, 20% ESUS). Widespread aortic or supra-aortic trunks wall calcifications (91%) and valvulopathy with calcific aortic stenosis or mitral annulus calcifications (54%) were reported. Mean number of emboli was 1,5 (1-3) and mean attenuation was 170,5 (67-315). Almost all emboli were unilateral in MCA territory, of which 45% with a documented occlusion on CT angiography; in one case they were bilaterally located in the anterior circulation. In two cases we reported fragmentation of emboli after clinical onset. Five patients (45%) underwent thrombolysis, whereas no patients had mechanical thrombectomy. In 55% of all patients, there was an NIHSS improvement at discharge (60% among patients undergoing thrombolysis).

Discussion: For CCE, we identified some common features: they were preferentially unilateral and located in MCA territory, had higher attenuation than that of intraluminal thrombi, and sometimes underwent fragmentation. As expected, significant carotid artery stenosis and cardioembolic sources represent the most frequent etiology with a typical concomitant calcific valvulopathy. Thrombolysis appeared however quite effective in our cohort, despite the different embolus architecture, although this is debated [2,3].

Conclusions: CCE are not so uncommon entities. Looking for a calcific cerebral embolus should always be performed on the baseline CT scan of an ischaemic stroke patient. Reperfusion strategies seem to be safe in these patients, but their efficacy as compared with other stroke patients needs further study.

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THE IMPACT OF REPERFUSION TREATMENTS ON OUTCOME OF MIDDLE-OLD AND OLDEST-OLD STROKE PATIENTS

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Objectives: Intravenous thrombolysis (IT) and mechanical thrombectomy (MT) are the most effective treatments for acute ischaemic stroke (AIS) and recently the time window for both these treatments has been largerly extended. In clinical practice, older patients are often treated only with antiplatelet therapy (AT), probably for the higher risk of complications as brain haemorrhage, infection or death.

Aim of this study was to evaluate, in a population of middle-old (75-84 years) and oldest-old (≥85 years) subjects, the efficacy and safety of different treatments for AIS (IT, IT+MT, MT or AT). Moreover, we evaluated mortality and incidence of serious complications in this sample.

Patients and Methods: All patients aged over 75 years admitted for AIS in a 4-year period in two Stroke Units (Azienda Ospedali Riuniti di Ancona; Istituto di Ricerca Geriatrica INRCA, Ancona) were enrolled. The physician in each case considered all treatment options and chose the best approach. NIHSS and modified Rankin Scale (mRS) were calculated and differences between admission and discharge scores, defined as delta (NIHSS) and delta(mRS), were evaluated. We analyzed the relationship between delta (NIHSS), delta(mRS) and type of procedure with a GLM/Multivariate model. Differences in mortality and incidence of serious complications were analysed with the chi-square test.

Results: 273 patients, mean age 84.07 (±5.47) years were included. The Delta (NIHSS) was significantly lower in patients treated with AT than in those treated with IT and MT ($p<0.009$ and $p<0.005$, respectively). Haemorrhagic infarction occurrence was significantly lower ($p<0.0001$) among patients treated with AT (10.6%) or IT (16.7%) compared to MT (34.9%) or MT+IT (37.0%). No significant difference was observed for in-hospital mortality. Age did not influence the outcome.

Conclusions: Our results suggest that IT and MT are effective approaches also in middle-aged and older patients, with the better outcome and lower disability. On the other side, MT is associated to a higher quote of complications. These results underlined the need of a good selection of the patients to submit to these procedures, not based only on age but on a more global evaluation of pathological conditions.

DUAL ANTIPLATELET THERAPY FOR SECONDARY PREVENTION IN INTRACRANIAL ATHEROSCLEROTIC DISEASE: A NETWORK METANALYSIS

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Objectives: Intracranial arterial stenosis (ICAS) is a non-marginal cause of stroke/TIA and is associated with high stroke recurrence rate. Some studies have investigated the best secondary prevention ranging from antithrombotic therapy to endovascular treatment (ET). However, no direct comparison between all the possible treatments is currently available especially between single and double anti-platelet therapy (SAPT and DAPT). We aimed to establish whether DAPT is more effective than SAPT in preventing the recurrence of ICAS-related stroke, by means of a network metanalysis (NMA).

Materials: We performed a systematic review of trials investigating secondary prevention (Single or Double antiplatelet therapy, Anticoagulant treatment or Endovascular treatment) in patients with symptomatic ICAS available in Medline, Scopus, Web of Science from January 1989 to May 2021. We included adult patients (>18 years old) with ischemic stroke or TIA of presumed ICAS origin within 30 days from symptom onset.

Methods: We defined the primary outcome as early recurrence of ischemic stroke or TIA at 90 days and the secondary efficacy outcome as a composite of ischemic stroke/TIA, myocardial infarction, any hemorrhage, and death from any cause. We defined the safety outcome as the occurrence of any major hemorrhage. We performed a network metanalysis (NMA), which is a statistical method that allows performing indirect comparisons between treatments, in accordance to PRISMA guidelines.

Results: We identified 815 studies and included 5 trials in the NMA. DAPT was superior to SAPT and DAPT+ET in preventing stroke/TIA

recurrence (respectively OR 0.59, CI 0.39-0.9 and OR 0.49, CI 0.26-0.88), while no difference was found between DAPT and oral anticoagulant therapy (OAC). DAPT was safer than OAC (OR 0.48, CI 0.26-0.89) and DAPT+ET (OR 0.50 CI 0.35-0.71), while no difference was found between DAPT and SAPT in terms of safety.

Discussion: We found that DAPT is more effective than SAPT in reducing the risk of recurrence of ischemic stroke and it does not increase the risk of hemorrhage. The use of DAPT for 90 days followed by aspirin alone is currently suggested as secondary prevention for patients with 70-99% ICAS, but it is more an experts' opinion than an actual comparison of quantitative data. Therefore, the purpose of this analysis was to offer an objective statistical comparison of all the data currently available on this topic.
Conclusions: This NMA suggests that DAPT is more effective than SAPT for secondary stroke prevention in patients with ICAS, without increasing the risk of hemorrhage.
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DEGENERATIVE DISEASES CLINICAL RELATIONSHIPS BETWEEN MOTOR AND COGNITIVE CAPACITIES IN PARKINSON'S DISEASE – DESCRIPTIVE DATA FROM GECO-PARKINSON STUDY

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Objectives: In its evolution, Parkinson's disease (PD) shows a progressive loss of both motor and cognitive functions (particularly executive and attentional domains) (1). Different studies consistently demonstrate the evidence of gait involvement by executive functions impairment; that makes possible to formulate the hypothesis that a motor parameter may acts as a cognitive decline marker possibly to catch early in the disease progression (2) and that is our major objective.

Materials: We use standardized clinical scales to assess motor (H&Y, UPDRS-III), cognitive (MMSE, MoCA, FAB), psychiatric (BDI-II, BAI), non-motor symptoms (RBD Screening Questionnaire, Hyposmia Rating Scale) of patients with PD. Other factors have been taken in account: levodopa equivalent daily dose (LEDD), quality of life (PDQ-8), motricity (IPAQ-SF), risk of fall (Tinetti's scale, Berg's scale, Falls Efficacy Scale). Gait related motor aspects are otherwise described through the use of a medical device (G-Walk®) worn around the waist by patients while performing standardized gait tests (6MWT and eTUG).
Methods: This is a multicentric study, with the aim of studying a sample of 60 PD patients along three years of observation. Inclusion criteria: diagnosis of idiopathic PD; H&Y between 2-3; age between 55-74 years. Exclusion criteria consider dementia and those clinical conditions that may limit locomotor capacities or cardio-pulmonary resistance (assessed with Cumulative Illness Rating Scale). Patients were assessed at baseline and annually.

Results: We enrolled 63 patients (M/F ratio 43/20), with a mean age of 65,2±5,1, equally distributed for clinical presentation (rigid-akynetic/tremor 31/32), mainly in H&Y fase 2 of the disease (84,2%). As the study is proceeding, we are so far completed the first-year follow-up of 43 patients (2 drop-outs) and the second-year follow-up of 15 patients (1 drop-out). Along the first year of observation we observed inconsistent changes in motor characteristics (UPDRS-III); in the 6MWT, mean cycle length and mean speed showed slight decreasing trend (-0,07 meters ±0.01 and -0,02 m/s ±0.01 respectively). Cognitive tests showed no significant changes among patients during time, and with not consistency among different tests; however, for the overall subset of the attentional-executive domains z-score there is a mean decrease of –1,17 (± 0.08).
Discussion: This study is designed to observe in real-life clinical activity what research in the laboratory setting (3) has currently postulated about the evolution of PD.

Conclusions: Although at a preliminary stage and without having the full data of the planned observation, what has been observed so far seems to support the initial hypothesis.
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ATYPICAL ALZHEIMER'S DISEASE: A MULTIMODAL NEUROIMAGING APPROACH

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Aims: The pathophysiological characterization of Alzheimer's disease (AD) variants requires a multimodal approach to define an individualized assessment. An Italian multicenter study (AMY-ITA) was designed, involving 15 centers, especially focusing on amyloid-PET characteristics in patients with atypical cognitive presentations of suspected AD origin.

Materials: We are enrolling consecutive patients with suspected atypical AD. They undergo a battery of neuropsychological tests, 3T brain MRI, amyloid-PET with F18-Florbetaben (FBB) and 18F-FDG-PET. FBB-PET is acquired also with an early scan (5 min soon after tracer injection), in order to obtain a surrogate map of regional cerebral blood flow (rCBF).

Methods: The main objectives are to evaluate the variants in terms of i) global and regional amyloid load, computed with a multiparametric approach (SUVr, ELBA, TDr); ii) analysis of rCBF with voxel-based (e.g. SPM) and ROI-based methods; iii) compare the rCBF maps with cerebral metabolism maps obtained with FDG-PET; iv) global and regional volumetry on MRI; v) correlation with clinical-neuropsychological features.

Results: The study is ongoing and we present the preliminary results regarding the first 7 patients (3 men, 4 women, aged between 55 and 78 years, mean: 69± 7.7; MMSE score ranging from 14 to 29, mean: 22 ±5.9), including three posterior-variant, two logopenic-aphasia and one each with frontal-variant and corticobasal syndrome. All patients but the corticobasal syndrome and the frontal-variant ones showed brain amyloidosis. The five patients with amyloidosis ranked between 0.57 and 0.70 in a 0-1 scale for global amyloid load, as derived by the integration of the three semi-quantification methods. The two negative patients ranked 0.2 and 0.25, respectively. The comparative analysis of rCBF and FDG-PET maps showed consistency, revealing hypometabolism/hypoperfusion especially in posterior parietal and lateral temporal regions. Individual analysis of MRI reveals parietal-atrophy in 5 patients (Koedam scale 2), while no one presented significant mesial-temporo-atrophy (maximum Scheltens scale 1.5).

Discussion: In the patients analyzed so far there is a good consistency between brain metabolism and rCBF, while AD etiology was confirmed in 5 of 7 patients.

Conclusions: Individual imaging phenotyping of atypical presentation of AD appears essential. If the correspondence between rCBF and FDG-PET was confirmed, it can be hypothesized to use dual acquisition of amyloid-PET to obtain both a marker of amyloidosis and of neurodegeneration (rCBF).

INSIDE THE KURU-PLAQUE VARIANT (MV2K) OF SPORADIC CREUTZFELDT-JAKOB DISEASE: A DETAILED CLINICAL AND HISTO-MOLECULAR APPRAISAL

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Aims: To investigate in-depth the clinicopathological heterogeneity characterizing the kuru-plaque variant (MV2K subtype) of sporadic Creutzfeldt-Jakob disease (sCJD).

Methods: We evaluated neurological histories, results of cerebrospinal fluid (CSF) biomarker studies (RT-QuIC, 14-3-3 protein, total-tau, NfL), brain diffusion-weighted resonance imaging (DW-MRI), and electroencephalographic recordings (EEG) in 126 patients with a definite (n=87) or probable (n=39) diagnosis of sCJDMV2K. In definite cases, the histo-molecular assessment included PrPSc typing by western blot, standard histologic stainings, and PrP immunohistochemistry in several brain areas. Additionally, we investigated the prevalence and topographic extent of mixed histotypes (i.e., MV2K+MM2C) and the number of cerebellar kuru plaques and their effect on clinical phenotype.

Results: The mean disease duration was 18.0±11.8 months. Duration correlated positively with the severity of pathologic change and the number of cerebellar kuru plaques (rho=0.397, p=0.002). At onset and iduring early stages patients manifested prominent, often mixed, cerebellar symptoms and cognitive complaints (mainly memory loss), variably associated with behavioral/psychiatric, and sleep disturbances. Gait instability was the most frequent isolated presentation (19.8%). Full-blown dementia was rare in the early stage. No significant clinical differences were detected by comparing pure and mixed histotypes (MV2K+MM2C). CSF prion RT-QuIC was positive in 74/76 (97.3%) cases, while 14-3-3 protein and total-tau (cut-off >1250 pg/ml) in 52.6% and 75.9% respectively. NfL was increased in all tested cases (mean 8447.6±4772.6 pg/ml). Brain DW-MRI showed hyperintensity of striatum, cerebral cortex, and thalamus in 81.4%, 49.3%, and 33.8% of cases, and a profile typical for CJD in 71 out 77 (92.2%). An abnormal cortical signal was most frequently detected in mixed MV2K+MM2C than pure MV2K (64.7% vs. 16.7%, p=0.007). EEG revealed periodic sharp-wave complexes in only 8.7% of cases.

Conclusions: sCJDMV2K is a relatively common subtype showing some "atypical" features. Consequently, often patients do not fulfill diagnostic criteria in the early disease stages. Atypical features include the long disease duration, the relative slow worsening of cognitive decline, and the poor sensitivity of some diagnostic tests such as CSF 14-3-3 protein detection and EEG. Moreover, this subtype uniquely accumulates PrP in the form of cerebellar amyloid kuru plaque. Clinicians should consider sCJDMV2K in any patient presenting (or early developing) mixed cognitive and cerebellar dysfunctions. CSF prion RT-QuIC and brain DW-MRI represent the most sensitive diagnostic tests. These data strongly suggest that, despite some atypical features, sCJDMV2K can be clinically diagnosed accurately based on clinical data, DW-MRI, CSF prion RT-QuIC assay, and codon 129 genotyping.

CEREBROSPINAL FLUID ß-SYNUCLEIN AS A SYNAPTIC BIOMARKER FOR PRECLINICAL ALZHEIMER'S DISEASE

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Background: β-Synuclein is a presynaptic protein whose cerebrospinal fluid (CSF) concentrations are elevated in Alzheimer's diseases (AD), at similar extents at the mild cognitive impairment (MCI-AD) and dementia stages (dem-AD). Here, we aimed to investigate CSF β-synuclein levels in cognitively unimpaired subjects with AD (preclinical AD, pre-AD). Moreover, we compared β-synuclein with another synaptic protein, α-synuclein, and two surrogate biomarkers of neuroaxonal damage, namely total tau protein (t-tau) and neurofilament light chain protein (NfL).

Methods: We measured CSF β-synuclein, α-synuclein, NfL and t-tau levels in 75 AD patients and 35 controls (subjective memory complaints, SMC-Ctrl n=13, non-degenerative neurological disorders, Dis-Ctrl n=22). First, we compared AD subgroups (pre-AD n=17, MCI-AD n=28 and dem-AD n=30) with all controls. Then, we focused on pre-AD cases with respect to SMC-Ctrl subjects. Finally, we assessed the correlations among biomarker levels and their diagnostic accuracy in the identification of AD cases.

Results: CSF β-synuclein, α-synuclein, NfL and t-tau levels significantly increased in AD patients compared to controls ($p<0.0001$ for all comparisons). Pre-AD subjects showed higher CSF β-synuclein ($p<0.0001$), α-synuclein ($p=0.02$) and t-tau ($p<0.001$) concentrations compared to controls and lower t-tau levels in comparison to MCI-AD ($p=0.04$) and dem-AD ($p=0.01$). NfL increased only in dem-AD patients versus controls ($p=0.001$). In pre-AD patients, CSF β-syn showed significant correlations with t-tau ($r=0.88$, $p<0.0001$) and NfL levels ($r=0.59$, $p=0.01$). Based on receiver operating characteristic (ROC) analysis, CSF β-synuclein showed a good accuracy for the discrimination of AD versus controls (AUC: 0.91, sensitivity: 86.7%, specificity: 82.5%), pre-AD versus controls (AUC: 0.97, sensitivity: 94.1%, specificity: 95.0%) and pre-AD versus SMC-Ctrl (AUC: 0.99, sensitivity: 94.1%, specificity: 100%).

Discussion: Here, we report on the increase of CSF β-synuclein levels at all AD stages, since the preclinical phase and without differences among clinical subgroups. While β-synuclein and α-synuclein concentrations might reflect the very first synaptic damage occurring in AD, the progressive rise of t-tau and NfL may rather mirror the increasing burden of neurodegeneration along the disease continuum.

Conclusions: β-Synuclein significantly increases in CSF of AD patients independently of disease stage and before biomarkers of neuroaxonal damage. CSF β-synuclein might, thus, serve as a novel biomarker of synaptic dysfunction in the whole AD continuum.

CAN THE USE OF HUMANOID ROBOTS IMPROVE THE DIAGNOSTIC SENSITIVITY OF THE MMSE IN DIAGNOSING MCI?

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Objective: In the field of healthcare, the last few decades have witnessed an increasingly shift towards technologizing healthcare. The use of technology, like robots, is now routine in most countries of the world, although their spread across the globe is not uniform. Specifically, in healthcare, humanoid robots were introduced essentially to facilitate the rehabilitative processes [1], to improve patient's recreation, recovery and communication. Aim of this study is to evaluate the effectiveness of humanoid robots in a diagnostic process.

Materials: We applied humanoid robot technology in outpatient activities in order to increase the diagnostic sensitivity of Mini Mental State Examination (MMSE) in diagnosing mild cognitive impairment (MCI).
Methods: We enrolled twenty MCI patients (9 males and 11 females) with mean age of 73.10 ± 7.97 years at our Centre. According to a randomized design, patients included in the study underwent MMSE administered by a neurologist/psychologist (Group-H) or administered by a semi-humanoid robot manufactured by SoftBank Robotics, called Pepper (Group-R). In order to avoid learning bias, each patient underwent to MMSE for the first time. Scores obtained at MMSE of both groups were analysed. Furthermore, to produce parameters capable of evaluating patient's compliance to MMSE, a multiple-choice questionnaire (Q1), consisting of 7 items, was created and administered to each patient after the MMSE to explore different psychological aspects. Indeed, we would like to speculate that higher adherence to the MMSE test is able to increase the diagnostic sensitivity for MCI of the test. Statistical analysis was performed on averaged traces from each participant by using the R 3.0 software package. A 95% of confidence level was set with a 5% alpha error. Statistical significance was set at $p<0.05$.

Results: There were no significant differences between two groups in questionnaire and MMSE scores. Chi-square test did not show a significant difference between psychic domains relatively to the questionnaire Q1, while, Mann-Whitney U test did not show differences in MMSE scores between the two groups.

Discussion: Based on the results obtained from the analysis of these preliminary data, we can argue that there are no significant differences between the effectiveness of humanoid robots and humans in administering MMSE in MCI diagnostic process.

Conclusions: The results obtained suggest that the use of robots, as Pepper, in clinical practice can be supportive but not more effective in the diagnostic process of MCI. However, a larger sample is needed to further validate these initial results.

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GLIAL, MICROGLIAL AND APOE CONTRIBUTIONS ALONG THE ALZHEIMER'S CONTINUUM: CSF STREM-2, GFAP AND B-S100 IN SYMPTOMATIC SPORADIC AD

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Background: Neurodegeneration and astrogliosis are classically held as final events in the cascade of biological changes leading to Alzheimer's Disease (AD). However, many transversal mechanisms act synergistically at different time-points during this cascade [1], and amyloid (Aβ) pathology, tau-mediated mechanisms, neuroinflammation and astrogliosis influence each other's progression. We aimed at exploring the role of non-neuronal cellular contributions – namely Apolipoprotein E (ApoE), microglial activation and astrocytic reactivity – in a cohort of symptomatic patients with sporadic AD stratified according to the ATN system and ε genotype, compared with a group of healthy controls (HC).

Materials and Methods: We compared the CSF levels of sTREM-2 and two markers of astrocytic activation, GFAP and β-S100, between a cohort of 71 patients with AD (23 A+T- and 48 A+T+; 30 ApoE4 and 31 ApoE3) and 14 HC. Then, we performed a correlation analysis to explore the relationship between glial biomarkers and markers of neurodegeneration in each condition, first stratifying patients according first to the ATN system and second to ApoE genotype.

Results: A+T- and A+T+ showed higher mean values of sTREM-2 than HC (pholm <.001), with values being even higher in the latter (pholm=.045), regardless of ε genotype. Neither GFAP nor β-S100 levels resulted different across groups. Stratifying by ATN, we retrieved a positive correlation between sTREM-2 and Aβ42 in the ADc (p=.025) and in the A+T- group (p=.007). GFAP positively correlated with Aβ42 in the ADc (p=.007) and in the A+T+ group (p=.006), and also with sTREM-2 in the latter (p=.042). Stratifying by ApoE, carriers of ApoE4 showed a positive correlation between sTREM-2 and p-tau (p=0.046), which was absent in the ApoE3 group. Finally, we found a strong positive correlation between CSF sTREM-2 and β-S100 in the ADc (p <.001), that was retrievable even after stratification by both criteria.

Discussion: The increase of CSF sTREM-2 could delay the progression of Aβ pathology [2] in the A+T- group, but mediate neurotoxic effects when tauopathy sets in. Moreover, in our cohort the progression of tau-pathology seems to be driven by microglia in an ApoE-dependent manner [3]. Finally, astrocytic reactivity seems to be tied to both a non-specific compensatory inflammatory response to damage and to the acquisition of a neurotoxic phenotype induced again by disease-associated microglia. Overall, our results highlight complex in-vivo reciprocal influence between astrocytes, microglia, ApoE and both amyloid and tau pathology, adding evidence that the integrity of the neural system is much more complex than neuronal integrity alone.

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EFFECTS OF GENETIC VARIATIONS OF NGFR/P75NTR GENE ON ALZHEIMER'S DISEASE

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Objective: Alzheimer's Disease (AD) is the most widespread neurodegenerative disorder. AD is commonly categorized as either early onset (EOAD) or late onset (LOAD) based on an age cutoff, typically 65 years [1]. It has been shown that Single Nucleotide Polymorphisms (SNPs) of the Nerve Growth Factor Receptor (NGFR/p75NTR) gene could represent risk factors for AD. However, to date only a few studies have investigated this relationship with conflicting results [2,3]. The general aim of this study was to better characterize the association between NGFR/p75NTR SNPs in EOAD and LOAD patients.

Material and Methods: This study was conducted on 168 AD patients (60 EOAD and 108 LOAD) recruited at the Regional Neurogenetic Centre (CRN) – ASPCZ of Lamezia Terme (CZ, Italy). Nineteen tag-SNPs were selected and genotyped using TaqMan SNP genotyping assays on DNA extracts prepared from blood samples. The associations between tag-SNPs and AD were assessed by linear regression models after adjustment for gender, APOE genotype and level of education.

Results: The variability of two polymorphisms (rs2072446 and rs734194) was related to the onset of LOAD. LOAD patients carrying a single copy of the G allele of the rs734194 polymorphism had a mean age of onset of about 2.5 years higher than those who were homozygous for the T allele ($p = 0.024$). A similar effect was also detected for the rs2072446 polymorphism for which the carriers of the T allele showed a delayed age of onset of about 3.5 years than homozygotes for the C allele ($p = 0.048$). The variability of three investigated polymorphisms was correlated with MMSE score in EOAD patients. In particular, carriers of the rare alleles of the rs741071, rs2072446 and rs734194 polymorphisms showed a lower score on MMSE ($p = 0.048$; $p= 0.021$ and $p < 0.001$, respectively).

Discussion and conclusion: Our results suggest that polymorphisms in NGFR/p75NRT gene may influence the age of onset and the severity of AD revealing a new role of NGFR/p75NTR in both EOAD and LOAD from a genetic perspective. NGFR/p75NTR SNPs analysis should be considered for the genetic screening of AD and may have important implications for the understanding of AD pathogenesis, as well as for the development of novel therapeutic strategies. Further studies are needed to verify if these polymorphisms also determinate an increased risk for developing AD.

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VISUAL HALLUCINATIONS IN LEWY BODY DISEASE: PATHOPHYSIOLOGICAL INSIGHTS FROM PHENOMENOLOGY

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Objective: Visual hallucinations (VH) in Lewy body disease (LBD) have a heterogenous phenomenology classified into minor phenomena (MVH) and complex hallucinations (CVH). Mechanisms underpinning VH and their temporal aspects are largely unknown. According to the hodotopic model, we investigated whether changes in distinct cognitive domains and neural networks in the hallucination trait underpin temporal aspects of MVH and CVH in the hallucination state.

Materials and method: Thirty-five LBD patients with VH underwent a complete neuropsychological evaluation and resting-state fMRI. North-East-Visual-Hallucinations- Interview was used to assess their typical VH content, duration, and frequency.

Results: We found that MVH was not associated with cognitive impairment, while CVH was associated with impairments in visuoperceptual processes, attention and visual abstract reasoning. In seed-to-seed functional connectivity (FC) analysis we identified functional couplings associated with MVH and CVH temporal severity (duration x frequency), duration and frequency. MVH severity was negatively associated with FC between early visual areas (EVA) and ventral-visual-stream regions, and negatively associated with FC between brainstem and EVA, which may be linked to LBD brainstem neuropathology. CVH duration was positively associated with FC between ventral-visual stream and salience network (SN). CVH frequency was negatively associated with FC between DMN and SN.

Discussion: Functional alterations in distinct visual and attentional networks and their dynamic interaction in trait LBD hallucinators are linked to both the phenomenology of state content and its temporal characteristics. Within a network, VH frequency and duration may be linked to different types of functional alterations: increased connectivity leading to sustained activity prolonging VH (duration) and decreased connectivity increasing dysregulated, spontaneous activity (frequency).

Conclusion: These findings support the hodotopic hypothesis of VH and may reflect a link between VH phenomenology, LBD neuro- pathological progression and the involvement of specific neurotransmitter systems.

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RELATIONSHIP BETWEEN CSF TAU BIOMARKERS AND STRUCTURAL BRAIN MRI MEASURES IN FRONTOTEMPORAL LOBAR DEGENERATION

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Background: Recently in the field neurodegenerative diseases increasing attention has been pointed to CSF biomarkers and their integration with neuroimaging [1]. Frontotemporal lobar degeneration (FTLD) refers to a heterogeneous group of clinical syndromes with different underlying proteinopathies including tau pathology. CSF biomarkers have been proposed as diagnostic and prognostic factors. Aim of our study was to evaluate the relationship between CSF tau biomarkers and structural MRI brain measures in FTLD.

Methods: We included early FTLD patient. All included patients underwent lumbar puncture to evaluate amyloid, total-tau (t-tau), phospho-tau 181 (p-tau); p-tau/t-tau ratio was also calculated; brain MRI was performed to estimate whole brain volume, volume of principal deep grey matter structures and regional cortical thickness.

Results: Demographic characteristics of the 28 included patients were as follows: female/male: 9/19; mean±SD age: 68.1±7.8 years. The p-tau/t-tau ratio was significantly correlated with whole brain volume (r=0.69; p: 0.001), left putamen volume (r=0.55 p: 0.009), left pallidum volume (r=0.41; p: 0.01), right accumbens area (r=0.47; p: 0.02). P-tau/t tau ratio showed also a significant correlation with cortical thickness of left temporal lobe (r=0.74; p: 0.001) and right lateral orbital frontal cortex (r=0.45; p: 0.03). Linear regression showed a significant relationship between p-tau/t-tau ratio and left temporal pole (p = 0.01; r2: 0.60) and brain volume (p:0.002; r2: 0.56) after controlling for age and gender.

Conclusions: Our data suggest that CSF biomarkers, especially p-tau/t-tau ratio, could play a role as prognostic factor in FTLD. Further longitudinal investigations are needed to confirm these findings.

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MORPHOREGULATORY ROLE OF CONTACTIN-1 AXONAL GLYCOPROTEIN AND EPIGALLOCATECHIN GALLATE POLYPHENOL IN A MICE MODEL OF FRIEDREICH ATAXIA

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Friedreich's ataxia (FDA) corresponds to an autosomal recessive spinocerebellar ataxia, which also implies a cardiomyopathy phenotype and depends upon the mutation of the Frataxin (FXN) gene. Frataxin is a mitochondrial protein involved in the biogenesis of iron-sulfur cluster and therefore in ATP production. This disorder is caused by a homozygous GAA triplet repeat expansion in the Frataxin gene (9q21.11), whose length is related to the age of onset and to the severity of the corresponding phenotype. In this experimental study we used an FDA transgenic mouse models based on the Fxntm1MknTg (FXN–) YG8Pook/J mutant line carrying the human Frataxin gene in emizygosis (Pook), as well as a variable number of supernumerary GAA triplets. In the present study the phenotypes of 6-month-old wild type littermates and FXN mutant mice line were compared in spinal cord and cerebellar cryostat sections of both genotypes through an immunohistochemical procedure by using specific antisera to the Contactin-1 axonal glycoprotein, to the neuronal marker β-tubulin, and to glial marker as, the glial fibrillary acidic protein (GFAP). Furthermore, both phenotypes were subjected to epigallo catechin gallate antioxidant (EGCG) administration, and then underwent the same immunohistochemical protocol. In the mice mutant lines the neuronal population was significantly counteracted, and in addition an upregulation of the glial lineage was also observed and, as for Contactin-1, a reduced expression was observed, thus suggesting a role of a mutation of the underlying gene in FA pathogenesis. Finally, in the FDA phenotype, the administration of the EGCG polyphenol by means of its antioxidant properties seems to counteract the degenerative processes which occurs in the disorder and which therefore is likely to play a role in the pathophysiological mechanisms of the FDA.

IMAGING CORRELATES OF PREMORBID PERSONALITY IN THE FRONTOTEMPORAL DEMENTIA–AMYOTROPHIC LATERAL SCLEROSIS (FTD-ALS) SPECTRUM

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Background: Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are the two opposite poles of a neurodegenerative continuum – the FTD-ALS spectrum – which includes, on the one end, a pure behavioral/cognitive phenotype, and, on the opposite end, a motor phenotype. Factors determining phenotypic expression are still unknown; however, it is common observation that personality differs between the two opposite phenotypes: ALS patients tend to display a pleasant and nice attitude, while FTD patients frequently exhibit antisocial behaviors and lack of empathy. These traits are often described by the patients' caregivers as longstanding and preexisting the disease onset. We therefore aimed at testing if FTD and ALS patients have different premorbid personality traits, and whether these are related to a different functional organization of the brain in networks involved in social behavior and motor function.

Methods: We recruited FTD and ALS patients presenting to the Neurology Clinic of Modena University Hospital, as well as control groups composed by cognitively healthy subjects and patients with Alzheimer's disease. Patients' premorbid personality was assessed through the NEO Personality Inventory 3, which evaluates five main personality factors (Neuroticism, Extraversion, Openness, Agreeableness, Conscientiousness). Brain MRI scan including T1-weighted and resting state fMRI sequences was performed. Data were analyzed with voxel-based morphometry and probabilistic independent component analysis.

Results: 50 patients were recruited. A significant difference in premorbid personality emerged in the Extraversion and Openness domains, meaning that ALS patients – in their premorbid life – showed higher sociability, loquacity and optimism, and were more prone to new experience, ideas, and emotions than FTD patients. Between-group comparisons of fMRI data showed greater functional connectivity (FC) in ALS compared to both FTD patients and controls within the Salience Network (SN). FC within the SN positively correlated with premorbid Openness across all patients.

Conclusions: Patients with FTD and ALS differ in their premorbid personality profile in at least two domains, Extraversion and Openness, and these differences are associated with variable degrees of FC within the Salience Network. This suggests that premorbid personality may

represent a vulnerability marker to the development of specific phenotypes along the FTD-ALS spectrum.
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PERIPHERAL MARKERS OF INFLAMMATION IN INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENT

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Background and aim: Recent evidence suggests that neuroinflammation plays a crucial role in the pathogenesis of Alzheimer's disease (AD). However, the role of peripheral inflammation is debated. Among peripheral markers of inflammation, platelets, leukocytes, and related ratios, including the neutrophil-lymphocyte ratio (NLR), represent inexpensive and easily addressed markers that can be abnormal in AD. Specifically, NLR was described higher in elderly and AD subjects. This study aimed to explore the peripheral markers of inflammation in mild cognitive impairment (MCI), a transitional condition between normal aging and dementia, often associated with the future development of AD.

Methods: We included 95 MCI from the Centre for Dementia and Cognitive Disorders in Vercelli, Piedmont, Italy, with a follow-up ranging from two to five years (mean 2,9 ± 0,7 years). Global cognitive status was annually assessed by the mini mental state examination (MMSE) score. Baseline peripheral markers of inflammation, including global count of leukocytes, lymphocytes, monocytes, neutrophiles, platelets, and the relative ratios, including the NLR, the lymphocyte-to-monocyte ratio (LMR), the platelet-to-lymphocyte ratio (PLR) and the monocyte-to-lymphocyte ratio (MLR), were derived and correlated with cognitive measures. Included subjects were retrospectively classified in CONVERTERS (patients converting to AD dementia over the disease course) and NON-CONVERTERS (subjects showing stability at the last follow-up).

Results: CONVERTERS and NON-CONVERTERS showed no difference regarding age at baseline, sex, and educational level. CONVERTERS showed lower baseline MMSE scores (p=0.01) than NON-CONVERTERS, together with a higher NLR (p=0.02) and a higher PLR (p=0.03). The baseline Clock Drawing Task score, the total lymphocytes count, and the NLR score significantly correlated with the loss of MMSE points per year. Among the cognitive, neuropsychological and peripheral inflammation variables, baseline MMSE scores and NLR predicted conversion to dementia in the subsequent linear regression analysis. The ROC analysis revealed that a NLR value of 2.35 had moderate sensitivity (0.65) in predicting the conversion from MCI to dementia.

Discussion: CONVERTERS MCI had significantly higher NLR and PLR than NON-CONVERTERS MCI, and a worse baseline global cognitive status. Only the NLR predicted conversion to dementia among peripheral inflammation markers, directly correlating with the degree of cognitive decline. A dysregulation of peripheral inflammation, involving both lymphocytes and neutrophils, may play a role in the pathogenesis of AD, even at the early stages of neurodegeneration. Integrating cognitive, neuropsychological and peripheral inflammation markers may aid clinical classification and prognostic stratification in MCI subjects.

Conclusion: Integrating neuropsychological, inflammation markers may aid clinical and prognostic MCI subjects stratification.

DE NOVO PARKINSON'S DISEASE WITH CONSTIPATION: PRESENTING PHENOTYPE, BIOCHEMICAL SIGNATURE, AND CLINICAL PROGRESSION

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Objective: Constipation may long precede the motor onset of PD ("prodromal" constipation, PC), representing a sort of early disease stage. Clinical-biochemical profile of PD patients with PC (PD+PC) may theoretically differ from those without (PDwoPC), as a consequence of different neurodegenerative trajectories [1–3]. In this study we analysed clinical features, CSF composition and mid-term progression of de novo PD patients with and without PC, to establish the grouping effect of PC.

Methods: Baseline parameters, including Hoehn and Yhar stage (HY), MDS-UPDRS-pars III, Non-Motor Symptoms Scale (NMSS), MMSE, levodopa equivalent daily dose (LEDD), were assessed in n=57 de novo PD+PC patients and n=73 de novo PDwoPC. Baseline CSF biomarkers (α-synuclein, amyloid and tau peptides, lactate, CSF/serum albumin ratio or AR) were also examined into a smaller sample and in controls (n=46). Clinical progression was estimated by comparing HY and LEDD change 2.06±1.35 years from diagnosis.

Results: At onset, PD+PC patients had higher HY (p<0.001) and MDS-UPDRS-pars III scores (p=0.004) compared to PDwoPC, and higher CSF AR (p=0.045) compared to both controls and PDwoPC. PDwoPC, instead, had higher NMSS-domain-2 score (p=0.018), and lower CSF α-synuclein level (p=0.003) than both PDwoPC and controls. At follow-up, PD+PC had greater LEDD (p=0.004).

Discussion: According to our results PC identifies a group of de novo patients with greater motor impairment at onset, biochemical signature suggestive of impairment of blood brain barrier integrity, and higher needs of dopaminergic therapy along the disease course; conversely, PDwoPC de novo patients present a selective burden of fatigue and sleep disorders at onset and show more pronounced synucleinopathy.

Conclusions: Our study supports the matter that PC marks a de novo PD subgroup with specific clinic-pathological aspects either at onset or during disease progression. According to the most recent pathogenetic theories, it also hypothesizes that PD+PC and PDwoPC may correspond to "body-first" and "brain-first" models respectively.
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BRAIN NETWORKS IN AMNESTIC MILD COGNITIVE IMPAIRMENT: A STUDY OF EEG RESTING-STATE FUNCTIONAL CONNECTIVITY

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Objective: To explore neurophysiological biomarkers of MCI, we investigated resting-state EEG data of patients with amnestic Mild Cognitive Impairment. It offers several advantages over other investigation methods: it is cheap and easy to administer, available in almost all neurology laboratories, not invasive, repeatable over time, and, last but not least, has a very high temporal resolution of the signal. From a practical point of view, it would be ideal as screening approach.

Methods: 115 patients with aMCI and 70 healthy elderly (HE) were enrolled. Sixthy seconds of artifact-free EEG data were selected and compared between patients with MCI and HE. We applied the standard low resolution brain electromagnetic tomography-ICA (sLORETA-ICA) algorithm to resting-state EEG data to evaluate differences between healthy elderly and patients with MCI.

Results: Seventeen spatio-temporal patterns of connectivity were revealed as independent resting-state networks (RSNs); they were common to both groups and congruous with physiological assumptions that are topography and frequency of known networks. Statistical analysis showed that MCI patients used some networks differently than healthy subjects. In particular, MCI showed a greater delta activity, especially at the level of unimodal and multimodal association cortices, lower alpha activity at the level of posterior cortices, and a twofold beta pattern: in MCI patients, most beta sources were more active, as compared to controls, probably reflecting a compensation mechanism; only in few cases it was observed a reduced beta activity.

Conclusions: Our study indicated that aMCI and healthy elderly had different patterns of EEG-RSN connectivity. In aMCI, sLORETA-ICA can detect EEG-RSN connectivity disruptions between certain brain regions. In particular, this is the first electrophysiological study which pointing out that the greater beta spectral density of the anterior default mode network may compensate a reduction of the alpha synchrony of the posterior part of the default mode network which is early affected by the neurodegenerative process. Therefore, it may potentially represent a neurophysiological biomarker during the early clinical stage of the disease.

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LONG-TERM EFFICACY AND SAFETY OF IDEBENONE IN PATIENTS WITH LHON IN THE CHRONIC PHASE: RESULTS FROM THE LEROS STUDY

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Purpose: Leber's hereditary optic neuropathy (LHON) is a rare mitochondrial disorder resulting in severe and bilateral vision loss. Idebenone is approved in Europe for the treatment of LHON, but data in chronic patients is relatively sparse. Here, we report results from LEROS, a Phase 4, externally controlled, open-label interventional study (ClinicalTrials.gov NCT02774005), which included chronic patients (1 to ≤5 years since onset) with LHON treated with idebenone for up to 24 months.

Methods: LEROS included patients with LHON ≥12 years old and with a disease onset ≤5 years prior. Overall, 199 patients were enrolled, 181 of which formed the mITT population (excluded patients without a confirmed primary causative mtDNA mutation). Natural history (NH) data were available from 372 patients. Patients were divided into 2 groups for analysis based on time since onset in the most recent eye: subacute/dynamic (≤1 year) and chronic (>1 year). Outcomes in the idebenone-treated group were compared to retrospective data from the NH cohort, matched based on time since disease onset. Outcome measures (from baseline) were clinically relevant recovery (CRR): improvement from 'off-chart' VA to at least 1.6 logMAR, or a ≥0.2 logMAR improvement if already 'on-chart'; clinically relevant stabilization (CRS): maintenance of VA <1.0 logMAR; and clinically relevant benefit (CRB): reaching a CRR, a CRS, or both.

Results: LEROS met its primary endpoint, showing in patients with disease duration ≤1 year a significant increase in the proportion of subacute/dynamic eyes with a CRB from baseline following 12 months of treatment, compared to the matched external NH cohort. A secondary endpoint, identical to the primary but in chronic patients, was also successfully met; CRB was observed in 50.3% (72/143) of treated, chronic eyes versus 38.6% (59/153) from the NH cohort ($p = 0.0087$). CRB was largely driven by CRR, observed in 32.9% (47/143) of treated eyes versus 19.6% (30/153) in the NH cohort ($p=0.0034$). In treated chronic patients, the median best VA at baseline was 1.48 logMAR (n=87) and showed an improvement over the study duration to 1.32 (n=81), 1.23 (n=70), 1.26 (n=66) and 1.16 (n=55) logMAR at 6, 12, 18 and 24 months, respectively.

Conclusions: LEROS provides evidence of a significant therapeutic benefit of idebenone treatment in patients with LHON in the chronic stage, a group for whom viable treatment options are otherwise severely limited.

LONG-TERM EFFICACY AND SAFETY OF IDEBENONE IN PATIENTS WITH LHON IN THE SUBACUTE/DYNAMIC PHASE: RESULTS FROM THE LEROS STUDY

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Purpose: Leber's hereditary optic neuropathy (LHON) is a rare mitochondrial disorder resulting in severe bilateral vision loss. Idebenone is approved in Europe for the treatment of LHON, but controlled data beyond a 6-month treatment duration are lacking. Here, we report results from

LEROS, a Phase 4, externally controlled, open-label interventional study (ClinicalTrials.gov NCT02774005), in which visual acuity (VA) outcomes following 24 months of idebenone treatment were compared to an external, matched, natural history (NH) cohort.

Methods: LEROS included patients with LHON ≥12 years old and with a disease onset ≤5 years prior. Overall, 199 patients were enrolled, 181 of which formed the mITT population (excluded patients without a confirmed primary causative mtDNA mutation). NH data were available from 372 patients. Patients were divided into 2 groups for analysis based on time since onset in the most recent eye: subacute/dynamic (≤1 year) and chronic (>1 year). Outcomes in the idebenone-treated group were compared to retrospective data from the NH cohort, matched based on time since disease onset. Outcome measures (from baseline) were clinically relevant recovery (CRR): improvement from 'off-chart' VA to at least 1.6 logMAR, or a ≥0.2 logMAR improvement if already 'on-chart'; clinically relevant stabilization (CRS): maintenance of VA <1.0 logMAR; and clinically relevant benefit (CRB): reaching a CRR, a CRS, or both.

Results: The primary endpoint, the proportion of subacute/dynamic eyes with a CRB from baseline following 12 months of treatment, compared to the matched external NH cohort, was successfully met. CRB was observed in 42.3% (60/142) of treated eyes versus 20.7% (40/193) from the NH cohort (p=0.002). At 24 months, this significant difference was maintained, at 52.9% (64/121) versus 36.0% (27/75) (p=0.0297). In treated subacute/dynamic patients, the median best VA at baseline was 1.28 logMAR (n=109) and showed an initial worsening at 6 months to 1.41 logMAR (n=90). A recovery was then observed to 1.30 (n= 81), 1.20(n=75) and 1.07 (n=70) logMAR at 12, 18 and 24 months, respectively. No new safety concerns were observed for idebenone.

Conclusions: LEROS corroborates the outcomes of previous studies, demonstrating that long-term treatment with idebenone results in prolonged clinical benefit in patients with LHON in the subacute/dynamic phase.

AWARENESS IN NEURODEGENERATIVE DISORDERS: A SYSTEMATIC MRI REVIEW

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Objectives: The present review aims to: (a) highlight the importance of awareness and related disturbances in neurodegenerative conditions, including Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) spectrum of disorders; (b) provide an update of the available scientific literature on the use of MRI in the study of awareness in these conditions.

Materials: A formal literature review was performed using PubMed on relevant articles, published in peer-reviewed journals with the use of three macro areas: (1) awareness, (2) neurological condition, (3) MRI. Specifically, articles were selected according to predefined inclusion criteria: (a) studies focusing on awareness; (b) on neurodegenerative syndromes with awareness-related disturbances, such as AD and behavioural variant of frontotemporal dementia (bvFTD); (c) the use of structural and functional MRI; (d) on humans; (e) available in English and in full-text.

Method: We obtained 1340 articles, and we imported our research string in Rayyan Intelligent Systematic Review Tool for double-blind title/abstract screening, which was performed by two independent reviewers (ML, AP). A third reviewer (EC) solved conflicts when present. Subsequently, 43 articles were selected for unblind full-text screening and, at last, consensus was reached on including 36 papers. Included studies were grouped in macro-areas according to different aspects of awareness: anosognosia, insight, social cognition, including theory of mind (ToM) and emotional processing, free-will and autonoetic awareness.

Results: Both AD and FTLD patients tend to overestimate their overall functioning, and overestimation is associated with atrophy of right frontal and subcortical regions. Unawareness of memory deficits is related to hippocampus and mesial temporal atrophy in amnestic mild cognitive impairment, and to reduced functional connectivity between mesial temporal and other default mode network regions in AD. In AD, deficits in autonoetic awareness are attributed to morphological changes of the hippocampus. ToM impairment is explained by affective interpretation disruption in bvFTD and by episodic memory dysfunction in AD patients. Finally, ToM impairment in FTLD cases is related to prefrontal atrophy and altered brain functional connectivity of the salience network.

Discussion: Awareness is a complex domain consisting in multiple aspects. Some of these aspects are affected at different stages of AD and FTLD and are subtended by either common or distinct brain circuits.

Conclusions: We highlighted the importance of awareness and related disturbances in neurodegenerative conditions, and we provided a general overview of its structural and functional correlates.

Supported by: European Research Council (StG2016_714388_NeuroTRACK) and the Foundation Research on Alzheimer Disease.

APOE GENOTYPE AND BLOOD-BRAIN BARRIER PERMEABILITY IN NEURODEGENERATIVE DISEASES: IMPLICATIONS FOR BLOOD-BASED BIOMARKERS?

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Objective: The ε4 isoform of ApoE, a major genetic risk factor for developing Alzheimer's disease (AD), has been shown to be associated with increased blood-brain barrier (BBB) permeability in animal models of AD, while in vivo studies have reported conflicting results. The aim of the present study was to evaluate the effects of ApoE-ε4 genotype on BBB permeability in a large cohort of patients with neurodegenerative disorders.

Methods: Two hundred patients fulfilling current clinical criteria for AD (n=130), frontotemporal dementia (n=33), dementia with Lewy bodies (n=10), vascular dementia (n=11) and subjective cognitive decline (n=16) were recruited. All subjects underwent a clinical and neuropsychological evaluation, routine laboratory examination, cerebrospinal fluid analysis, ApoE genotyping and brain structural imaging (CT o MRI). BBB permeability was assessed with the CSF/plasma albumin ratio. The sample was subdivided into three ApoE subgroups according to the number of ApoE-ε4 polymorphism (0, 1 or 2).

Results: CSF/plasma albumin ratio (p<0.001), CSF/plasma kappa (p=0.006) and lambda (p=0.018) light chains were increased in patients with two ApoE-ε4 genes, using the analysis of covariance (ANCOVA) method, with diagnosis, disease duration and severity as covariates. In addition, these patients showed lower CSF Aβ1-42 level (p=0.003). When diagnostic subgroups were considered

separately, we observed comparable findings. Increased CSF/plasma kappa light chains were found only in patients with AD.

Conclusions: Our results support the hypothesis that ApoE genotype increases BBB permeability in major dementia disorder, having potential implications for disease pathophysiology and blood-based biomarkers measurements.

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OPICAPONE ADHERENCE: THE EXPERIENCE OF THE MOVEMENT DISORDER UNIT OF TRIESTE- ITALY

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Objective: Describe the clinical experience with Opicapone and assess the patients' adherence to this treatment in the movement disorders centre of Trieste-Italy.

Background: Opicapone is the latest monoamine catechol-O-methyltransferase inhibitor (I-COMT) approved in EU for the treatment of Parkinson's disease (PD). It is recommended for PD patients with motor fluctuations, especially when facing prolonged "off" episodes, as add-on therapy to levodopa/carbidopa. Evidences coming from both randomized-controlled trials and real life observational studies, showed that Opicapone is generally safe and well tolerated.

Methods: All PD patients referred to the Movement Disorders Unit of the Neurology Department of Trieste, Italy (about 600) have been evaluated. Upon them, patients who had received Opicapone at any time between January 2017 and December 2021, have been enrolled. For each patient, the following clinical data were collected: sex, age, disease duration, concomitant PD therapies, treatment duration, treatment discontinuation and reason for discontinuation (side effects, lack of efficacy, disease progression or death). Patients with incomplete data or with disconfirmation of the diagnosis of PD during the follow up period, were excluded from the analysis.

Results: Opicapone was recommended in a total of 59 patients during the time of observation. 25 patients (41%) were still in treatment with Opicapone at the end of the observation. In 34 patients the drug was discontinued, in 6 subjects this occurred during the first year of treatment. The reason for discontinuation were: side effects (17 patients), disease progression (6), lack of efficacy (10) and death (2). Dyskinesias, hallucinations and behaviour disorders were the main causes of drug discontinuation. Patients who were still taking Opicapone at the end of observation seem to have shorter mean disease duration and be younger compared to patients who discontinued the drug. 17 patients switched to Opicapone from a different I-COMT, upon this group of patients, the adherence was extremely low (only 3 kept the new drug). No correlation between suspension of Opicapone and sex was found in our group.

Conclusion: Our real-life study confirmed that Opicapone is generally well tolerated in almost half of patients. For those that dropped out the treatment, the main reasons were side effects and lack of efficacy. Opicapone is likely to be more tolerated in younger patients and in earlier stage of the disease.

HEART RATE VARIABILITY DURING WAKE AND SLEEP IN HUNTINGTON'S DISEASE PATIENTS: AN OBSERVATIONAL, CROSS-SECTIONAL, COHORT STUDY

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Introduction: Autonomic dysfunction has been reported as one of nonmotor manifestations of both presymptomatic and manifest Huntington's disease (HD). The aim of our study was to evaluate heart rate variability (HRV) during wake and sleep in a cohort of patients with manifest HD.

Methods: Thirty consecutive patients with manifest HD were enrolled, 14 men and 16 women, mean age 57.3 ± 12.2 years. All patients underwent full-night attended video polysomnography. HRV was analyzed during wake, NREM sleep, and REM sleep, in time and frequency domain. Results were compared with a control group of healthy volunteers matched for age and sex.

Results: During wake, HD patients presented significantly higher mean heart rate than controls (72.4 ± 9.6 vs. 58.1 ± 7.3 bpm; $p < 0.001$). During NREM sleep, HD patients showed higher mean heart rate (65.6 ± 11.1 vs. 48.8 ± 4.6 bpm; $p < 0.001$) and greater low frequency (LF) component of HRV (52.9 ± 22.6 vs. 35.5 ± 17.3 n.u.; $p = 0.004$). During REM sleep, we observed lower standard deviation of the RR interval in HD subjects (3.4 ± 2.2 vs. 3.7 ± 1.3 ms; $p = 0.015$).

Conclusion: Our results show that HD patients have higher heart rate than controls, during wake and NREM, but not during REM sleep. Among HRV parameters, the most relevant difference regarded the LF component, which reflects, at least partially, the ortho-sympathetic output. Our results confirm the involvement of autonomic nervous system in HD and demonstrate that it is evident during both wake and sleep.

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THE ADDED VALUE OF PRION CSF RT-QUIC TO THE DIAGNOSIS OF CREUTZFELDT-JAKOB DISEASE: A TEN-YEAR STUDY

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Aims: The updated WHO criteria [1] for diagnosing probable sporadic Creutzfeldt-Jakob disease (sCJD) require the combination of a typical clinical course and the positivity of at least one supportive biomarker (CSF 14.3.3 assay, EEG, or MRI). The 2017 EU criteria [2] expand the previous ones by allowing the probable diagnosis also in patients with progressive neurological syndromes and a positive prion RT-QuIC assay. In this study, we compared the diagnostic performance of the two criteria in a significant patient cohort.

Methods: We studied patients with suspected CJD whose CSF was submitted between 2010 and 2020 to two Italian CJD reference centers. From a total of 3347 patients received, we included those fulfilling at least one of the following criteria: positive 14.3.3 assay, t-tau>600 pg/ml, positive MRI or clinical course compatible with the "possible sCJD" definition according to criteria. All patients received either a clinical diagnosis of probable or non-CJD based on the available clinical data, including the follow-up, or a definite diagnosis when they underwent neuropathological examination or carried known-pathogenic PRNP mutations. We then formulated two different clinical diagnoses according to the two distinct criteria based on CSF examination data and the clinical characteristics at the time of CSF collection.

Results: Selection criteria identified 1251 subjects, comprising 850 CJD and 401 non-CJD. 448 CJD patients had a definite diagnosis, including 297 with definite sCJD and 151 with genetic CJD, while 402 had a final diagnosis of probable sCJD. In the non-CJD group, 61 received an alternative neuropathological diagnosis. At the time of CSF collection, the WHO revised criteria and the 2017 EU criteria allowed a diagnosis of "probable" CJD in 346 and 440 definite CJD subjects, yielding 77.2% and 98.2% sensitivity. The specificity against the definite non-CJD cohort was 82.0% for both criteria. RT-QuIC alone tested positive in 417 definite CJD patients but in none of the definite non-CJD cases, obtaining 93.1% sensitivity and 100% specificity. Finally, 112 probable sCJD patients received this diagnosis due to the RT-QuIC, given the lack of supportive biomarkers or suggestive clinical course.

Discussion e conclusions: Most (94 out of 102, 92.1%) of definite CJD patients who did not fulfill the updated WHO criteria at CSF collection could be reclassified as "probable CJD" based on RT-QuIC results. RT-QuIC is a highly sensitive and specific biomarker for diagnosing CJD in vitam. Its introduction to current diagnostic criteria has led to a significant improvement in epidemiologic surveillance.

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24S-HYDROXYCHOLESTEROL AND CEREBELLAR DEGENERATION: INSIGHTS FROM SCA2

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Objective: 24S-hydroxycholesterol (24S-OHC), is the major elimination metabolite of neuronal cholesterol in the brain and is formed by the neuronal 24-hydroxylase CYP46A1. Since almost all the 24S-OHC is produced in the brain, its serum concentrations were demonstrated to be representative of the amount of metabolically active neuronal cells. A reduction of serum 24S-OHC can correlate with a loss of metabolically active neurons, as observed in many neurodegenerative diseases [1,2]. Cortical neurons concentration is higher in the cerebellum than in other brain regions, therefore a decrease of plasmatic 24S-OHC could represent a reliable marker of neurodegeneration in patients affected by cerebellar disorders. Here we studied 24S-OHC in spinocerebellar ataxia type 2 (SCA2), which represents a well-known model of cerebellar degeneration [3].

Materials: Six patients with a genetic diagnosis of SCA2 were evaluated at our Clinic, and serum was collected, in order to perform a biochemical analysis for 24S-OHC. Patients' levels were confronted with a 77 age matched healthy controls group. We looked for an eventual correlation between 24S-OHC levels and clinical-anamnestic parameters.

Method: Serum levels of 24S-OHC in SCA2 patients were compared with control group investigated with isotope dilution gas chromatography mass spectrometry method. Comparison statistical analysis was performed applying unpaired t-test.

Results: Our subjects were affected by ataxia which was clinically and genetically assessed, and showed cerebellar atrophy at brain MRI. Interestingly, significantly lower levels of 24S-OHC were observed in SCA2 patients compared to normal controls, and the decrease tended to correlate with disease duration.

Discussion: Our findings represent the first data on plasma 24S-OHC in a cerebellar disease and support the hypothesis that serum 24S-OHC may reflect the grade of cerebellar degeneration, thus becoming a useful tool in the follow up of ataxia.

Conclusions: It will be interesting to evaluate a higher number of patients with SCA2 and other ataxias, and also to correlate serum 24S-OHC with cerebellar atrophy measured with quantitative MRI.

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IMPACT OF COVID-19 PANDEMIC IN PATIENTS WITH HUNTINGTON DISEASE

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If Huntington disease (HD) may represent a risk factor for Covid-19 is debated. The aim of our work was to assess the impact of Covid-19 pandemic on HD disease progression, to evaluate patients' vulnerability to Covid-19 infection and the incidence of severe manifestations compared to the general population.

Methods: After obtaining oral informed consent, we conducted a telephone interview directed to patients or caregivers, using an ad hoc developed semi-structured questionnaire. The questionnaire was composed of two sections. The first was dedicated to all patient and included: demographic and clinical patient's data, development of new signs or symptoms, type of disability, psychiatry therapy changes, new sleep disorders,

discontinuation of physiotherapy and neurological examination. The second section was performed in HD patients with positive nasopharyngeal swab for Covid-19; it included information about infection related symptoms, need for hospitalization, access to emergency care, neurological status after Covid-19 disease resolution.

Results: We interviewed a total of 112 HD patients. Since the beginning of the pandemic, 72.3% of patients experienced a progression of the basal clinical condition. Specifically, 31% underwent a generalized decline. 22% of patients experienced new isolated motor symptoms or had a motor deterioration, 10% underwent an isolated psychiatric worsening, whereas 8% had motor and psychiatric decline. 31% of patients changed their pre-existing psychiatric therapy or started a new one. Interestingly, 50% described the onset of a new sleep disorder. Analysis of the standards of care showed that 78% of the patients missed their scheduled medical visit and 64.7% stopped physiotherapy. Within the observed cohort 10.8% of patients tested positive for Covid-19 infection, 6 experienced symptoms and 5 of them had comorbidities. Despite resolution of the infection 3 patients underwent a rapid progressive and generalized clinical worsening.

Conclusion: Our study was among one of the first to investigate the impact of the Covid-19 pandemic on HD patients. Our results shown that most patients experienced a global clinical worsening since the beginning of the pandemic. Despite the more severe confinement measure adopted by HD patients, the incidence, and the morbidity of Covid-19 infection seemed to be higher than the general population [1]. Whether HD represents per se a risk factor for COVID-19 is unclear. However, a negative impact of HD on the immune system has been described, and difficulties in swallowing and clearing secretions may have negatively impacted the disease course.

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CSF MOLECULAR CHARACTERIZATION OF PARKINSON'S DISEASE WITH MILD COGNITIVE IMPAIRMENT

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Objectives: Specific diagnostic criteria for Parkinson's disease (PD) with mild cognitive impairment (PD-MCI) have been validated in 2012 by the Movement Disorders Society (MDS) [1]. However, the validity of PD-MCI construct is controversial, and its neurobiological basis still need to be clarified [2]. Thus, we sought to investigate whether PD-MCI shows specific features in cerebrospinal fluid (CSF) profile, compared to cognitively unimpaired PD.

Materials and Methods: We included a retrospective cohort of patients categorized as PD-MCI (n.48) according to the MDS criteria, with available cerebrospinal fluid (CSF) samples collected during the diagnostic work-up as well as a group of cognitively unimpaired PD patients (n.40). We included also patients with prodromal Alzheimer's disease (MCI-AD, n.25) and cognitively healthy individuals with other neurological diseases (OND, n.44), as control groups. We measured multiple CSF biomarkers reflecting different pathophysiological pathways, namely AD-related pathophysiology (sAPPα and β, Aβ42/40, p-Tau, t-Tau), amyloid-independent neurodegeneration (NfL, p-NfH), synaptic dysfunction (α-syn, neurogranin) and glial activation (sTREM2, YKL-40). A thorough neuropsychological evaluation including screening tests and further assessment for each cognitive domain was carried out both at baseline and after two years.

Results: All the measured biomarkers showed similar concentrations in PD-MCI and PD, with the exception of NfL and p-NfH which displayed a trend toward increased levels in PD-MCI. CSF NfL/p-NfH provided a better discrimination, being significantly higher in PD-MCI vs. PD ($p=0.02$). In PD-MCI group, NfL and NfL/p-NfH significantly correlated with MMSE worsening along time ($\rho=-0.56$, $p<0.01$ and $\rho=-0.62$, $p<0.001$, respectively).

Discussion and Conclusion: Our findings are consistent with the role of NfL as unspecific amyloid-independent marker of worse cognitive outcome [3]. The role of NfL/p-NfH deserves further investigation in larger PD cohorts. Overall, in our retrospective cohort, PD-MCI did not showed a specific neurochemical profile with respect to cognitively unimpaired PD, which justifies the question whether PD-MCI is a distinct biological entity from PD.

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ANALYSIS OF C9ORF72 WILD-TYPE REPEAT LENGTH AS POSSIBLE DISEASE MODIFIER IN AMYOTROPHIC LATERAL SCLEROSIS

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Objectives: The C9orf72 hexanucleotide repeat (HR) expansion is the most common genetic cause of ALS and FTD, with expansions from 30 to >4000 units (u). C9orf72 HR wild-type (wt) length ranges from 2 to 24 repeats, whereas alleles ≥9u show a low frequency in the general population and have been investigated as a possible risk factor in several neurodegenerative diseases. A previous luciferase reporter assay showed that HR alleles ≥9u decreased transcription in a length-dependent manner, but the influence on C9orf72 gene expression in human samples has not been proved yet. Aim of this study was to determine whether wt HR length may modify C9orf72 gene expression acting as disease modifier in ALS patients without C9orf72 HR expansion (ALS-C9Neg).

Materials: Genomic DNA was extracted from whole blood of ALS patients, selected according to El Escorial revised criteria, negative for C9orf72 mutation, and control individuals without neurological diseases. Written informed consent was obtained from all participants. Total blood RNA was isolated with NucleoSpin RNA Blood Kit. Methods: HR size was evaluated by a combination of amplicon-length analysis and repeat-primed PCR. The gene expression of C9orf72 total mRNA and its isoforms (V1, V2, V3) was evaluated by q-PCR in blood.

Results: In our cohort of 247 ALS-C9Neg patients and 245 healthy control we observed a trimodal and not significantly different distribution of C9orf72 wt alleles, also when considering the mean HR length, the longer allele only or the sum of both wt alleles. By arbitrarily defining 2-8u alleles as short (S) and ≥8u as long (L), the allele distribution in our ALS cohort was 55% S/S, 40% S/L and 5% (n=13) L/L. We evaluated C9orf72 gene expression in blood from all the 13 ALS-C9Neg patients carrying L/L alleles (8-18u) and 13 S/S patients homozygous for the 2u-allele. No significant changes were found in V2 transcript expression, the major C9orf72 variant in which the HR maps in the promoter. We instead found significantly increased expression of both the V3 isoform and total C9orf72 mRNA levels in L/L carriers. No association with clinical parameters, including age at onset and survival, were found in L/L ALS-C9Neg.

Discussion: Larger ALS-C9Neg cohorts and also brain tissues need to be investigated to confirm our results.

Conclusion: Our findings suggest that the C9orf72 wt HR length does not act as a disease modifier in ALS-C9Neg patients, although long alleles ≥8u increase C9orf72 gene expression, at least in blood.

GUT MICROBIOME ALTERATIONS IN LEWY BODY SPECTRUM

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Objectives: Microbiome alterations have been found in Parkinson (PD) and Alzheimer's disease and might impact on brain vulnerability within the spectrum of Lewy body disorders. Aim of the study was to evaluate shared and divergent microbiome alterations in PD and dementia with Lewy bodies (DLB) compared to age-matched controls.

Method: Seventy-seven subjects including 28 PD, 21 DLB matched for age and disease duration and 24 age-matched controls entered the study. Each subject underwent an extensive clinical evaluation including motor, cognitive and dietary assessment and underwent stool and blood collection. Stool DNA was amplified using primers targeting the V3-V4 region of the bacterial 16S rRNA gene. Sequencing was performed according to the 16S-protocol on MiSeq (Illumina). Ecological measures as beta diversity, the similarity or difference in microbiota composition between individuals, as well as taxonomic abundance were computed with the free software package QIIME 2.

Result: Compared to HC, DLB and PD patients exhibited a shift in the abundance of the phylum Synergistetes (in DLB increased by 3.5 times than HC) and Actinobacteria (in PD increased by 1.5 times than HC). At genus level, DLB patients exhibited decreased abundance of Clostridium sensu stricto 1, Fusicatenibacter, Lachnospiraceae ND3007 group, Rikenellaceae RC9 gut group and Ruminiclostridium 6 than HC as well as less Fusicatenibacter and Lactobacillus than PD (Linear discriminant analysis effect size (LEfSe), P<0.046).

Conclusion: PD and DLB are accompanied by specific alterations in the abundance of specific gut microbes. Further analyses are needed in order to understand whether differences in gut microbiota composition between PD and DLB might explain different brain vulnerability and disease progression within the Lewy bodies spectrum.

THE ROLE OF ADAPTIVE PERIPHERAL IMMUNITY IN THE MECHANISM OF NEUROINFLAMMATION IN ALZHEIMER'S DISEASE: A PILOT STUDY

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Aims: In recent years neuroinflammation has been hypothesized as an important contributing factor of Alzheimer's Disease (AD) pathogenesis [1]. Several evidences suggest that adaptive immune cells play a key role into neuroinflammation [2-3]. Based on these assumptions, we've designed a case-control pilot-study, with the aims of analysing the pattern of expression of CD4+Tcells transcriptional-factors and pro/anti-inflammatory cytokines profile, in patients with Mild-Cognitive-Impairment (MCI) and AD, compared with No-Cognitive-Impairment (NCI) subjects.

Materials and Methods: Between December 2019 and October 2021, we recruited 50 patients, selected from Centre-for-Cognitive-Disorders of Neurology-Department, ASST-Settelaghi-Hospital. During each visit, data concerning demographic, clinical, instrumental (brain-CT/MRI/FDG-PET) variables were recorded and blood samples were collected for CD4+Tcells isolation and for blood cytokines dosing (TNF-α, IL-10, IFN-γ, IL-6). CD4+Tcells were processed for identification of transcriptional-factors-mRNA-levels (Nurr1/RORγC/GATA3/Tbet1/FoxP3/STAT1/STAT3/STAT4/STAT6). Statistical analysis of demographic, clinical, instrumental and lab-data were performed. Statistical significance difference among groups was analysed by means of Student's t-test, chi-q test for continuous variables (ANOVA).

Results: We've enrolled 50 subjects: 25-NCI-group, 9-MCI-group and 16-AD-group, equally distributed for anamnestic and demographic variables. In terms of "gene-pattern" of CD4+Tcells, only Tbet1 transcriptional-factor, related to Th1 differentiation, was more expressed in MCI-group, compared to AD and NCI-groups (p=0,02). No statistically differences were found between TNF-α, IFN-γ, IL-10 and IL-6, within the three groups. Examining the correlation between the presence of microvascular encephalopathy and the specific "gene-pattern" of CD4+Tcells, Nurr1, related to Treg cells-lineage, was less expressed in MCI with microvascular encephalopathy (p= 0,02), while STAT4, related to Th1-lineage, was more expressed in MCI with microvascular encephalopathy (p=0,03). No statistically differences emerged in Tbet1 expression (p=0,12). A final analysis was conducted on FDG-PET pattern and peripheral lymphocytes profile. In MCI-group Nurr1 was less expressed in "bilateral frontal-parietal-temporal-occipital-hypometabolism" (p=0,02). In the AD-group "bilateral-temporo-parietal-profile" was related with an increased Nurr1, GATA3, STAT1, STAT4 expression (p<0,05). In "bilateral-frontal-parietal-temporal-occipital-hypometabolism" there was a reduced RORγC and STAT-4 expression (p<0,05). In "bilateral-frontal-parietal-temporal-hypometabolism" there was a STAT-1 reduction(p<0,05).

Discussion: MCI shows an inflammatory state, that is no longer detectable in NCI and AD. The higher expression of Tbet1 in MCI-group is not related to higher incidence of associated vascular-encephalopathy, but to the presence of AD itself. The most-diffuse-brain-AD-hypometabolism showed a reduced expression of transcriptional-factors, implied in pro-inflammatory immune response. A less-advanced-AD-hypometabolism showed an increased expression of transcriptional-factors, implied in anti-inflammatory immune response.

Conclusions: These data confirm the hypothesis that a pro-inflammatory process could be exist in an early Alzheimer's Disease stage and gradually it could be decrease in advanced stages.

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CORTICOBASAL SYNDROME (CBS) ONSET WITH RAPIDLY PROGRESSIVE LANGUAGE AND BEHAVIOUR DETERIORATION MIMICKING CREUTZFELDT-JAKOB (CJD) DISEASE: CASE REPORT AND REVIEW OF THE LITERATURE

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Objective: Corticobasal degeneration (CBD) is a rare neurodegenerative disease characterized by the predominance of pathological tau deposition in various anatomical regions. CBD pathology is associated with multiple phenotypes and CBS is the most common. Conversely, CBS itself can be due to several pathologic disorders other than CBD, including Alzheimer disease (AD), Parkinson disease (PD) and other neurodegenerative disorders.

Method: A single case report of a male patients admitted to the Neurology ward at our institution for suspected CJD later diagnosed with CBS-AD is described and discussed. An updated review of the literature is also provided.

Materials: Electronic medical records, Picture archiving and communication system (PACS), neurophysiological reports and laboratory results were reviewed. A literature search on PUBMED was carried out and a narrative review of findings was compiled.

Results: A 62-year-old caucasian man with 18 years of education was admitted to the neurology ward with 5-months history of rapidly progressive language disturbance, with frequent phonemic and semantic paraphrases and occasional anomies and recent progressive speech and behaviour deteriorations within few weeks. He showed moderate calculation and attention deficits in neuropsychological testing and asymmetric hypometabolism in fronto- temporo- parietal lobes on PET scan; EEG showed widespread electrogenic dysfunction and figures of uncertain interpretation in the left hemisphere. Neurobehavioral exam shows unilateral ideomotor apraxia. CSF analysis showed a highly elevated total tau protein (1458), a mild-reduced Ab42 levels (347) but a negative RT-QuIC. The visual evoked potential (PEV) and follow-up EEG at 10 days and 1 month were not significant.

Discussion: CBS is characterized by the following clinical symptoms: asymmetrical parkinsonism, alien limb syndrome, cortical sensory loss, apraxia, and myoclonus. However, the presentation of CBS could be expressed as a language disturbance in up to 40% of patients. Language impairment was the primary manifestation in the current case, and verbal fluency disruption was the most prominent symptom. The CSF profile and neuroimaging were suggestive for CBS-AD and excluded the initial hypothesis of prion pathology.

Conclusion: This case report and literature review highlighted the importance of cerebrospinal fluid (CSF) biomarkers for either confirming or excluding a tau- or prion-based disorder in similar clinical scenarios; it reviewed the value of differential diagnosis and future research perspectives.

LONG-TERM IDEBENONE TREATMENT CAN PROMOTE FAVOURABLE VISUAL ACUITY OUTCOMES IN PATIENTS WITH LEBER'S HEREDITARY OPTIC NEUROPATHY: RESULTS FROM THE PROSPECTIVE, NATURAL HISTORY CONTROLLED LEROS STUDY

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Background: The LEROS study met its primary endpoint; long-term idebenone treatment resulted in clinically relevant benefit to patients with Leber's hereditary optic neuropathy (LHON). Here, we report on additional LEROS outcomes – clinically relevant worsening (CRW) of visual acuity (VA), and the transition between clinically relevant VA categories over time.

Aims and methods: Patients with LHON treated for up to 24 months (N=181) were stratified (subacute/dynamic [≤1 year from onset]; chronic [>1 year]) and compared to an external natural history (NH) cohort (N=372), matched by time since onset. CRW is the loss of 2 ETDRS chart lines and/or a worsening to off-chart.

Results: In treated subacute/dynamic and chronic patients, CRW was less frequent than in matched NH patients at 12 months (subacute/dynamic: 35.9% [23/64] vs 64.6% [53/82]; chronic: 6.3% [3/48] vs 18.6% [11/59]) and 24 months (subacute/dynamic: 33.3% [19/57] vs 57.6% [19/33]; chronic: 4.9% [2/41] vs 21.6% [8/37]). At baseline, 66.0% of treated subacute/dynamic patients had a best VA ≥1.0 logMAR. This increased at 6 months (76.7%) and decreased thereafter (57.1% at 24 months). At baseline, 70.1% of chronic patients had a best VA ≥1.0 logMAR (34.5% off chart) with a decrease thereafter (58.2% at 24 months; 16.4% off chart).

Conclusions: In LEROS, long-term idebenone treatment reduced worsening of VA. In addition, idebenone reduced the proportion of patients with a best VA that was ≥1.0 logMAR – the threshold of 'legal blindness' in many countries – or a best VA that was off chart.

VAGUS NERVE HIGH RESOLUTION ULTRASOUND SHOWS CHANGES SUGGESTING AXONAL DEGENERATION IN IDIOPATHIC PARKINSON'S DISEASE (IPD)

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Background and aims: Histopathological studies revealed that degeneration of the dorsal motor nucleus may be present early in the course of Idiopathic Parkinson's Disease (IPD). Vagus Nerve (VN) axons degeneration should be today detectable by High–Resolution Ultrasound (HRUS) as a thinning of the VN. In this study, we investigated whether patients (pt.) with IPD exhibit or not an atrophy of vagus nerve in comparison with age-matched controls.

Material and Methods: We measured the caliber (cross-sectional area, CSA and perimeter) of the vagus nerve at med-cervical level in 10 pt. with IPD (4 females and 6 males, mean age 73.0 + 8.6 yrs, disease duration range 2-10 yrs) and in age-matched controls using HRUS. Evaluation were performed by blinded raters using an Esaote MyLabGamma device in conventional B-Mode with a 19 MHz probe.

Results: In both sides, the VN-CSA was significant smaller in IPD pt. than in controls (rigth 0.023, left 0.19 mm2; $p < 0.001$), perimeter (rigth 5.1, left 4,8 mm; $p < 0.001$). There was no significant correlations between VN-CSA and age, the Hohen & Yahr scale, and disease duration.

Discussion and conclusion: Our findings provide evidence that atrophy of the VNs is present in IPD patients and can be easy detected in-vivo by HRUS. Moreover, HRUS of the VN represent a non-invasive bedside imaging modality of screening in IPD pt. independent of disease stage and duration, and may represent in the future a possible interesting additional index to identify pt. at risk of disease.

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THE ROLE OF MOTOR RESERVE IN SPINOCEREBELLAR ATAXIA TYPE 2

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Pre-existing or enhanced cognitive abilities likely have an influence on the onset and severity of symptoms in neurodegenerative diseases, enhancing individuals' ability to cope with neuropathological lesions resiliently. This process is recognised as cognitive reserve [1]. Along with the interest in this concept, importance is being given to motor reserve (MR), likely to be boosted by physical activity during life time and allowing resilient coping with motor dysfunctions [2]. Nevertheless, the literature on this topic is scarce. Therefore, in the present study we aimed to assess MR in Spinocerebellar Ataxia type 2, a rare cerebellar neurodegenerative disease, and whether it affects cognitive and motor abilities. Additionally, we aimed to investigate the existence of a motor reserve network, expressed in terms of compensatory mechanisms driven by cerebral-cerebellar functional connectivity. To this aim, we assessed the MR of twelve SCA2 patients using the Motor Reserve Index Questionnaire (MRIq), developed ad-hoc for estimating indexes of acquired motor reserve during life-span. The International Cooperative Ataxia Rating Scale (ICARS) was used to assess cerebellar clinical motor features and a detailed neuropsychological battery was used to evaluate patients' functioning in several cognitive domains. Finally, patients underwent a functional magnetic resonance imaging examination and the Network Based Statics (NBS) analysis was used to assess MR-associated functional brain networks. The correlational analysis performed by Spearman's Test revealed significant correlations between MRIq measures, specifically the one relating to physical exercise in the life time, and measures of educational and intellectual levels, executive functions and processing speed. Additionally, we found that the higher the motor reserve, the lower the severity of motor symptoms as assessed by ICARS. The NBS analysis revealed patterns of higher internodal connectivity within subnetworks consisted of cerebellar vermis, cerebellar anterior lobules (IV-V), and areas in the cerebral cortex related to motor and cognitive control (i.e. supplementary motor area, middle frontal gyrus). Remarkably, positive correlations resulted between MR indexes and those functional patterns, likely indicating the identification of a motor reserve network. To conclude, this is the first study aimed at investigating MR in cerebellar disease and revealing its relation to cognitive functions and to the ability to cope with ataxia-related symptoms. Moreover, we suggest that the identified MR network might reflect a MR biomarker likely to be used to supervise neural and motor reserve prompted by physical activity, education, and cognitive functioning, leading to keystones for therapeutic and pre-morbid interventions.

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PSP AND FTD: COMPARISON OF MOTOR, COGNITIVE AND BEHAVIOURAL FEATURES

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Objective: The aim of this study is to compare motor and cognitive performances between Frontotemporal degeneration (FTD) and Progressive Supranuclear Palsy (PSP) patients.

Materials: In our outpatients clinic we recruited 15 consecutive patients within the FTD spectrum (9 with behavioural variant, 5 with Primary Progressive Aphasia, 2 with logopenic and semantic variants, 1 patient with FTD-Motor neuron disease) and 15 patients with PSP (14 with Richardson's syndrome and 1 with PSP with predominant parkinsonism).

Methods: All patients underwent motor evaluation including MDS-UPDRS III, evaluation of eye movements, myoclonus and dystonia. All patients performed an extensive cognitive/behavioural battery of tests.

Results: FTD and PSP did not differ in terms of demographic features, As expected, PSP showed a greater impairment in saccadic eye movements ($p<0.05$). As for the movement disorders evaluation, PSP showed more frequently face dystonia, while FTD presented more frequently rest and stimulous-sensitive myoclonus ($p<0.05$). MDS-UPDRS part III was greater in PSP ($p<0.05$). As for the cognitive evaluation, FTD presented greater impairment in global cognitive status (assessed with Mini Mental State Examination and Montreal Cognitive Assessment), memory and language (evaluated with deferred recall of Ray's 15 words and repetition of words and auditory understanding of words, respectively). As for the behavioural evaluation (performed with the Neuropsychiatric Inventory), FTD and PSP failed to disclose major differences except for apathy which was more frequent in FTD ($p<0.05$).

Discussion: Despite being two different diseases, FTD and PSP share similar cognitive/behavioural impairment. PSP present a greater impairment in ocular movements and more frequent face dystonia, while myoclonus is more common in FTD.

Conclusions: In this study we want to reinforce the idea that FTD and PSP share similar clinical features which can sometimes overlap.

EFFECTS OF GENDER DIFFERENCE IN EFFICACY AND ADVERSE REACTION TO SAFINAMIDE

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Several studies have documented numerous sex-based differences in Parkinson's disease. However, the studies that investigate the impact of gender on medical treatments are still scarce. The aim of this study is to investigate the effects of safinamide according to gender in PD patients treated in real-life conditions. In this retrospective observational study we enrolled all patients belonging to the Parkinson's center in L'Aquila who had started taking safinamide as add-on therapy in the period January-December 2018 and followed up for two years. A total of 65 patients were enrolled. Out of the 65 patients enrolled 42 (64%) were men and 23(35,38%) were women. Women were older than men at the enrolment (71years women vs 69.5 years men). Analysis of UPDRS scores showed significant improvements in 66.6%of men and 56% of women in sections III and IV. Adverse effects occurred in 11.9% (5) of men and 13.04% of women (3). In men, the highest percentage incidence among adverse

events was related to sleep disturbances. Women reported suffering more from headache, dizziness and hallucinations. Gender differences could influence the pharmacological response of Safinamide. Based on the findings, new management strategies need to be developed in relation to the patient's biological sex.

EYE MOVEMENTS ABNORMALITIES AS EARLY BIOMARKER OF ALZHEIMER'S DISEASE

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Objectives: Alzheimer's disease (AD) is the most common type of dementia. Often AD patients are diagnosed after the onset of cognitive symptoms, when the neurodegenerative process has already reached an advanced stage. Thus, the challenge around the world is to find early and easy-to-obtain biomarkers. Interestingly, some brainstem structures, including the Superior Colliculus (SC) which has a key role in fixations maintenance and saccade programming, show neurofibrillary changes earlier than cortical areas [1]. Moreover, SC shows an intrinsic vulnerability to tau pathology and neuronal loss in AD patients. We hypothesised that AD-related eye movements abnormalities commonly observed in structured laboratory tasks [2] could potentially be detectable even in early stages of dementia (e.g., Mild Cognitive Impairment, MCI) and in free-viewing.

Materials: We asked participants to freely explore a series of 20 real-world images presented on a computer screen while recording eye movements (sampling-rate: 1000Hz).

Methods: N=29 AD (14F, Mage=75.9, SD=8.5), 29 MCI (11F, Mage=72.1; SD age=7.8) patients and 18 age-matched healthy controls (HC; 10F, Mage=71.7 years; SD age=8.8) were recruited at the Memory Clinic of the Hospital of Padua (Italy). Participants cognitive status was assessed by means of the Montreal Cognitive Assessment (MoCA) before the eye-tracking session. Then, a set of standard eye movements metrics was computed, as well as, an additional metric potentially highlighting subtle impairments in saccade inhibition (i.e., the number of fixations out of the image area), and two measures of gaze entropy, i.e., the Stationary Gaze Entropy (SGE), and the Gaze Transition Entropy (GTE) [3].

Results: AD patients showed a lower mean saccade amplitude (p=.035) and a less variable pattern of fixation duration (i.e., SD; p=.037) compared to HC. The number of out-of-image fixations negatively correlated with the MoCA score only in AD (r=-.37, p=.047) and MCI (r=-.46, p=.49). We also found a negative correlation between SGE and GTE (r= -.41; p=.031) only in AD.

Discussion: Free-viewing in AD was characterized by shorter saccades and difficulties in the inhibition of unwanted saccades, which was found also in MCI patients. On the other hand, the negative correlation between SGE and GTE revealed that AD patients were characterized by higher distractibility and weaker gaze control [3].

Conclusions: Spontaneous eye movement behavior can reveal subtle alterations in MCI and AD patients. Further research is needed to strengthen our observations and link them to standard biomarkers.

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MOTOR NEURON DISEASES

ALTERATION OF INTEROCEPTIVE SENSITIVITY: EXPANDING THE SPECTRUM OF BEHAVIOURAL DISORDERS IN AMYOTROPHIC LATERAL SCLEROSIS

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Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder with progressive loss of upper and lower motor neurons. Non-motor-symptoms, such as cognitive, emotional, autonomic, and somatosensory alterations, have been also described. Interoception represents the link between the body and brain, since it refers to the ability to consciously perceive the physical condition of the inner body, including one's heartbeat (i.e., interoceptive sensitivity, IS).

Objectives: To evaluate IS in ALS patients by means of a well-established task: the heartbeat perception task. Moreover, we evaluated possible correlations between IS and neuropsychological, affective, and disease-related characteristics.

Methods: Fifty-five ALS patients (mean-age= 60.3±12.5 years; mean disease-duration= 20.9±18.8 months) and 41 caregivers (CG) underwent the heartbeat perception task and an extensive evaluation of motor, cognitive, body awareness, affective and emotion domains.

Results: ALS patients showed lower IS than CG (0.68±0.24 vs 0.82 ±0.16; p=0.003). Significant correlations were found between IS and self-reported measures of alexithymia (subscale of Toronto Alexithymia scale-20 "difficulties in describing feelings"; rho= -.391, p= .003) and interoceptive awareness (subscale of Multidimensional assessment of interoceptive awareness "not worrying about pain"; rho= .405, p= .002). No significant differences were found on questionnaires for depression and anxiety between patients with ALS and their caregivers (p> .05).

Conclusions: ALS patients show reduced interoceptive sensitivity that is associated with poorer ability to describe feelings and with lower focalization on pain, regardless of cognitive and motor impairment. Alteration of interoception may represent a specific behavioural sign within the spectrum of emotion processing deficits described in ALS patients.

CLINICAL CHARACTERIZATION OF C9ORF72-MUTATED ALS PATIENTS IN A LARGE CENTER FOR MOTOR NEURON DISEASE OF CENTRAL ITALY

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Objectives: The expansion of a hexanucleotide repeat in C9Orf72 is associated with a wide spectrum of neurodegenerative disorders that ranges from Amyotrophic Lateral Sclerosis (ALS) to Fronto-temporal Dementia

(FTD) and Parkinson Disease. C9Orf72 is the most frequent cause of genetic ALS. Due to its pleiotropic significance, affected members also in a same family can show different phenotypes. Contrarily to other ALS-related genes, C9Orf72 shows a wide variability in terms of penetrance, sometimes with low penetrance at such extent that it may cause ALS at a very late onset, so that a familial track record is not always recognizable. Here, we report the characteristics of C9Orf72-mutated ALS patients in charge at our Center for Motor Neuron Diseases in Pisa, Italy.

Materials and Methods: Seven ALS patients with C9Orf72 mutation are currently followed at our Centre. They represent the 50% of patients with genetic ALS charged at our Centre, with a frequency in accordance with Literature data.

Results: Six patients had a positive family history for neurodegenerative disorders and a relatively early disease onset (55 years old on average). Two of them had a familial positive history for both Motor Neuron Diseases (MND) and dementia; three had a familial positive history for isolated ALS; one had a familial positive history for isolated dementia. Among the six patients, one had dementia, one had non-fluent aphasia and one had irritability at disease onset. One patient developed isolated ALS without cognitive impairment. One of the patients developed a motor impairment consistent with Primary Lateral Sclerosis, with no cognitive impairment. The remaining patient had a late disease onset (80 years old) and no familial track record for neurodegenerative disorders.

Discussion: The C9Orf72 complex has been implicated in many cellular processes, including vesicle trafficking, lysosome homeostasis, mTORC1 signaling and autophagy. Several pathogenic mechanisms have been proposed for neurodegeneration, but the precise functions of C9Orf72 and the exact disease mechanisms are still unclear. This makes therapies targeting this gene especially challenging.

Conclusions: Our report confirms that C9Orf72 mutations are associated with a wide phenotypic variability, mainly linked to its pleiotropic behavior and its variable penetrance. Gene therapy has boosted the number of genetic tests that are being performed, sometimes with subsequent unexpected positivities. The analysis of large panels of patients may increase our knowledge of pathogenic mechanisms of neurodegenerative disorders caused by C9Orf72 expansion.

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THE ROLE OF CHI3L1 PLASMATIC LEVELS IN AMYOTROPHIC LATERAL SCLEROSIS

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Background and aim: Motor neuron diseases (MND) are neurodegenerative diseases characterised by complex and heterogeneous pathological mechanisms. Biomarkers could help in defining patients' prognosis and stratification. Recently, besides neurofilaments, chitinases seem to be a promising family of biomarker. They correlate with neuroinflammation status and they include CHIT1, CHI3L1 and CHI3L2. In one study CHI3L1 CSF levels have been correlated with cognitive impairment. Since blood samples are easy and less invasive to obtain compared to CSF, we wanted to evaluate CHI3L1 plasma levels in MND, MND mimics and healthy controls (HCs).

Methods: Sandwich ELISA was used to quantify plasma CHI3L1 from 44 MND (including 8 ALS/FTD), 7 HSP, 9 MND mimics (including myelopathy, radiculopathy, axonal neuropathies) and 19 HCs. ALSFRSr, MRC, spirometry, genetic tests, disease progression rate at diagnosis (PR), blood examinations, neuropsychological tests (MMSE, ECAS, TMT-A, TMT-B, RAVLT, ROCF, FAB, Digit Span, FRSBE). We analysed data using Kruskal-Wallis, ANCOVA and Cox regression analysis.

Results: CHI3L1 plasma levels result to be different between groups ($p= 0.029$), in particular Bonferroni's correction shows that MND mimics have higher levels of CHI3L1 compared to MND and HCs. No difference between HSP, MND and HCs ($p>0.05$). Differences are confirmed covariating for age and sex ($p= 0.022$). A sub-group analysis of MND patients (divided in PLS, ALS and PMA) do not show any difference in CHI3L1 levels. Moreover, CHI3L1 do not correlate to ALSFRSr, MRC, FVC, FEV1, PR and blood examination, except for red blood cells and for haemoglobin (respectively, $p<0.001$, $r=0.63$ and $p=0.022$, $r=0.52$). None of neuropsychological tests correlate to CHI3L1 plasma levels. Furthermore, comparing ALS/FTD patients with pure ALS and with HCs we do not observe any difference in CHI3L1 levels ($p> 0,05$).

Discussion: CHI3L1 plasma levels result to be increased in acute myelopathy, radiculopathy and neuropathies, compared to MND, HSP and HCs. This is consistent with the increase of CHI3L1 in neuroinflammatory processes. Contrarily to CHI3L1 CSF levels, CHI3L1 plasma levels are not able to differentiate between ALS and HCs and do not correlate with neuropsychological impairment. Further multicentre studies, including a huge number of patients, and testing together other fluid biomarkers, are needed to better explain the role of CHI3L1 in diagnosis and prognosis in MND and, also, in neuropathies.

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MODELLING ALS DISEASE BY 2D AND 3D IN VITRO MODELS OF PATIENT-DERIVED IPSC

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Objective: The study of Amyotrophic Lateral Sclerosis (ALS) is limited by the impossibility to obtain neuronal cells from alive patients in order to study pathomechanisms and to test pharmacological approaches. Induced Pluripotent Stem Cells (iPSCs), that can be obtained by reprogramming patient's peripheral blood cells and/or fibroblasts, represent an exceptional opportunity since they can be differentiated into different types of neurons

and glial cells maintaining the patient's genetic background. To model different forms of ALS in vitro.

Materials and Methods: We generated, by Sendai virus reprogramming, iPSCs from patients with mutations in C9orf72 and TARDBP genes as well as isogenic lines and a loss-of-function NEK1 iPSC line. iPSCs were characterized for the expression of stem cell markers and differentiated into motor neurons, positive for specific markers as previously described [1]. We analyzed the presence of ALS-associated pathological markers, such as aggregates of the TDP-43 protein and formation of RNA foci of mutant C9orf72 gene, as well as response to oxidative stress and to DNA damage. Since the 2D cultures of iPSC-motor neurons can be maintain in vitro for a limited time and do not allow to study non-cell autonomous mechanisms, we set up 3D cultures to follow the spontaneous development of cerebral ALS organoids and the spatial distribution of the different neuronal cell types. The organoids were generated following a validated protocol [2] and analyzed by immunofluorescence performed on whole organoids or cryostat sectioning slices.

Results: iPSC-motor neurons from ALS patients showed the presence of all these defects compared to healthy controls, confirming the validity of this in vitro model. At 64 days of differentiation, the organoids showed positivity for specific markers of neuroepithelial cells, radial glial cells, and immature neurons, such as Doublecortin, Sox2, Nestin, NeuN, MAP2, and BetaIII-tubulin. On the other hand, no positivity was found for the astrocytic marker GFAP. At 73 days, no more positivity was observed for Nestin, demonstrating a maturation of neuronal cells over time, and no signs of necrosis were detected.

Discussion and Conclusion: Considering these encouraging preliminary results, the organoids of ALS patients will be cultured for longer times, up to 7 months, in order to observe their evolution and in particular the appearance of markers of more mature neuroglial cells as well as their spatial distribution and number. We have obtained reliable patient-tailored in vitro platforms using iPSC in 2D and 3D cultures to study ALS pathomechanisms.

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SALIVARY GLANDS RADIOTHERAPY FOR REFRACTORY SIALORRHEA IN AMYOTROPHIC LATERAL SCLEROSIS: A MONOCENTRIC PILOT STUDY

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Objective: To evaluate salivary glands radiotherapy (RT) for refractory sialorrhea in Amyotrophic Lateral Sclerosis (ALS).

Materials: Advanced stage ALS patients, attending our Centre, tracheostomy and percutaneous gastrostomy carriers, with problematic sialorrhea unsuccessfully treated with at least two different therapies.

Methods: Patients received a low-dose regimen of 20 Gy divided into 4 fractions along two weeks, performed with intensity-modulated radiation therapy (IMRT) through Cone Beam computed tomography (CT). The sublingual and upper portion of parotid glands were excluded from target volume to preserve saliva production and avoid mucositis and xerostomia. A week before the first RT session, CT-based 3D dose-planning and fixation with a thermoplastic head mask were performed. Efficacy and impact on quality of life of salivary glands RT was assessed using item 2 of ALS Functional Rating Scale revised (ALSFRS-r).

Results: We enrolled two patients, who developed significant sialorrhea during their disease course. Both received amitriptyline drops as first-line treatment, with different outcomes: one had a one-year response, the other experienced tongue hypoesthesia without any benefit. Then, both tried with scopolamine patches, obtaining further five months of relief for the first patient and again no response for the second one, who also underwent two Botulinum toxin type A injections in salivary glands at four months from one another, without clear benefit. Thereafter, severe sialorrhea relapsed in both cases, scoring 1 point in ALSFRS-r item 2 at the time of enrolment and complaining about consequences of drooling (constant need for napkins and aspiration, sensation of burden in the oral cavity and frequent skin abrasions). After RT, both patients reported immediate significant relief, with ALSFRS-r item 2 improvement from 1 to 3 points, maintained for the 10 months follow-up. The only side effect was a mucosal fibrosis with local hypoesthesia in the site of irradiation, reported by one of the patients.

Discussion: Our results support literature evidence of efficacy and tolerability of low-dose RT, in particular the longer response in comparison to botulinum toxin, but further studies with larger sample size, longer follow-up, quantitative outcome measures and standardized regimens are needed. The major limitation of RT is the need of a thermoplastic mask, that requires the patient to lie down for at least 15 minutes, not easily feasible for patients with swallowing and respiratory difficulties without tracheostomy.

Conclusion: Our study suggests that salivary glands radiotherapy could be a promising long-term effective treatment for refractory sialorrhea.

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AMYOTROPHIC LATERAL SCLEROSIS PRESENTING AS ANTI-MYELIN-ASSOCIATED GLYCOPROTEIN NEUROPATHY: A CASE REPORT

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Introduction: Literature suggests that patients with motor neuron disorder may have a higher incidence of monoclonal gammopathy, but the validity of this association and the potential pathogenic link between these two conditions have not been elucidated.[1] Anti-myelin-associated-glycoprotein antibodies (anti-MAG) have been related to distal acquired demyelinating symmetric (DADS) polyneuropathy phenotype.[2] Although atypical electrophysiological and clinical phenotypes have been

described, only anecdotal case report described the presence of anti-MAG antibodies in motor neuron disease.[3]

Case description: We report the case of a 51-year-old man presenting with an 8 months history of progressive sensory-motor neuropathy. Symptoms were predominant in upper limb, that showed marked amyotrophic changes. Electrophysiological tests revealed a sensory-motor demyelinating neuropathy with disproportionate increase in distal motor latency. Motor evoked potentials were within normal limits. Combined neurophysiological evaluation, albumin cytological dissociation of the cerebrospinal fluid and high serum anti-MAG antibodies title (91346 Buhlmann Titer Units, normal value < 1000) led to an initial diagnosis of anti MAG neuropathy. Despite slight symptomatic benefits after immunotherapy, in the next six months the patient complained progressive diffuse fasciculations, bulbar impairment and, lastly, pyramidal signs. Subsequent clinical and neurophysiological progression was consistent with amyotrophic lateral sclerosis (ALS). The patient died two years after the onset of symptoms.

Conclusions: Although the co-occurrence of anti-MAG neuropathy and motor neuron disease could be incidental, the low prevalence of both diseases and their close presentation play against the chance of a coincidence. We think that this case could stimulate reflection on the common pathogenic mechanisms between paraproteinemic neuropathies and ALS.

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BRAIN METABOLIC DIFFERENCES BETWEEN PURE BULBAR AND PURE SPINAL ALS: A 18F-FDG-PET STUDY

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Introduction: Some MRI studies reported that patients with bulbar and spinal onset ALS showed focal cortical changes in the corresponding regions of the motor homunculus. 18F-FDG-PET has been employed to investigate the brain metabolic changes associated with bulbar and spinal onset ALS, with inconsistent findings. We aimed at evaluating the capacity of brain 18F-FDG-PET to disclose the cerebral metabolic features that characterize patients with pure bulbar or spinal motor impairment, since neuroimaging studies focused on this issue are lacking.

Methods: We classified as pure bulbar (PB) the patients with bulbar onset who showed a normal score in the spinal items of the ALSFRS-R at PET. We considered as pure spinal (PS) the patients with spinal onset, displaying a normal score in the bulbar items of the ALSFRS-R at PET. We included 63 PB, 271 PS subjects, and 40 healthy controls (HC). ALS patients underwent brain 18F-FDG-PET at diagnosis. We compared PB and PS ALS patients, and each patient group with HC through the two-sample t-test model of SPM12. Metabolic clusters showing a statistically significant difference between PB and PS patients where tested to evaluate their accuracy in discriminating the two groups. First, we performed a Leave-One-Out Cross-Validation (LOOCV) over the entire dataset. Four classifiers were considered for comparison: Support Vector Machines (SVM), K-Nearest Neighbours, Linear Classifier, Decision Tree. Then, we used a separate test set, composed of 10% of the patients, with the remaining 90% composing the training set.

Results: PB subjects showed a relative hypometabolism compared to PS cases in bilateral precentral gyrus in correspondence with the regions of the motor cortex involved in the control of bulbar function. SVM showed the lowest LOOCV error rate (4.19%). In the hold-out validation SVM showed the lowest error rate on the test set ($9.09 \pm 2.02\%$).

Discussion: We found clusters of relative hypometabolism in bilateral motor cortex in PB compared to PS patients, closely overlapping with the somatotopic representation of bulbar functions in the motor homunculus. The metabolism of such regions showed very high capacity to discriminate between PB and PS patients. Our data provide in vivo support for the concept of the focality of ALS onset and strengthen the idea that 18F-FDG-PET can play a role as a biomarker for precision medicine oriented clinical trials.

DOES FAMILIARITY FOR NEURODEGENERATIVE DISEASES INFLUENCE AMYOTROPHIC LATERAL SCLEROSIS PRESENTATION? AN EXPLORATORY CLINICAL STUDY

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Objectives: It has been previously suggested that familial and sporadic amyotrophic lateral sclerosis (ALS) entities are clinically indistinguishable. However, there are currently different definitions of familial ALS (fALS), and the identification of other neurodegenerative disorders, in particular frontotemporal dementia (FTD), in patients' pedigree has been lately proposed as an additional criterion for the classification of this entity. Despite these considerations, studies in fALS patients as recently defined are still rare, and little is known about the influence of familiarity for neurodegenerative conditions on the clinical presentation of ALS. The aim of our study was therefore to investigate whether ALS patients with a positive family history for either ALS or other neurodegenerative diseases may exhibit distinct clinical features compared to sporadic cases.

Materials: 98 patients with a clinical diagnosis of ALS, thorough clinical examinations and complete genetic screening were included in the study.

Methods: By evaluating family history, patients were categorized in ALS with positive family history for either ALS, other neurodegenerative disorders, or both (fALS/ND) and sporadic ALS (sALS). Demographic and clinical features were compared between the two groups using chi-squared and Mann-Whitney U tests, as appropriate.

Results: 17 patients (17.34%) were classified as fALS/ND, while the remaining 81 cases (82.66%) as sALS. No significant differences were observed between the two groups in demographic features and onset clinical presentations. Conversely, relative to sALS cases, fALS/ND exhibited significant greater neck flexor weakness (p=0.05), higher ALSFRS-r progression rate (p=0.03), more severe impairment in fluency

measures (p=0.03) and, as expected, greater frequency of genetic mutations (p=0.01).

Discussion: Despite common onset presentations, fALS/ND cases exhibited more severe clinical impairment across multiple domains compared to sALS patients. Notably, all the clinical features found to differentiate fALS/ND from sALS cases (neck flexor weakness, high ALSFRS-r progression rate and fluency impairment) are well-known markers of more severe clinical decline, suggesting a greater vulnerability to more aggressive disease course in familial disease forms.

Conclusions: While further studies are warranted to confirm our preliminary observations, our data suggest that familiarity for neurodegenerative diseases may play a negative prognostic role in ALS.

GENETIC CHARACTERIZATION OF A LARGE COHORT OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS: THE ADDED VALUE OF COMBINED CARE IN A DEDICATED NEUROMUSCULAR CLINICAL CENTER

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Introduction: Genetic characterization of patients with Amyotrophic lateral sclerosis (ALS) is now common. Patients with sporadic and familial forms are typically screened for SOD1, TDP43, FUS and C9Orf72 genes. However, genetic results need to be interpreted considering clinical findings. Family members with no symptoms, but with definite gene mutations are particularly challenging. The clinical heterogeneity in patients carrying the same mutation is remarkably high and there may be fast and slow progressors with similar genotypes. The aim of this study is to present the genetic characteristics of a large cohort of patients with ALS who have been regularly followed at one single neuromuscular dedicated center in the last 10 years.

Materials and Methods: 1182 patients with ALS diagnosis were screened for SOD1, FUS, TDP43, C9ORF72 genes.

Results: Among 1182 examined patients, 70 were affected by familial ALS (fALS) accordingly to clinical history and 1112 by sporadic ALS (sALS). Mutations were found in 43/70 (61.5%) fALS patients and in 105/1112 (9,5%) sALS cases. In the fALS group, 53.5% of patients were C9ORF72 mutated, 25.5% SOD1 mutated, 13.9% TDP43 mutated and 7% FUS mutated. In the sALS group, 53.5% of patient were C9ORF72 mutated, 20% SOD1 mutated, 12.4% TDP43 mutated and 13.3% FUS mutated.

Discussion: Our data confirm the high incidence of the four most common gene mutations usually associated in sALS (1), accounting for 10% of the population with the prevalence of C90rf72 hexanucleotide expansions as high in sALS as in fALS (2). The retrospective and prospective clinical findings from our cohort of patients confirm the remarkable clinical heterogeneity amongst patients with sporadic mutations and also amongst patients within families carrying the same gene mutations. The analysis of single mutations on the same gene also confirm that patients carrying the same gene mutation may have different phenotypes and trends of progression. While the genetic heterogeneity in ALS is well-known, more is to be done to identify mutation-related and gene-mutation trajectories that may better tailor management and care. This is important in clinical trials too. In the new era of second-generation antisense oligonucleotide (ASO) treatments, identifying the genetic background knowing the clinical trajectories can better guide inclusion criteria.

Conclusions: This data confirms the importance of genetic testing in sporadic as well as in familial forms. Retrospective and prospective data from a single, dedicated neuromuscular center where patients are fully-characterized from a genetic point of view, is an added value to provide valuable information to design clinical trials and improve our understanding of disease mechanisms and progression.

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VALIDATION OF THE PENN UPPER MOTOR NEURON SCORE IN AN ITALIAN COHORT OF PATIENTS WITH MOTOR NEURON DISEASE: RELATIONSHIP WITH CLINICAL PHENOTYPE AND PROGNOSIS

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Objectives: The Penn Upper Motor Neuron Score (PUMNS) has been proposed as a measure of UMN disease in amyotrophic lateral sclerosis (ALS) [1]. However, very few reports tested the reliability of PUMNS in measuring UMN signs or tried to correlate it with other biomarkers of UMN injury in ALS [1,2,3]. In our study, we evaluated the association between PUMNS with demographic, clinical and neurophysiological parameters to confirm whether PUMNS represents a good marker of UMN impairment and if it can be used as a tool to better define clinical phenotype and prognosis of the disease.

Materials: We recruited at Istituto Auxologico Italiano IRCCS a cohort of 875 patients diagnosed with motor neuron disease according to the El Escorial revised criteria.

Methods: We collected the following clinical parameters: age and site of onset, survival, MRC scale, lower motor neuron score (LMNS), PUMNS, ALSFRS-R, ΔFRS, MITOS and King's Staging systems. Transcranial magnetic stimulation was performed on a subgroup of patients and central motor conduction time (CMCT) and cortical silent period (CSP) were calculated.

Results and Discussion: We observed that patients with an earlier age at onset and bulbar onset had more UMN impairment. Higher PUMNS values were associated to lower ALSFRS-R (p=3.5x10-11) and to higher ΔFRS scores, as well as to higher MITOS and KSS stages, indicating that a greater UMN burden correlates with disease severity. Conversely, we did not appreciate any association between PUMNS and survival, suggesting that the global burden of UMN signs does not have a major role in determining disease's prognosis. Furthermore, we did not find any correlation between PUMNS and markers of LMN disease indicating that UMN and LMN pathologies progress at least partly independently from each other during the disease course in ALS patients. This finding could also indicate that the increasing burden of LMN signs does not mask the UMN disease to the point of significantly impairing the capability of PUMNS to measure UMN signs. With regard to neurophysiological parameters, PUMNS values showed a strong direct association to CMCT (p=3.46x10-16) and inverse association to CSP (p=0.011) values, suggesting that this scale is a reliable proxy of UMN pathology.

Conclusion: Our results confirm that PUMNS represents not only a reliable measure clinical UMN dysfunction, but also a tool to better characterize phenotype, functional disability, disease progression and prognosis in patients affected by ALS. PUMNS also display a strong correlation to other markers of UMN impairment.

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LONELINESS IN ALS IS LINKED TO BEHAVIORAL CHANGES AND THINNING OF BILATERAL FRONTOPARIETAL CORTEX

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Background: Loneliness, also termed perceived social isolation, impacts on neurobiological architecture, ensuing significant consequences on mental and physical health [1]. In elderly people, it represents a risk factor for dementia [2]. The impact of loneliness on frontotemporal dysfunctions of patients with amyotrophic lateral sclerosis (ALS) has not been investigated. The study aimed to explore the association of loneliness with behavioral and cognitive symptoms of ALS, verifying the underpinning cortical signatures.

Methods: Loneliness was measured using the 3-item UCLA Scale (UCLA-3L) in 200 consecutive ALS patients. Cognitive efficiency, behavioral changes, mood, emotional regulation, and quality of life were also assessed. Seventy-seven ALS patients performed also 3T MRI scans for the measurement of cortical thickness. Spearman rho and Jonckheere-Terpstra tests examined neuropsychological profiles and cortical signatures of loneliness.

Results: One-hundred twenty-five patients reported no loneliness, 65 were classified as low/moderately lonely; 10 felt highly lonely. UCLA scores were associated with behavioral change, mood, emotional dysregulation and QoL ($p < 0.001$). Cognitive and motor disabilities were not related to loneliness. A significant cross-sectional effect of cortical thinning was observed in bilateral rostral-middle frontal cortex, left inferior parietal cortex, right superior parietal cortex and right precuneus ($p < 0.01$). Correlation analyses showed that the thickening of left inferior parietal cortex was also related to depression and emotional dysregulation ($p < 0.01$).

Discussion: The satisfaction of social environment is associated with a sense of life well-being that is not limited to the functional motor status. Loneliness was strongly related to behavioural functioning and affective state and not with cognitive abilities. Altered structure in extra-motor brain regions involved in processing socially relevant information underpin loneliness levels in ALS. These include the bilateral rostral-middle frontal cortex and right medial and the superior parietal cortex. Further longitudinal studies with comprehensive assessment of social functioning in ALS are deserved to better explore structural anomalies in the social brain.

Conclusion: Our findings suggest that loneliness may act as a risk factor or may exacerbate behavioural symptoms in ALS patients. Paying attention to social isolation in patients with ALS will help clinicians to intervene in neurobehavioral and psychiatric symptoms at an early stage.

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A141D SOD1 MUTATION: DESCRIPTION OF A NOVEL VARIANT WITH AGGRESSIVE ALS PHENOTYPE

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Objectives: To describe a patient affected by Amyotrophic lateral Sclerosis with a novel A141D variant in SOD1 gene.

Case description: A 66 year-old female was admitted to our ALS referral centre for a 4 months history of progressive weakness of lower limbs muscles, characterized by walking impairment and frequent falls. Our first neurological examination showed weakness and hypotrophy in upper and lower limbs, where fasciculations were observed. Deep tendon reflexes were absent. No bulbar signs were present. Needle electromyography showed active and chronic denervation in muscles of four limbs. No cognitive impairment was detected. A diagnosis of Amyotrophic Lateral Sclerosis was formulated. After 5 months from disease onset the patient needed respiratory support: a non-invasive mechanical ventilation (NIV) and cough assist device were provided. During follow-up period, a fast progression of disease on motor and respiratory function was observed, without involvement of speech and swallowing. One year after the onset, the patient died for respiratory failure. No family neurological history was referred, but genetic analysis for major ALS genes was proposed. Sanger sequencing of coding regions of SOD1 gene (NM_ 000454.5) was performed on genomic DNA.

Results: The missense variant c.422 C>A was identified (chr21:33040848) in exon 5, leading to the replacement of an Alanine with an Aspartic acid (p. Ala141Asp – A141D). The variant was not found in controls reported by the Genome Aggregation Database (https://gnomad.broadinstitute.org). It involves a highly conserved aminoacidic residue and it has been classified as "likely pathogenic" according to the American College of Medical Genomics criteria.

Discussion: To date more than 200 different mutations in the SOD1 gene have been described in ALS. Mutations in the SOD1 gene have been found in 13-20% of familial ALS cases and in 1-2% of sporadic cases. We have identified a novel SOD1 mutation in a sporadic ALS patient. A predominant lower motor neuron involvement and aggressive disease course are associated to this A141D variant. We provide a review of the literature about other known variants in SOD1 gene, associated with a poor prognosis.

Conclusions: To our knowledge this SOD1 A141D variant was never described in ALS patient. The spectrum of SOD1 gene variants was enriched. In the current era of gene therapy for SOD1-ALS, we emphasize the importance of offering genetic testing, at time of the diagnosis, to all patients, even for those with sporadic form of disease.

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CORRELATION BETWEEN CLINICAL PHENOTYPE AND ELECTROMYOGRAPHIC PARAMETERS IN AMYOTROPHIC LATERAL SCLEROSIS

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Introduction: Even if Electromyography (EMG) is routinely used to confirm the diagnosis of Amyotrophic Lateral Sclerosis (ALS), few studies analysed correlation between electrophysiological parameters and clinical characteristics of ALS. We assessed if the quantification of active denervation (AD) and chronic denervation (CD) provides clinicians information about phenotype, disease progression and survival in ALS patients.
Methods: We collected the following clinical parameters on a cohort of 689 ALS patients: survival, MRC scale, lower motor neuron score (LMNS), ALSFRS-R, ΔFRS, MITOS and King's Staging systems (KSS). We performed EMG and we calculated AD and CD scores for each predefined muscle analyzed in every district according to a fixed scheme; then we calculated AD and CD of the spinal region summing the partial scores for each limb.

Results: We found that spinal AD and CD were strongly directly correlated to LMNS (respectively p=4.4x1037 and p=2.79x10-45) and inversely to MRC (respectively p=4.5x10-35 and p=2.97x10-35). Furthermore, patients with higher spinal AD and CD scores had significant lower ALSFRS-R scores, higher KSS and MITOS stages; conversely, only AD was directly associated to deltaFRS (p=1.0x10-6) and inversely to survival (p= 1.1x10-5).

Conclusion: Our results confirmed that EMG examination represents not only a diagnostic instrument, but also a prognostic tool. In this context, AD seem to be a reliable predictor of disease's progression and survival, conversely CD seems to better describe functional disability.
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EMOTIONAL LABILITY IN A COHORT OF INCIDENT PATIENTS WITH ALS: THE ROLE OF PATHOLOGICAL LAUGHER AND CRYING

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Introduction: The pathological laughter and crying, also termed pseudobulbar affect or emotional lability (EL), is an involuntary or exaggerated emotional expression that is a recognized symptom reflecting damage to corticobulbar motor neurons and loss of inhibition in prefrontal and limbic areas in Amyotrophic Lateral Sclerosis (ALS) [1,2,3]. There is little information on the interplay or overlap of crying and laughter and social cognition deficits, behavioural anomalies and emotional dysregulation. The current study aims to verify the role, if any, of EL on behaviour, cognition, emotional distress, QoL and feelings of loneliness. To accomplish this, we examined crying and laughter as separate outcomes and adjusted for mood disorder.

Methods: Incident ALS cases completed the CNS Emotional Lability Scale (CNS-LS). Clinical and psychological profiles of patients with pathological EL (CNS-LS≥13; ALSel+) were compared to those with CNS-LS score within the normal range (ALSel-). Partial correlation analysis (controlled for mood, age and education; Bonferroni correction: p=0.001) were performed with Bootstrapping validation between CNS-LS scores of crying and laughter with measures of motor functional status and a number of neuropsychological test assessing cognition, with focus on social cognition, behaviour, and psychological measures including mood, emotional regulation, alexithymia, and quality of life (QoL).

Results: We enrolled 155 patients: 52 (34%) ALSel+ and 103 (66%) ALSel-. From a clinical perspective, ALSel+ had more severe bulbar symptoms than ALSel- patients. ALSel+ had higher mood disorder, greater behavioural changes, difficulties in emotional regulation and lower QoL than ALSel-. Partial correlation analyses revealed a strong association between CNS-LS laughter scores and bulbar symptoms. CNS-LS crying scores were associated with depressive mood, anxiety and emotional dysregulations. Cognitive performances were not related to EL.

Discussion: In a cohort of incident patients with ALS, one-third present pathological EL. The occurrence of this condition is associated with bulbar symptoms, psychological and behavioural alterations. Specifically, laughter is linked to bulbar dysfunctions and can be a determinant of behavioural changes. Pathological crying may bean expression of the disorder of voluntary emotional regulation linked to patients' underlying mood and poor quality of life. Conversely, EL seems not to impact cognitive abilities.

Conclusion: Pathological laughter and crying deserve to be considered separately in ALS due to their different implications. Paying attention to the early manifestations of EL will help healthcare professionals and caregivers cope with the emotional and behavioural alterations of patients.
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EXPLORING POTENTIAL MARKERS OF PRE-DEMENTIA RISK STATES IN MOTOR NEURON DISEASES: A LONGITUDINAL STUDY OF MILD BEHAVIORAL IMPAIRMENT AND ITS RELATION TO COGNITION

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Objectives: Mild behavioral impairment (MBI) has been increasingly regarded as the neurobehavioral axis of pre-dementia risk states, but a specific investigation of its detection as a potential marker of prodromal dementia in motor neuron diseases (MNDs) is still lacking. The aims of our study were therefore to explore MBI in MNDs both at onset and over disease course, and to evaluate its relationship with baseline and longitudinal cognitive features.

Materials: 60 MND patients with cognitive/behavioral, mood and motor examinations were recruited and followed longitudinally for up to 15 months.

Methods: Associations between baseline MBI symptoms and clinical features were tested using the Spearman's correlation coefficient. Based on longitudinal data, relative deltas of variation for each cognitive measure were generated, and linear regression models were then used to evaluate the role of baseline MBI symptoms in predicting longitudinal rates of cognitive decline.

Results: At disease onset, the most impaired MBI domain was affective/emotional dysregulation, followed by impulse dyscontrol, apathy and social inappropriateness. Greater MBI symptoms correlated with more severe baseline motor, cognitive/behavioral and mood disturbances (p values from <0.001 to 0.05). Longitudinally, the greatest decline was observed in the affective/emotional dysregulation domain, followed by impulse dyscontrol, apathy and social inappropriateness. Greater MBI symptoms at onset were significant predictors of more severe longitudinal cognitive decline in both ALS-specific and non-specific functions (p values from <0.001 to 0.03).

Discussion: By the time of first examination multiple MBI domains were already impaired in MND patients, and these further worsened over time. Additionally, more severe MBI symptoms at onset were significant predictors of greater cognitive decline. Taken together, these findings suggest that a closer focus on mild behavioral alterations rather than on overt behavioral symptoms may enable an earlier identification of pre-dementia risk states in MNDs.

Conclusions: MBI represents a valuable clinical marker of incident cognitive decline in MNDs, and its evaluation has good potential for detecting dementia in its preclinical/prodromal phase.

THE SEVERITY OF COGNITIVE AND EMOTIONAL DEFICITS IN ALS CORRELATES WITH THE KING'S CLINICAL STAGING SYSTEM

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Objective: Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disease primarily affecting the motoneurons. ALS phenotypic variability is remarkable and often unpredictable. Among non-motor symptoms described in ALS, cognitive impairment characterized by features overlapping with frontotemporal dementia is reported in up to 50% of patients. These include emotional and social cognition deficits, whose assessment is still poorly standardized. Our aim was to evaluate a consecutive cohort of ALS patients with a battery of tests including the latter domains and to correlate test scores with clinical scales.

Materials and Methods: We enrolled 45 Italian patients (F=19, M:F=1.52) with probable or definite sporadic ALS, according to El Escorial criteria. The median age was 65 years (range 32-85), median disease onset 63.5 years (30-84) and median disease duration 14.5 months (4-55). 80% had a spinal onset versus 20% with bulbar onset. We used the ALS Functional Rating Scale-revised (ALSFRS-r) to assess disability (median 41, range 18-48) and to score the King's Staging System (KSS, stage 0=1, stage 1=34%, stage 2=31%, stage 3=33%). The Penn Upper Motor Neuron Score (PUMNS) scored the pyramidal burden (median 10, range 0-26). All patients underwent a comprehensive neuropsychological battery of standardized tests for the evaluation of cognitive and behavioral deficits (Edinburgh Cognitive and Behavioural ALS Screen - ECAS), language (Screening for Aphasia in NeuroDegeneration scale - SAND), emotion recognition (Ekman test), and social cognition (Story-based Empathy Task – SET).

Results: 20% of the patients were impaired on ECAS global score. Overall, SAND and SET global and partial scores were normal. Emotion recognition based on Ekman was mainly impaired for "surprise" (6.67%), "fear" (17.78%) "anger" (11.11%) and "disgust" (6.67%). The group comparison showed worse results for the SET-EA in patients with >15 months disease duration (p=0.0024); for some SAND subdomains, SET-IA (p=0.0047) and Ekman (p=0.0375) in bulbar onset patients; for ECAS ALS-specific subdomains (p=0.0407) in patients with PUMNS>10. Regarding KSS, stage 3 patients had significantly worse results in ECAS, SAND and Ekman scales compared to stage 0-1, while no group differences were seen with El Escorial staging system.

Discussion and Conclusions: ALS patients can show multiple, mild cognitive and emotional deficits, especially those with bulbar onset or more pyramidal signs. Cognitive impairment appears to worsen along the disease course. Furthermore, higher KSS stages correlate with a more severe cognitive impairment across domains, while such differences are absent when considering diagnostic criteria. The predictive role of KSS for cognitive dysfunction in ALS needs confirmation by longitudinal studies.

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ANALYSIS OF HTT CAG AND NOTCH2NLC GCC REPEAT EXPANSIONS IN ITALIAN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

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Introduction and aims: The discovery of hexanucleotide repeat expansion (HRE) in C9ORF72 as the main genetic cause of Amyotrophic Lateral Sclerosis (ALS) and the association between intermediate repeats in ATXN2 with this disorder suggests that repetitive sequences in human genome play a major role in ALS pathophysiology. HTT full-penetrance pathogenic repeat expansions, the genetic cause of Huntington's disease (HD), have been recently reported in a minority of frontotemporal dementia/ALS patients (0.13%). An abnormal number of GGC repeats in NOTCH2NLC has been recently reported in 0.7% of sporadic ALS patients from mainland China. The aim of this study was to evaluate the presence of expansion repeats in HTT and NOTCH2NLC genes in our Italian cohort of ALS patients.

Material and Methods: A screening analysis of HTT CAG and NOTCH2NLC GCC repeats was conducted by repeat-primed polymerase chain reaction (RP-PCR) in a cohort of patients, who were diagnosed with ALS according to the El Escorial criteria. The length of expanded alleles was estimated by RP-PCR and confirmed by fluorescent PCR.

Results: Among a cohort of 476 subjects, including 6.6% familial cases, we identified one patient with ALS who harbored two expanded alleles in the HTT gene with 42 and 37 CAG repeats. The proband's brother and his two nephews were diagnosed with HD. No disease-causing mutations were detected in genes implicated in Motor Neuron Disorders in the proband. The absence of HD typical symptoms and the clinical picture consistent with ALS, corroborated by the diagnostic assessment, apparently excluded a misdiagnosis of HD. Expanded repeats in NOTCH2NCL were not found in a subset (n=350) of the main cohort.

Discussion: Several reports have described the occurrence of ALS in patients with a family history of HD and a positive genetic testing for high-penetrance pathogenic CAG repeat expansion in HTT. These findings suggest that HTT expansion might predispose a subset of individuals to develop clinical and pathological features consistent with ALS and this hypothesis cannot be definitively excluded in our patient. However, the direct involvement of HTT in ALS pathogenesis, emerged by novel sequencing technologies, should be interpreted with great prudence. Although it is possible that HD and ALS are part of the same neurodegenerative disease landscape, available data so far are limited.

Conclusion: Further investigations in larger cohorts are required to confidently confirm the pathogenic role of HTT repeat expansions in ALS. NOTCH2NLC expanded alleles might be absent or at least extremely rare in ALS Italian patients.

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DEVELOPMENT OF PHENOTYPE-SPECIFIC PROGNOSTIC MODELS IN MOTOR NEURON DISEASES

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Objectives: Motor neuron diseases (MNDs) encompass a wide continuum ranging from classic amyotrophic lateral sclerosis (ALS) to pure/predominant upper motor neuron (pUMN) and pure/predominant lower motor neuron (pLMN) disease forms. While it is widely accepted that these phenotypes are characterized by distinct survival rates, their longitudinal trajectories of clinical decline are still largely unknown. Additionally, the majority of prognostic studies have mainly focused on classic ALS, while the need to evaluate diverse prognostic features in pUMN and pLMN has been largely neglected. The aims of our study were therefore to investigate longitudinal trajectories of clinical decline across MND phenotypes, and to develop phenotype-specific prognostic models.

Materials: 60 MND patients (26 classic ALS, 14 pUMN and 20 pLMN) were recruited and followed longitudinally with clinical evaluations approximately every 3 months, for up to 15 months. Clinical examinations included: functional impairment (evaluated using the ALS functional rating scale revised "ALSFRS-r"), muscle strength (evaluated using the Medical Research Council "MRC" scale), UMN involvement (evaluated using the UMN score), cognitive and behavioral impairment (evaluated using the Edinburgh Cognitive and Behavioural ALS screen "ECAS") and mood disorders (evaluated using the Hospital Anxiety and Depression scale "HADS"). For each of these measures, a baseline progression rate was further estimated.

Methods: Based on longitudinal ALSFRS-r data individual slopes of decline were generated, and linear regression models were applied to isolate, among baseline features, significant predictors of a more aggressive disease course in each clinical phenotype.

Results: Longitudinally, the ALSFRS-r delta of variation was higher in classic ALS patients (-13.67), followed by pLMN (-11.89) and pUMN cases (-5.76); significant differences were selectively observed for pUMN compared to classic ALS (p=0.05). In classic ALS, significant predictors of a more aggressive longitudinal decline included greater baseline rates of overall functional impairment (p=0.003) and UMN involvement (p=0.04), as well as greater baseline lower limbs UMN involvement (p=0.02). In pUMN, significant predictors of a more aggressive longitudinal decline were male gender (p=0.05) and side of symptom onset (right p=0.001, bilateral p=0.003). In pLMN, significant predictors of a more aggressive longitudinal decline included greater baseline cognitive impairment (total ECAS score p=0.003, ECAS ALS-specific functions score p=0.01) and more severe mood disturbances (p=0.01).

Discussion: The obtained results suggest that distinct features are predictive of differential clinical decline trajectories in MND phenotypes.

Conclusions: Our study confirms the need for phenotype-specific prognostic models in order to improve patient's management and clinical trials implementation in MNDs.

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CSF SERPINA1 LEVELS INCREASED IN RAPIDLY PROGRESSING ALS PATIENTS

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Objective/introduction: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative motor neuron disease that causes death of the upper and lower motor neurons. Although the etiology of the disease is not yet fully understood, neuroinflammation plays a key role in ALS progression. A pivotal role in neuroinflammation is played by dysfunctional microglia. SerpinA1, an acute phase inflammatory player, has been involved in microglia polarization and in formation of neurofilaments conglomerates. To date, only few studies specifically focused on CSF SerpinA1 determination in ALS patients. Our study aimed to determine the levels of serpinA1 in serum and CSF specimens from ALS patients with different progressions.

Methods/materials: We analyzed serum and CSF samples from 110 ALS patients who underwent lumbar puncture during the diagnostic process and defined as "rapidly progressing" those whose disease progression rate runs higher than the 75th percentile according to reference values obtained from our ALS regional registry [1]. SerpinA1 levels were determined using the custom-designed cartridges Ella (ProteinSimpleTM). Between-group comparisons were drawn by Mann-Whitney test and ROC analysis to assess diagnostic performance.

Results: We measured the CSF and serum biomarkers of 12 "rapidly progressive" ALS patients in comparison to 108 patients with a slower disease progression. SerpinA1 levels resulted significantly higher in CSF ($p = 0.005$) but not in serum of catastrophic ALS patients compared to others ALS patients. In line with literature data, "rapidly progressive" ALS patients had higher levels of NFL in CSF ($p < 0.001$) and serum ($p < 0.001$), compared to other ALS patients, whereas pNFH were significantly elevated in CSF ($p=0.004$), but not in serum.

Conclusions: Our preliminary study shows an increased level of serpinA1 in CSF of "rapidly progessive" ALS patients, prompting its significance as an indicator of microglial activation. Furthermore, this study suggests a possible role for serpinA1 in combination with other known biomarkers to discriminate ALS patients with different prognosis at diagnosis.

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PROFILING MORPHOLOGIC MRI FEATURES OF MOTOR NEURON DISEASE CAUSED BY TARDBP MUTATIONS

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Objective: Mutations in the TARDBP gene are a rare cause of genetic motor neuron disease (MND). Morphologic MRI features of MND patients carrying this mutation have been poorly described in literature. Our objective was to investigate distinctive clinical and MRI features of a relatively sized sample of MND patients carrying TARDBP mutations.

Materials: Eleven MND patients carrying a TARDBP mutation were enrolled. Eleven patients with sporadic MND (sMND) and no genetic mutations were also selected and individually matched by age, sex, clinical presentation and disease severity, along with 22 healthy controls. Patients underwent clinical and cognitive evaluations, as well as 3D T1-weighted and diffusion tensor (DT) MRI on a 3 Tesla scanner.

Methods: Grey matter (GM) atrophy was first investigated at a whole-brain level using voxel-based morphometry (VBM). GM volumes and DT MRI values of the main white matter (WM) tracts were also obtained. Clinical, cognitive and MRI features were compared between groups.

Results: MND with TARDBP mutations was associated with all possible clinical phenotypes, including isolated upper/lower motor neuron involvement, with no predilection for bulbar or limb involvement at presentation. Greater impairment at naming tasks was found in TARDBP mutation carriers, compared with sMND. VBM analysis showed significant atrophy of the right lateral parietal cortex in TARDBP patients, compared with controls. A distinctive reduction of GM volumes was found in the left precuneus and right angular gyrus of TARDBP patients, compared to controls. Significant WM microstructural damage of the corticospinal tract (CST) and inferior longitudinal fasciculi (ILF) was found in both sMND and TARDBP patients, compared with controls, although decreased fractional anisotropy of the right CST and increased axial diffusivity of the left ILF ($p=0.017$) was detected only in TARDBP mutation carriers.

Discussion: TARDBP patients showed a distinctive parietal pattern of cortical atrophy and greater damage of motor and extra-motor WM tracts compared with controls, that sMND patients matched for disease severity and clinical presentation were lacking.

Conclusions: Our findings suggest that TDP-43 pathology due to TARDBP mutations may cause deeper morphologic alterations in both GM and WM.

Funding. Italian Ministry of Health (GR-2011-02351217; GR-2013-02357415; RF-2011-02351193), AriSLA (ConnectALS), and European Research Council (StG-2016_714388_NeuroTRACK)

THE NOVEL P.GLU134 SOD1 DELETION MAY BE ASSOCIATED TO FAMILIAL AND SPORADIC ALS

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Introduction: More than 180 mutations in SOD1 have been reported to be associated with amyotrophic lateral sclerosis (ALS), representing the second most frequent genetic cause for ALS in European cohorts. With few exceptions, SOD1-related-ALS shared some phenotypic signatures: longer duration of disease, earlier age of onset, predominant motor symptoms at the lower limbs and rare occurrences of cognitive disturbances. Here we firstly describe the phenotypic features of two unrelated Italian ALS patients, with and without family history of ALS, carrying the same, previously undescribed, SOD1 mutation.

Case description and results: Both patients had a spinal onset at lower limbs, progressive muscular weakness with early respiratory involvement and spared bulbar function. One patient was apparently sporadic, the other reported family history for ALS (brother). After an extensive diagnostic work-up, the diagnosis of ALS was established based on the Revised El Escorial Criteria. Interestingly, upper motor neuron involvement was revealed with MRI as hypointensity along the bilateral motor cortex on T2-weighted images, with a reduction in the fractional anisotropy (FA) values of the pyramidal bundle in tractography acquisitions. NGS probe-based customized panel was performed revealing in SOD1 the c.400_402 deletion in both patients, resulting in heterozygous p.Glu134 deletion. This deletion cause an in-frame 3-nucleotide deletion with loss of glutamic acid at position 134 (p.Glu134) in SOD1 protein. p.Glu134del causes a SOD1 polypeptide with one glutamine instead of two between positions 131 and 134, where previous experimental studies have shown that missense change disrupts SOD1 protein function. Co-segregation of p.Glu134del mutation within specular ALS phenotypes and molecular effect on SOD1 stability, suggest a possible pathogenic role of this mutation. Both patients are now treated with intrathecal Tofersen within its early access program.

Discussion and conclusions: Signalling new SOD1 mutations and corresponding phenotypes is gaining importance as it can shed light on underlying pathogenetic mechanisms in this scientific era with incoming personalized genetic-based approaches.

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PERIPHERAL IMMUNITY ASSOCIATION WITH CLINICAL FEATURES IN ALS

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Background and Objective: Systemic inflammation has been postulated to be a relevant mechanism in the neurodegenerative process of Amyotrophic Lateral Sclerosis (ALS). Serum haematological indices such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII) and lymphocyte-to-monocyte ratio (LMR) are thought to reflect the strength and changes of peripheral immunity. Recent evidence shows the correlation of some of these indexes with survival in ALS, but data on their correlation with clinical phenotype are lacking. Here, we investigate the role of systemic immunity in ALS patients, using baseline inflammation markers.

Methods: We collected the complete blood count (CBC) of 1784 ALS patients population from the Piemonte and Valle d'Aosta Register for ALS (PARALS). NLR, PLR, SII and LMR were derived from CBC data. Clinical data such as age at diagnosis, sex, site of onset, presence of FTD or cognitive impairment, date of death/tracheostomy, ALSFRS-R score, weight loss and pulmonary function were collected using registry data. Association between peripheral immunity markers and clinical features were examined with multivariable linear or Cox regression models, as appropriate.

Results and Discussion: After adjustment for relevant covariates, neutrophils (p=0.0300) and markers reflecting an increased innate immunity (NLR, p=0.0375 and SII, p=0.0187) were associated with higher rates of disease progression. Similarly, elevated innate immunity markers correlated with worse pulmonary function and shorter survival. In females, the elevated immune response was driven by a low lymphocyte count (p=0.003) rather than neutrophil level. The effect of low lymphocyte count on survival was also observed among late-onset ALS cases (age at onset > 70 years, p=0.0340). Finally, ALS patients with FTD symptoms exhibited lower levels of monocytes (p=0.0415) and, although only in younger-onset ALS cases (age at onset < 70 years), higher levels of neutrophils (p=0.037) and NLR (p=0.021).

Conclusions: Our results confirm that a dysregulated systemic immune system participates in ALS progression. More specifically, elevated innate immune inflammatory status, reflected by neutrophils and NLR, is associated with faster progression and reduced survival. The stratified analysis revealed that the immune response varies according to sex and age: it could be therefore speculated that involved immune pathways are patient-specific. Finally, we observed that ALS patients with greater cognitive impairment showed a reduction in monocytes count. Those data revealed that systemic inflammation plays a multifaceted role in ALS: how to translate those findings into clinical practice or targeted treatment will however require further studies.

PHENOTYPE ANALYSIS OF FUS MUTATIONS IN ALS

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Background: Mutations in Fused in Sarcoma (FUS) are among the most common genetic causes of ALS worldwide. They are supposedly characterized by a homogeneous pure motor phenotype with early-onset and short disease duration. However, a few FUS-mutated cases with a very late disease onset and slow progression have been reported.

Objective: To analyze genotype-phenotype correlations and identify the prognostic factors in FUS-ALS cases.

Methods: We identified and cross-sectionally analyzed 22 FUS-ALS patient histories from a single-center cohort of 2615 genetically tested patients and reviewed 289 previously published FUS-ALS cases. Survival analysis was performed by Kaplan–Meier survival curves followed by log-rank test and multivariate Cox-analysis.

Results: Survival of FUS-ALS is age-dependent: in our cohort, early-onset cases had a rapid disease progression and short survival (p=0.000003), while the outcome of FUS-mutated patients with mid-to-late onset did not differ from non-FUS ALS patients (p=0.437). Meta-analysis of literature data confirmed this trend (p=0.00003). This survival pattern is not observed in other ALS-related genes in our series. We clustered FUS-ALS patients in three phenotypes: (a) axial ALS, with upper cervical and dropped-head onset in mid-to-late adulthood; (b) benign ALS, usually with a late-onset and slow disease progression, (c) juvenile ALS, often with bulbar onset and preceded by learning disability or mild mental retardation. Those phenotypes arise from different mutations.

Discussion: We observed specific genotype-phenotype correlations of FUS-ALS and identified age at onset as the most critical prognostic factor. Our results demonstrated that FUS mutations underlie a specific subtype of ALS and enable a careful stratification of newly diagnosed FUS-ALS cases in terms of clinical course and potential therapeutic windows. This will be crucial in the light of incoming gene-specific therapy.

GREY MATTER CROSS-SECTIONAL AREA OF THE SPINAL CORD AS A PROMISING BIOMARKER OF RESPIRATORY FUNCTION AND SURVIVAL IN ALS PATIENTS

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Background: Respiratory system dysfunction represents the terminal event for most amyotrophic lateral sclerosis (ALS) patients. To date, several feasible and repeatable measures have been proposed to evaluate respiratory functions in ALS patients (e.g. forced vital capacity (FVC), sniff nasal inspiratory pressure (SNIP), blood artery gas parameters, such as partial pressure of CO2 (pCO2)). Aim of this study was to evaluate the cross-sectional area of the gray matter in the cervical region from C3-C5 as a novel magnetic resonance imaging (MRI) measure able to reflect the impairment of lower motor neurons innervating respiratory muscles, particularly the diaphragm.

Material and methods: At the time of diagnosis, 30 incident ALS patients underwent sagittal T2-weighted fast spin-echo MRI spine and axial T2*-weighted multi-echo gradient-echo sequences from C3-C5. Spinal cord toolbox was used to calculate cross-sectional areas of the grey matter at C3 (C3gm), C4 (C4gm), and C5 (C5gm) levels. Correlations between these MRI measures and FVC, SNIP, and pCO2 were assessed using Spearman's correlation. Patients were then dichotomized into lower and higher C3gm, C4gm, and C5gm areas, by applying a k-means clustering algorithm. Differences in overall survival from symptom onset between the groups were assessed using log-rank tests. Significance was set at $\alpha \leq 0.05$.

Results: C3gm, C4gm, C5gm areas significantly correlated with FVC (rs: 0.684, rs: 0.743, rs: 0.699 respectively), SNIP (rs: 0.424, rs: 0.482, rs: 0.368 respectively), and pCO2 (rs: -0.394, rs: -0.414, rs: -0.365). Among all MRI metrics, only C4gm areas showed a significant impact on survival in the univariate analysis. Patients with lower C4gm area (centroid: 16 mm2, number of patients: 19) showed a lower estimated median survival compared to those with higher one (centroid: 10 mm2, number of patients: 11) (estimated median survival: 18 vs 52 months respectively, p=0.009).

Discussions: Our study demonstrated that the cross-sectional areas of the grey matter at C3-C4-C5 levels reflect the impairment of the lower motor neurons which innervate the respiratory muscle. These measures could be used as valuable biomarkers to evaluate the respiratory functions in ALS patients, especially in whom the correct execution of the spirometric/SNIP evaluation cannot be guaranteed (e.g. bulbar ALS patients with impaired tight lip seal, or non-compliant ALS patients). Furthermore, our study revealed that C4gm area had a significant predictive role in survival in ALS patients since it contains the largest amount of motor neurons innervating the diaphragm.

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CAMPTOCORMIA AS THE PRESENTING SYMPTOM OF AMYOTROPHIC LATERAL SCLEROSIS: A NEW DISEASE PHENOTYPE?

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Background and Objective: "Camptocormia" also referred to as "bent spine syndrome" is characterized by marked flexion of the thoracolumbar spine, which increases during walking and abates in the recumbent position. Though it is considered as a distinctive feature of parkinsonian and dystonic disorder, recent studies highlighted that neuromuscular diseases primarily affecting paraspinal muscles can lead to camptocormia. Amyotrophic Lateral Sclerosis is a neuromuscular disease, where paraspinal muscles can be severely affected. In this study we describe a case of an ALS patient with camptocormia as presenting symptom, subsequently we reviewed all patient referring to our ALS center with camptocormia as one of the main disease features.

Methods and Results: A 61-year-old man was referred to our clinic because of a 10-month history of progressive difficulty in walking upright. He denied back pain, and also dysarthria, dysphagia, dyspnea and grip weakness, but he had noted diffuse muscle cramps. He needs to use his hands to rise from a sitting position, and this was followed within a few seconds by his bending over at the waist and holding on to his thighs. Diffuse fasciculations were evident in paraspinal muscles, in shoulder and pelvic girdle muscles bilaterally. All deep-tendon reflexes were absent. Brain and spinal cord MRI were within normal limits. MRI of the thoracic

muscles revealed mild fatty infiltration and atrophy of the erector spinae muscles. The electrophysiologic study revealed spontaneous activity (i.e., fibrillation potentials, fasciculation) and long MUP duration mainly in the thoracic muscular districts (i.e., paraspinal muscles). Nerve conduction studies and transcranial magnetic stimulation were within normal limits. After three-months his clinical conditions significantly deteriorated especially from respiratory point of view. A diagnosis of ALS based on Gold-Coast criteria was made. After this case, we systematically revised clinical data of ALS patients belonging to our database (n= 67 patients) and we found that camptocormia was present in 4 patients (6%): in 3 patients camptocormia was the presenting symptom while in 1 patient, with bulbar phenotype, camptocormia developed after two months. The presence of camptocormia was associated to a more severe respiratory impairment and disease progression rate, assessed by the ALSFRS-rate.

Discussion and conclusion: Camptocormia can be the symptom onset of ALS. A prompt diagnosis is important since such disease phenotype is associated to respiratory failure and a fast disease progression. An accurate EMG evaluation of paraspinal muscles as well as MRI of the thoracic muscles can help in the diagnosis.

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CSF TOTAL-TAU AND PTAU/TTAU RATIO AS BIOMARKERS IN AMYOTROPHIC LATERAL SCLEROSIS: A SINGLE-CENTER STUDY

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Introduction: The clinical usefulness of total-Tau (tTau), phosphorylated Tau (pTau) and pTau/tTau ratio as diagnostic biomarkers in ALS is still debated.

Objectives: To evaluate diagnostic performance of tTau and pTau/tTau ratio in cerebrospinal fluid (CSF) as amyotrophic lateral sclerosis (ALS) biomarkers.

Materials and methods: We performed a retrospective study on 102 consecutive ALS patients (57.8%, males) admitted to our Department between January 2013 to May 2022. CSF samples were obtained in 84 patients and tTau (n.v. < 400 pg/ml) and pTau (n.v. < 30 pg/ml) levels were tested by using commercially available enzyme-linked immunosorbent assay (ELISA) kits. Statistical analysis adopted the Mann–Whitney U test for continuous variables, Chi-square test for dicotomic categorical variables, Spearman's Rho for correlations between CSF biomarkers levels and clinical variables.

Results: Median age at disease onset was 67 (±12) years and median disease duration at first neuromuscular evaluation was 10.7 (±10.2) months. Thirty-one patients presented with bulbar onset, while seventy-one with spinal onset. Patient were classified as suspected ALS (n=5, 4.9%), possible ALS (n=43, 42.2%), clinical probable laboratory-supported ALS (n=14, 13.7%), clinical probable ALS (n=35, 34.3%) and definite ALS (n=5, 4.9%) at baseline. Median ALSFRS-R score at first evaluation was 45. Median Massachusetts General Hospital (MGH) upper motor neuron (UMN) score assessed at baseline was 25.5 (± 10) and median low motor neuron (LMN) score was 3 (±5). Median concentration of t-tau and p-tau in CSF were respectively 313.5 (± 185.8) pg/mL and 40.5 (± 19.5) pg/mL, resulting in median pTau/tTau ratio of 0.13 (± 0.04). Increased levels of total and phosphorylated tau levels were associated with advanced age of onset. Lower pTau/tTau ratio was found in patients with upper motor neuron involvement and a diagnosis of clinically probable or definite disease according to El Escorial criteria. By focusing on lower pTau/tTau ratio, an association with bulbar onset was present together with a trend of increase in the levels of total-tau compared to spinal onset.

Discussion: A lower pTau/tTau ratio is probably related to severe neuroaxonal damage in ALS and may reflect increased CSF tTau levels. UMN involvement may influence pTau/tTau ratio. Patients with at least two regions with clinical signs of upper and lower motor neuron involvement showed lower pTau/tTau ratio, which was not influenced by disease duration at CSF samples compared to patients with milder signs.

Conclusions: Our study suggests that pTau/tTau ratio may be a diagnostic marker of central neuron degeneration in ALS disease.

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ELECTROMECHANICAL COUPLING STUDY IN AMYOTROPHIC LATERAL SCLEROSIS PATIENTS AS A MARKER OF DIFFERENT PROGRESSION

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Background: ALS is a fatal adult-onset neurodegenerative disease involving motoneurons. Patients could be classified as slow or fast progressors according to the progression index (PI). The aim of this study is to analyze the differences between strength and amplitude of compound muscle action potential (cMAP) of a cohort of ALS

Materials: We have enrolled 42 ALS patients, divided in fast and slow progressors.

Methods: We recorded the latency and amplitude of cMAP from finger flexor muscles, and the force produced by supramaximal stimulation of the median nerve at the elbow. We used a force transducer (ZD10-100), fixed on a rigid surface, on which the patient rested his hand. We performed the test on both arms of the patients.

Results: 22 patients were slow progressors and 20 were fast progressors. We did not find any significant differences among latency (fast 2,54±0,55 ms vs slow 2,43±0,45 ms) and amplitude (fast 10,45 ±4,45 mV vs slow 9,49±4,78 mV) of cMAP among two groups. We found instead a significant difference between the peak force amplitude (slow 10.5 ± 5.7 N vs fast 6.3 ± 5.1 N, p=0,005) and the area under the curve (slow 6465 ± 5300 vs fast 3600 ± 3475, p=0,017) recorded among the two groups.

Discussion: The pathogenesis of ALS is not still clear, and there are two main hypotheses, a dying back, and a dying forward model. There is growing evidence that muscle plays a key role in the pathogenesis of ALS. We have shown that patients with different forms of disease had the same CMAP values but were able to develop different strengths, with higher values in slower progressors, as the muscle had a different role in those patients.

Conclusion: This study showed as fast and slow progressors develop the same muscle strength for the same cMAP, suggesting a possible role of the muscle in these patients, with a protective role for slow progressor patients.

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A CASE CONTROL STUDY SHOWS THAT SPG7 AND SPG11 RARE VARIANTS ARE NOT ASSOCIATED WITH ALS

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Objective: Recent findings showed that variants in the KIF5A gene, which cause an autosomal recessive hereditary Spastic Paraparesis (HSP), are associated with ALS [1]. Previous studies suggested that variants in SPG7 and SPG11 may contribute to ALS disease susceptibility.

Materials and Methods: We analyzed frequency of variants in SPG11 and SPG7 in 690 ALS consecutive patients and in 453 controls. We only considered genetic variants classified as pathogenic, likely pathogenic or of uncertain significance (VUS), according to ACMG guidelines.

Results: In SPG7 gene we detected variants in 19 patients (2.8%) and in 6 controls (1.3%; P=0.09). In SPG11 we found 18 variants in patients (2.6%) and 6 (1.3%) in controls; (P=0.17). When only pathogenic variants were considered, they were detected in 7 patients (1.01%) and 3 in controls (0.66) for SPG7 gene (P=0.5), and in 6 patients (0.86%) and 1 control (0.02%) in SPG11 gene (P=0.055).

Discussion: Several studies have investigated a possible association of SPG7 and SPG11 heterozygous variants with ALS, with inconsistent results. A recent work on 214 ALS patients suggested that SPG7 variants act as a genetic risk factor for ALS [1]. Our findings do not confirm these results as no difference was found between cases and controls. The gene SPG11 is also causative of ~40% of cases of autosomal recessive juvenile amyotrophic lateral sclerosis (JALS). One case-control study has showed an enrichment of heterozygous variants in ALS cases (n=242, 4.13%) compared to controls (n= 129, 3.1%), with no significant statistical difference [2]. We found an excess of pathogenetic variants in patients without statistical difference. SPG11 missense variants were located in the C-terminal domain in 6/570 patients and in 1/453 controls. This tendency of SPG11 variants to cluster in the C-terminal domain in ALS patients was previously reported, suggesting that the spatacsin C-terminal domain could represent a region of functional importance [3].

Conclusions: Although rare variants in SPG7 and SPG11 were enriched in patients with respect to control we have not found statistically significant differences.

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PHASE 2 CLINICAL TRIAL OF RAPAMYCIN FOR AMYOTROPHIC LATERAL SCLEROSIS

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Background: In several in vitro and in vivo studies, Rapamycin has been found to target two pillars of amyotrophic lateral sclerosis (ALS) pathogenesis linked in a vitious auto-maintaining cycle: neuroinflammation and impaired autophagy. Rapamycin, a drug that stimulates autophagy and expands regulatory T cells (Tregs) by inhibiting mTORC1, has never been tested in people affected by ALS.

Materials and Methods: In this multicenter, randomized, double-blind trial, we enrolled participants with probable or definite ALS who had had an onset of symptoms within the previous 18 months. Participants were randomly assigned in a 1:1:1 ratio to receive rapamycin 2 mg/m2/day, rapamycin 1 mg/m2/day or placebo. The primary outcome was the number of patients exhibiting an increase >30% in Tregs from baseline to treatment end. Secondary biological outcomes were

the changes from baseline of T, B, NK cell subpopulations, inflammasomes, cytokines, S6 ribosomal protein phosphorylation, neurofilaments, comparing rapamycin and placebo arm. Clinical outcome measures included the rates of decline on the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) total score, the rate of decline in muscle strength, forced vital capacity, the rate and time to nutritional and respiratory procedures, and survival. Safety and quality of life were also assessed.

Results: After screening 70 persons with ALS, 63 were randomly assigned to receive rapamycin or placebo. In intention-to-treat analysis, twice as many patients treated with rapamycin showed an increase in the number of T-reg cells compared to placebo (p=0.24). Treatment with Rapamycin 1 mg/m2/day reduced CD8 T-lymphocytes (p=0.032), IL-18 (p<0.001) and related inflammasome (p=0.023). The mean rate of change in the ALSFRS-R score was −1.03 points per month with the active drug and −1.35 points per month with placebo at week 30 (difference, 0.32 points per month; p=0.163). Patients treated with rapamycin had a better quality of life especially in the domains related to communication. Adverse events were equally represented among treatment arms. Based both on biological and clinical outcome measures, and on safety and plasma dosage stability, rapamycin 1 mg/m2/day resulted the best dosage to be tested in further clinical trials.

Discussion and Conclusions: A short treatment of 18 weeks with rapamycin showed promising effects on CD8 T-cells, inflammasome, IL18 and quality of life. Longer and larger trials are necessary to evaluate clinical efficacy of rapamycin in ALS (Funded by ARISLA; NCT03359538).

THE ROLE OF SERUM CHLORIDE AS A MARKER OF RESPIRATORY FAILURE IN AMYOTROPHIC LATERAL SCLEROSIS

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Objective: Serum chloride is a metabolic indicator of the degree of respiratory acidosis easily obtainable by routine blood analysis. Despite being already described as an useful prognostic marker obtainable by simple peripheral venous blood sampling, its use in clinical practice is somewhat limited. We investigated the role of serum chloride analyzed at diagnosis as a prognostic factor in a population-based series of ALS patients.

Materials and Methods: We collected all the serum chloride in patients followed up in Turin ALS Centre as part of the Piemonte and Valle d'Aosta Register for ALS from January 1st, 2007 to December 31st, 2019. We also collected clinical data such as age at diagnosis, sex, date of onset, site of onset, date of death/tracheostomy, ALSFRS-r score at diagnosis, weight loss and FVC at diagnosis. We performed survival analysis using the 31st of December 2021 as censoring date.

Results: One thousand four hundred and eighty-four ALS patients were included in the analysis. Serum chloride showed a significant but small correlation with FVC (R=0.149, p<0.001) and respiratory symptoms at diagnosis (R=0.179, p<0.001), measured using ALSFRS-R. Survival analysis performed using both Cox proportional hazard models, adjusted for different prognostic factors (age at onset, sex, deltaALSFRS-R score, site of onset, weight loss and FVC at diagnosis), and Kaplan-Meier curves (two groups according median value) demonstrated a significantly lower risk for death/tracheostomy for patients with high serum chloride (HR 0.982 95%CI 0.969-0.995, p=0.007; log rank test p<0.001). Stratifying patients according to NIV usage, baseline low serum chloride was associated with a shorter time-to-ventilation (median 11.5 months, 4.0-19.0 vs. 14.0 months, 8.0-26.0).

Conclusions: Serum chloride can be used as a low cost screening test at diagnosis and during follow-up to monitor respiratory dysfunction in ALS patients.

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PHENOTYPIC VARIABILITY IN AMYOTROPHIC LATERAL SCLEROSIS: THE EMERGING ROLE OF TMEM106B

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Objectives: The transmembrane protein 106B (TMEM106B) gene is a known susceptibility locus and disease modifier of frontotemporal lobar degeneration, whereas its role in amyotrophic lateral sclerosis (ALS) has been hardly explored. Therefore, we aimed to investigate the impact of the common single nucleotide polymorphism (SNP) rs1990622 of TMEM106B as determinant of phenotypic variability in ALS patients.

Materials and methods: Genotype data of the rs1990622 (A – major allele; G – minor allele) were extracted from a cohort of 865 ALS patients. Demographic and clinical variables were collected, including cognitive and behavioral features [Edinburgh Cognitive and Behavioral ALS Screen (ECAS) – Italian version; ECAS carer interview; Frontal Behavior Inventory (FBI)]; upper and lower motor neuron signs [Penn Upper Motor Neuron Score (PUMNS); Lower Motor Neuron Score (LMNS); Medical Research Council (MRC) score]; the ALS Functional Rating Scale Revised (ALSFRS-R) score at evaluation and its progression rate; age and site of onset; survival. Each variable was compared across the three rs1990622 genotypes using the additive, dominant, and recessive genetic models.

Results: Cognitive impairment was more severe among patients homozygous for the minor allele of rs1990622 (GG) compared to the other genotypes (AA + AG), with lower ECAS total (p=0.032), ALS-specific (p=0.047) and memory subdomain (p=0.050) scores. We found a higher LMN involvement in patients with at least one minor allele (G), as proved by both lower MRC scores [(AG + GG) vs. AA, p=0.001; AG vs. AA, padj=0.005], and higher LMNS [(AG + GG) vs. AA, p=0.011; AG vs. AA, padj=0.009]. Conversely, UMN signs predominated among patients carrying at least one major allele (A), who showed higher PUMNS [(AA + AG) vs. GG, p=0.015; AA vs. GG, padj=0.019]. The ALSFRS-R was higher in carriers of the GG genotype [(AA + AG) vs. GG, p=0.041]. We observed an association between site of onset and rs1990622 under the dominant model, with a higher proportion of bulbar onset among carriers of the AA genotype (p=0.023).

Discussion and conclusions: We showed that TMEM106B is a determinant of ALS phenotypic variability, involving site of onset, cognitive and motor functions, and, consequently, the functional status of patients. Although we could not explain the underlying mechanisms, the identification of different subgroups amongst ALS patients is warranted to develop targeted therapies and to guide the selection of patients for future clinical trials.

BETA AMYLOID AND TAU CONTRIBUTION TO MOTOR AND COGNITIVE MANIFESTATIONS IN AMYOTROPHIC LATERAL SCLEROSIS IN RELATION TO APOE HAPLOTYPE: A RETROSPECTIVE CLINICAL STUDY

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Objectives: The aim of this study is to assess if Alzheimer disease cerebrospinal fluid (CSF) biomarkers may predict neuropsychological and motor manifestations in Amyotrophic Lateral Sclerosis (ALS) also exploring the potential role of APOE haplotype in determining cognitive abnormalities.

Materials: Measurement of amyloid beta 1-42(Aβ1-42)), 1-40 (Aβ1-40), ratio 1-42/1-40 (Aβ42/Aβ40), tTau and pTau181 levels was performed, using chemiluminescent enzyme immunoassay (CLEIA) method on the Lumipulse platform (Fujirebio), on CSF samples of 106 ALS Italian patients, recruited at Istituto Auxologico Italiano IRCSS between 2014 and 2022. Identification of APOE haplotype was determined on a larger group of 276 ALS patients through genetic analysis on blood samples.

Methods: All patients underwent an extensive evaluation including the following clinical scales: Penn Upper Motor Neuron Score (PUMNS), MRC scale for muscle strength, Italian version of the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) and the amyotrophic lateral sclerosis functional rating scale-revised (ALSFRS-R).

Results: Low levels of CSF Aβ42/Aβ40 were significantly associated with worse performances in the memory tasks explored by ECAS ($p = 0.01$) while values of Aβ1-42 under the cutoff of 599 pg/ml seem to clearly identify patients with fluency impairment ($p = 0.017$). Furthermore, low levels of CSF Aβ1-42 and Aβ1-40 were significantly associated with lower scores at MRC. As for the tau protein, higher levels of CSF tTau were associated with a more rapid disease progression measured using ΔALSFRS-R ($p = 0.01$) and with higher scores on PUMNS accounting for bulbar region ($p = 0.02$). Finally, patients presenting with at least one allele epsilon4 (ε4) at the APOE haplotype obtained worse scores on memory tests. No associations were found between CSF pTau levels and neuropsychological or motor functions.

Discussion: Results from our report support the hypothesis that amyloid pathology, enhanced by the presence of allele ε4 in the haplotype APOE, may contribute to pathogenetic mechanisms involved in memory dysfunction in ALS patients. Moreover, low Amyloid peptide producers seem to have more widespread and/or more intense lower motor neuron degeneration, suggesting a potential protective role of amyloid (peptides) towards motor neuron. Ultimately, tTau seems to represent an interesting CSF biomarker to monitor disease progression.

Conclusion: Quantification of CSF amyloid and tau biomarkers may be useful in clinical setting to better characterize ALS phenotypes. Further studies on larger cohorts are required to confirm our results.

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REGIONAL SPREAD PATTERN IS ASSOCIATED WITH CLINICAL PHENOTYPE IN AMYOTROPHIC LATERAL SCLEROSIS

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Objectives: Increasing evidence shows that disease spread in amyotrophic lateral sclerosis (ALS) follows a preferential pattern rather than a random model with more frequent involvement of contiguous regions from the site of symptoms onset. Aim of our study is to assess if: 1) burden of upper and lower motor neuron involvement influence directionality of disease spread; 2) specific patterns of disease progression are associated with different ALS clinical phenotype.

Materials: A single center, retrospective cohort of 913 Italian ALS patients, recruited at Istituto Auxologico Italiano, has been evaluated to assess correlations between directionality of the disease process after symptoms onset and motor/neuropsychological phenotype. Order of affected regions was established from medical history.

Methods: All patients underwent an extensive evaluation including the following clinical scales: Penn Upper Motor Neuron Score (PUMNS), MRC scale for muscle strength, Italian version of the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) and the amyotrophic lateral sclerosis functional rating scale-revised (ALSFRS-R).

Results: The most frequent directionality of initial spread included adjacent horizontal regions (41%) and it was observed in patients with lower MRC ($p=0.049$) while vertical diffusion (17%) was associated with higher PUMNS ($p<0.0001$) and with reduced survival ($p= 0.001$). Noncontiguous disease spread was more frequently observed in older individuals ($p=0.001$) with a more severe impairment of UMN ($p < 0.001$), while contiguous disease pattern was more frequently associated with lower score at MRC.

Discussion: Result from our study raise the hypothesis that the disease process more likely spreads within the ipsilateral motor cortex and to contralateral anterior horn cells within the same spinal cord segment. These observations suggest that one of the mechanisms underling disease spread in ALS pathology is represented by diffusion of toxic factors by contiguity in the neuron microenvironment and by the different susceptibility to external damage among motor neurons.

Conclusion: Our study supports the hypothesis of a preferential pattern of disease spread according to prevalent involvement of upper or lower motor neuron and that different pattern of disease progression are associated with different clinical phenotypes.

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FOCUS ON CATASTROPHIC AMYOTROPHIC LATERAL SCLEROSIS: A BIOMARKER STUDY

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Background: Amyotrophic Lateral Sclerosis (ALS) is characterized by a wide range of clinical presentations with some patients who may be referred as "catastrophic" - having an extremely deleterious progression with death or tracheostomy within one year from onset. Even if a minority (<10% of the total ALS population), this group represents a great challenge as their conditions relentlessly worsen before support procedures are carried out. We hypothesize that systemic and neurological inflammation may aberrantly interact to precipitate ALS, especially in this specific population.

Objectives: The aim of the project is to describe immune profiles of "catastrophic" and "classical" ALS patients, including systemic inflammation and microglial biomarkers in order to delineate a panel of biomarkers useful for the diagnosis and prognosis linked to ALS progression.

Methods: Patients were recruited from a case series from the ALS Center of Modena University Hospital, from 2007 to 2021. A "catastrophic" evolution was defined as either a survival time less than 12 months from onset or a decline in ALSFRS-r greater than 3 points/month. "Classical" ALS progression runs an ALSFRS-R slope of 0.3-3 points/month, excluding slow progressors. Biomarkers panel included systemic inflammatory cytokines and interleukins, microglial, neuroaxonal and synaptic biomarkers.

Results: We measured the CSF and serum biomarkers of 12 catastrophic ALS patients in comparison to 85 patients with a classical evolution. Catastrophic ALS patients had higher levels of NFL in CSF and serum, compared to classical ALS patients ($p<0.001$ and $p = 0.001$, respectively), while pNFH were significantly elevated only in CSF ($p=0.005$). In CSF serpinA1, CHI3L1 and TREM-2 were significantly higher in catastrophic ALS patients ($p=0.0349$, $p=0.0390$ and $p=0.0049$ respectively). Neurogranin levels were equally distributed, regardless of cognitive status. All systemic inflammatory biomarkers had similar concentration between the two groups, with only IL-17BP levels being higher ($p=0.0778$ on CSF and $p=0.0506$ on serum) in catastrophic patients. ROC curves for discriminating catastrophic from classical forms showed an area under the curve (AUC) of 0.79 for CSF serpinA1 and 0.9 for CSF NfL, with AUC of 0.87 combining CSF NfL, serpinA1 and CHI3L1 together.

Conclusions: Despite some limitations due to our sample size, our study supports the idea that in catastrophic patients the microglial inflammatory response is highly activated compared to patients with a slower disease, while systemic inflammatory reaction seems to be marginal. Moreover, combining markers of neurodegeneration with CSF serpinA1 and CHI3L1 levels may hold promise to discriminate against aggressive evolution at presentation.

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DIFFERENTIATION BETWEEN MND PHENOTYPES: THE ROLE OF CLINICAL FEATURES AT THE TIME OF DIAGNOSIS

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Objectives: Motor neuron diseases (MNDs) can affect the upper motor neurons (UMN) and/or the lower motor neurons (LMN), and it is now widely accepted that pure/predominant UMN (pUMN) and pure/predominant LMN (pLMN) phenotypes have significantly better prognosis compared to classic amyotrophic lateral sclerosis (ALS). Despite this consideration, the heterogeneity of the initial manifestations often challenges an accurate differentiation between these MND phenotypes, with important consequences in terms of prognosis estimation. The aim of our study was therefore to determine which clinical features at the time of diagnosis may help differentiating pUMN and pLMN phenotypes from classic ALS.

Materials: 60 MND patients were included in this retrospective study (26 classic ALS, 14 pUMN and 20 pLMN). At the time of diagnosis patients underwent a detailed clinical characterization, including site (bulbar, proximal spinal, distal spinal) and side of disease onset, disease duration, overall degree of functional impairment (assessed using the ALS Functional Rating Scale-revised [ALSFRS-r]), regional UMN involvement (graded using the UMN score), muscle strength (evaluated using the Medical Research Council [MRC] scale) and their relative progression rates.

Methods: Mann-Whitney and Chi-squared tests were used to identify significant differences between pUMN and classic ALS as well as between pLMN and classic ALS. Logistic regression analyses were then applied to isolate significant predictors of pUMN and pLMN diagnoses.
Results: Significant predictors of a pUMN diagnosis included younger age at onset ($p=0.02$), longer disease duration ($p=0.05$), and greater cranial ($p=0.03$), upper limbs ($p=0.03$) and lower limbs ($p=0.01$) UMN involvement. Significant predictors of a pLMN diagnosis included longer disease duration ($p=0.01$), more severe gross motor functional impairment ($p=0.01$), lower muscle strength of the right ($p= 0.001$) and left ($p= 0.007$) lower limbs, less severe cranial ($p=0.02$), upper limbs ($p=0.002$) and lower limbs ($p=0.01$) UMN involvement, and slower rate of progression of the UMN signs ($p= 0.01$).

Discussion: Our results suggest that specific clinical features at the time of diagnosis may help differentiating between more benign and more aggressive MND phenotypes.

Conclusions: These findings have potential to facilitate appropriate stratification for clinical trials enrollment, clinical management, and prognosis estimation.

A CLUSTER-BASED APPROACH USING MAGNETIC RESONANCE IMAGING METRICS TO EVALUATE PATTERNS OF NEURODEGENERATION AND CLINICAL IMPLICATIONS IN AMYOTROPHIC LATERAL SCLEROSIS

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Background: Bilateral cortical thickness of precentral (PREct) and paracentral gyrus (PARAct), and medulla oblongata volume (MOv) have been suggested as prognostic biomarkers in amyotrophic lateral sclerosis (ALS). However, while most imaging studies first categorize patients based on clinical course, and then describe phenotype-associated imaging features, the aim of our study was to evaluate the natural segregation of patients according to magnetic resonance imaging (MRI) metrics using a cluster-based approach without a-priori categorization and then to assess clinical features cluster-associated.

Material and Methods: At the time of diagnosis, 90 incident ALS patients underwent 3D-T1 structural MRI. Bilateral PREct, PARAct, MOv, and total intracranial volume (TIV) were calculated using Freesurfer. For each subject, metrics of bilateral structures were averaged pairwise, and MOv was corrected using TIV as a covariate. Using min–max scaled composite regional integrity scores, a two-step cluster analysis was conducted. Differences between clusters in demographic, clinical variables, and overall survival from symptoms onset were assessed using Chi-squared, Mann-Whitney-U, and log-rank tests as appropriate.

Results: Three radiological clusters were identified: 41% of ALS patients belonged to "cluster-1", 48% to "cluster-2" and 11% to "cluster-3". Subjects in "cluster-3" exhibited significant cortical thinning of both PARAct and PREct and higher MOv, while "cluster-2" expressed exactly the opposite pattern of the MRI measures. Among the three clusters, subjects in "cluster-1" exhibited the lowest values of cortical thickness and MO volume. In the "cluster-1" ALS patients were significantly older than those in the other clusters. The three clusters were matched for sex. Among the twenty-three bulbar-onset ALS patients, 61% were allocated in "cluster-1", 39% in "cluster-2", and none in "cluster-3" "Cluster-1" was characterized by significantly lower ALSFRS-r score, compared to patients in "cluster-2" and "cluster-3", while no differences in disease severity were found between these two latter groups. Among the three clusters, "cluster-1" showed the lowest estimated median survival.

Discussion: Our data-driven MRI analysis showed distinct ALS subtypes according to different neurodegeneration patterns. The most intriguing finding was that a considerable proportion of patients (41%) showed wider impairment of both cortical and bulbar motor neurons, already at the time of diagnosis. These latter patients were characterized by higher disease severity and lower median survival and therefore, they should be carefully evaluated to timely intervene through therapeutic supports (e.g. use of non-invasive ventilation or positioning of a percutaneous endoscopic gastrostomy).

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ALS-PLUS SYNDROME: MORE THAN A RARITY. A CASE REPORT AND LITERATURE REVIEW OF CONCOMITANT AMYOTROPHIC LATERAL SCLEROSIS (ALS) AND PARKINSONISM

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Objective: Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disorder of the neuromotor system; median survival is about 3 to 5 years. According to the revised El Escorial Criteria, ALS-Plus syndrome is a peculiar form of ALS where, in addition to the classical phenotype, non-pyramidal features occur.

Subjects: We describe the case of a 74-year-old male patient admitted to our institution with concomitant pyramidal and extrapyramidal signs suggestive of ALS-Plus syndrome and we review the literature regarding ALS phenotype associated with Parkinsonism.

Methods: Medical records, radiological imaging, neuropsychological tests, electrophysiological studies, laboratory tests were reviewed. A literature search on PUBMED, DISCOVERY and ISI web of science was also provided, and a brief narrative review of findings was compiled.

Results: Clinical onset had occurred six months earlier with a slowly progressive ascending weakness at both his right limbs causing functional impairment; retropulsion and action tremor of both hands were already present for two years. On admission diffuse fasciculations, left arm hyperreflexia, right Hoffman's sign, episodical dysphagia, mild dyspnoea and dysarthria were additionally observed. Extrapyramidal signs were detected as hypomimic face, vertical gaze paralysis and bilateral palmomental reflex. Clinical progression resulted in respiratory failure and tetraplegia. Electromyography was suggestive of lower motorneuron disease (MND); spirometry revealed severe restrictive syndrome. On brain MRI cerebral peduncles and mesencephalon atrophy was observed, with a "hummingbird sign" suggestive of Progressive Supranuclear Palsy (PSP). All remaining investigations were negative. The patient died eight months after the onset of symptoms.

Discussion: We describe a case of a clinically-probable-ALS with additional features: (1) concomitant extrapyramidal signs and ocular motility disorder suggestive of ALS-Plus, in particular PSP-MND dual pathology; (2) severe clinical progression resulting in early death. Although ALS-Plus has always been considered a rare entity, a recent study suggests that it is actually underdiagnosed, with about 13.6% identified within a cohort of 550 ALS patients. Noteworthy, ALS-Plus is associated with a poorer prognosis [1]. One major clinical issue, still highly controversial, relies on the acceptable phenotypic boundaries of this syndrome [2]. In terms of neuropathology, TAR-DNA-binding-protein-43 (TDP-43) pathology, but sometimes also tauopathy (e.g. ALS/Parkinsonism-dementia complex syndrome of Guam), is demonstrated in brain regions associated with Plus-symptoms, suggesting a neurological multisystemic involvement where the topography of the lesions correlates with clinical manifestations rather than their molecular nature [2,3].

Conclusion: This case report and literature review on ALS-Plus emphasizes the multisystemic involvement of the disease and the relevance of an accurate diagnosis and prognosis.

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ROLE OF THE CHRONIC STRESS ON THE TDP-43 SUBCELLULAR LOCALIZATION IN FIBROBLASTS OF THREE DIFFERENT ALS-RELATED TARDBP MUTATIONS

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Aims: TAR-DNA-Binding-Protein 43 (TDP-43) forms cytoplasmic aggregates in ALS, thought to play a role in the pathogenesis of the disease. Here, we analyzed the subcellular localization of TDP-43 after chronic stress in fibroblasts of three patients, each affected by a specific TARDBP gene mutation.

Methods: Skin fibroblasts were purified from three ALS patients, each carrying a pathogenic TARDBP variant (G376D, familial; G294V, sporadic; A382T, sporadic). The G376D variant associated to a more aggressive phenotype. Control fibroblasts were from a sporadic ALS, without known mutations. Chronic stress was induced by arsenite for 30 hours. Immunofluorescence was performed at rescue, and 24,48,72 hours later. We used antibodies to TDP-43 and TIA-R (a marker for SG). The co-expression of TDP-43 and TIA-R in each mutant fibroblast was analyzed with the confocal microscope Nikon A1.

Results: Chronic stress induced the formation of TIA-R-positive SGs that persisted up to 48h after rescue. In all three cell types, TDP-43 formed cytoplasmic inclusions, which co-localized with TIA-R. The TDP-43 inclusions disappeared at 48h after rescue. Note that TDP-43 was diffusely expressed in the cytoplasm of the mutant G376D fibroblasts, but not in the other mutant cells.

Conclusions: Chronic stress induced TDP-43 translocation to the cytoplasm of all mutant cells, where it forms transient aggregates. Therefore, these inclusions are probably not related to the persistent aggregates found in the disease. Furthermore, the diffuse cytoplasm mislocalization of the G376D TDP-43 protein after stress might represent a biological correlate of the more aggressive phenotype that characterizes this mutation.

INVESTIGATING THE ROLE OF P.F46C-SOD1 VARIANT IN A SPORADIC ALS PATIENT

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Objectives: Amyotrophic Lateral Sclerosis (ALS) is a severe neurodegenerative disorder characterized by the selective death of motor neurons (MNs). Cupper-zinc-superoxide dismutase 1 (SOD1) is the first gene identified as mutated in ALS and accounts for approximately 20% of familial cases (fALS) and 2-4% of apparently sporadic cases (sALS). To date, more than 200 different SOD1 gene variants have been identified in ALS patients [1,2]. Current understanding indicates that there may be a complex interplay between different factors underlying the disease: oxidative stress, inflammation, excitotoxicity, protein aggregation, mitochondrial damage and axonal transport. However, the mechanism through which mutant SOD1 leads to MN degeneration has not been clearly identified. The present study aimed to investigate different molecular mechanisms, including oxidative stress, inflammatory profile, mitochondrial dysfunction and autophagic process, in human skin fibroblasts of a ALS patient carrying the p.F46C-SOD1 variant as compared to a control with a sporadic disease with no known mutations and a healthy control.

Materials and Methods: Fibroblasts of the two sALS patients and a control subject were characterized. Cell fluorescence, RT-PCR and western blotting were used to analyse the subcellular distribution, expression and function of the SOD1 protein. Seahorse biosciences XF analyzer and MitoTracker Orange CM-H2TMRos/Red probes were used to study bioenergetic pathways and to evaluate mitochondrial membrane potential and mitochondrial mass, respectively.

Results: We found an increase in the membrane potential ($p<0.02$) and a significant decrease in inflammatory cytokines (IL-1β) levels in F46C-SOD1 fibroblasts, in contrast to healthy control ($p<0.03$) and sALS ones ($p<0.002$). Furthermore, F46C-SOD1 fibroblasts showed a slight activation of the autophagic mechanism and, when under the effect of inhibitory agents, shifted from mitochondrial respiration to glycolytic processes.

Discussion: To understand the role of the F46C-SOD1 variant in ALS we performed a functional study demonstrating striking abnormalities in mutated-SOD1 compared to control and sALS fibroblasts. The same variant was previously identified in one fALS patient with slow progression of the disease [3]. Overall, the alteration of mitochondrial function, the increase in membrane potential as a compensatory mechanism for the ATP production inefficiency and the inflammatory profile alteration in F46C-SOD1 could be correlated with the mild clinical picture of this patient.

Conclusion: Functional characterization of the F46C-SOD1 variant was performed for the first time here. Further functional studies on a larger cohort of patient-derived fibroblasts could help overcome the complexity of the disease, identifying impaired cellular functions and their correlation with clinical features of ALS patients.

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TRACHEOSTOMY IN AMYOTROPHIC LATERAL SCLEROSIS IN SOUTH SARDINIA, AN EPIDEMIOLOGICAL STUDY

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Objective: We assessed the percentage of tracheostomy in ALS patients in South Sardinia, we evaluated the outcome and we studied the influence of some clinical and genetic patients's and disease's features on the choice of tracheostomy.

Materials and Methods: ALS patients from all neurological centers of the study area diagnosed during 2010–2019 were included. Interaction of patients' age, sex and education and disease's clinical and genetic characteristics on the choice of tracheostomy was studied in two groups: patients who died without tracheostomy and patients who underwent tracheostomy, considering this surgery as an analogue of death.

Results: Among the 344 incident ALS patients in the period 2010–2019, 107 (31.1%) underwent tracheostomy, 170 (49.4%) died without tracheostomy. The mean time from the onset of ALS to the tracheostomy was 33.5 months with a mean survival time after tracheostomy of 26.2 months. The mean survival time in patients who did not undergo tracheostomy was 35.3 months. The age at diagnosis was lower (62.8 vs 68.7 years, $p < 0.001$) in patients who underwent tracheostomy. There was an increased trend of respiratory clinical phenotype and familiarity of ALS and a downward trend of upper motor neuron (PUMN) clinical phenotype in patients tracheostomised. Furthermore, there weren't other significant differences in patients that chose or not invasive mechanical ventilation.
Discussion: The percentage of tracheostomy and mean survival time after this procedure in ALS patients in Sardinia was higher than other reported in Italy [1]. The same mean time from ALS onset to tracheostomy and form ALS onset to death in the two different groups made them comparable. The lower age at diagnosis in tracheostomised patients could be explained by the presence of different perspectives in younger patients. The trend of more respiratory and less PUMN phenotype in patients who underwent tracheostomy could be explained by the different progression towards respiratory failure of the two forms, being the respiratory form with a much faster course. Familiarity history of ALS could have a role in the choice, having the patients already experienced the course of the disease as caregivers.

Conclusion: Tracheostomy is more frequent in patients with ALS in Sardinia than in other regions, with a greater benefit. Age, clinical form, and family history appear to play a role in this choice. More studies are needed, however more important seems to be sociocultural and ethical factors.

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QUANTIFICATION OF TDP-43 IN SERUM OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS BY SIMOA TECHNOLOGY AND ITS RELATIONSHIP WITH UNC13A GENOTYPE

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Objectives: The lack of specific biomarkers makes the early diagnosis of ALS a challenge. Since ALS, together with ~50% of frontotemporal dementia (FTD) cases, is a TDP-43 proteinopathy characterized by neuronal cytoplasmic inclusions of phosphorylated and ubiquitinated TDP-43, this protein is considered a candidate disease biomarker to be measured in patients' biofluids. Attempts in this direction have been reported using different analytical approaches with no consistent results so far. Among ALS patients, the UNC13A genetic risk variant rs12608932 is associated to shorter survival, bulbar onset, older age at onset and increased behavioral disturbances, making the minor allele C a robust phenotype modifier. Aim of our study was to measure TDP-43 in both CSF and serum of patients with ALS, analysing possible correlations with the risk factor UNC13A genotype.

Materials: CSF and/or serum samples were obtained from sporadic ALS patients and control individuals. Genomic DNA was isolated from whole blood with commercial kits.

Methods: TDP-43 and NFL protein levels were quantified by Simoa technology on the SR-X platform (Quanterix) in duplicates. Genotyping of UNC13A rs12608932 was performed by allele-specific PCR.

Results: We failed to measure TDP-43 in the CSF of ALS patients (n=39) since all measures were under the lower limit of quantification (LLOQ). TDP-43 was undetectable also in the CSF of control individuals (n=5), both using diluted samples (4X, 2X) and undiluted ones. We instead were able to quantify TDP-43 in the serum of ALS patients (n=65) and healthy controls (n=36). Our results show that serum TDP-43 content was significantly higher in ALS compared to healthy controls (median, 394 pg/mL vs 286 pg/mL; $p<0.05$). When we stratified ALS patients according to the UNC13A risk allele C, we identified 24 A/A, 24 A/C and 17 C/C patients. ALS patients with the UNC13A risk minor allele in homozygous state (C/C) showed serum TDP-43 levels comparable to control samples, while A/A and A/C patients showed significantly higher levels. Conversely, when we measured NFL in the same serum samples, we found a significant increase of the protein in all ALS patients, regardless of their UNC13A genotype.

Discussion and Conclusion: Our data suggest that serum TDP-43 may be a potential biomarker in ALS and may be associated, in contrast to NFL, with the UNC13A genetic risk variant. However, the association of these two ALS biomarkers with specific clinical features needs to be further investigated.

GENETIC AND CLINICAL OVERLAP BETWEEN AMYOTROPHIC LATERAL SCLEROSIS AND PARKINSON'S DISEASE

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Aims: Neurodegenerative disorders (NDs) are increasingly being considered as part of a continuum spectrum. Extrapyramidal features are occasionally reported in Amyotrophic Lateral Sclerosis (ALS) patients, although genetic overlap between ALS and Parkinson's disease (PD) has not been explored yet. The aim of this study is to collect clinical and genetic data from ALS patients in order to assess the presence of mutations in specific PD related genes and their role in the resulting phenotype.

Materials: We enrolled a cohort of 201 ALS patients, all diagnosed according to international diagnostic criteria, between 2012 and 2021.

Methods: We performed the genetic analysis with Next Generation Sequencing on the DNA isolated from peripheral blood leukocytes of our cohort. We selected a panel of 97 genes involved in NDs and performed a bioinformatic analysis. Only the most relevant genes related to PD or ALS were taken into account. C9orf72 repeat expansion was assessed using the repeat-primed PCR assay.

Results: Thirteen patients had pathogenic of uncertain significance variants in the PD-genes analyzed, of whom five carried gene mutations in LRRK2, five in PRKN, two in PINK1 and one in PARK7. Four of

them presented clinical extrapyramidal features, of whom two have an essential tremor like syndrome, the other two have an akinetic- rigid-parkinsonism in a clinical phenotype characterized by overlap between frontotemporal dementia and ALS. None of these patients carried mutations in ALS-related genes.

Discussion: Mild extrapyramidal features are present in ALS patients and can be associated with PD specific gene mutations. No specific clinical phenotype could be associated with such variants. It is possible that in some case two disease coexist (ALS and essential tremor) otherwise it is possible that PD mutations could modify the clinical phenotype of ALS patients.

Conclusion: Further analysis needs to be performed to better define clinical and prognostic relevance of these mutations and the genetic overlapping between ALS and PD.

STRUCTURAL AND FUNCTIONAL CONNECTOME ALTERATIONS ACROSS KING'S STAGES IN AMYOTROPHIC LATERAL SCLEROSIS

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Objective: The identification of quantitative and reproducible markers of disease progression in amyotrophic lateral sclerosis (ALS) is of paramount importance for study design and inclusion of homogenous patient cohorts into clinical trials, as there is currently no validated disease-stage biomarker for ALS. Here, we explored the rearrangements of structural and functional connectivity within and among brain networks underlying the clinical spreading of ALS, as described by the King's staging system, in order to suggest objective, continuous measures mirroring disease progression.

Materials: 104 patients with ALS and 61 age- and sex-matched healthy controls underwent clinical and brain magnetic resonance imaging (MRI) on a 3T scanner. Patients were stratified into four groups, according to the King's staging system. No patient had comorbid frontotemporal dementia.

Methods: Structural and functional connectivity values within and between different anatomical brain regions were obtained using diffusion tensor and resting-state functional MRI data, respectively. Comparisons between groups were performed using age- and sex-adjusted ANOVA models, Bonferroni-corrected for multiple comparisons.

Results: Compared with controls, a significant, progressive reduction of structural connectivity within brain nodes of the sensorimotor network was observed in ALS patients across King's stages 2, 3 and 4 ($p<0.006$). Patients in stages 3 and 4 also showed significant loss of structural connectivity between frontal and sensorimotor regions ($p=0.001$), whereas patients in milder stages were comparable with healthy controls. A significant disruption of functional connectivity between frontal and temporal regions was found only in ALS patients in stage 4 ($p=0.025$).

Discussion: Brain MRI allows to demonstrate and quantify increasing disruption of structural connectivity involving the sensorimotor and frontal networks in ALS, mirroring disease spreading described by the King's staging system. Frontotemporal functional disconnection seems to characterize only advanced disease stages.

Conclusions: Our findings demonstrate the utility of MRI connectomics to stratify patients and stage brain pathology in ALS in a reproducible way, which mirrors clinical progression.

Funding: Italian Ministry of Health (GR-2011-02351217; GR-2013-02357415; RF-2011-02351193), AriSLA (ConnectALS), European Research Council (StG-2016_714388_NeuroTRACK), Foundation Research on Alzheimer Disease.

PRESENCE AND SEVERITY OF LANGUAGE DEFICITS IN COMPREHENSION, PRODUCTION AND PRAGMATICS IN A GROUP OF ALS PATIENTS: ANALYSIS WITH DEMOGRAPHIC AND NEUROPSYCHOLOGICAL DATA

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Aims: To outline the prevalence of language deficits in an ALS cohort and explore their profile along with demographic and neuropsychological data.

Materials: A full neuropsychological battery and language assessment was administered to 56 ALS patients. Neuropsychological assessment included tests of executive functioning, verbal fluency, social cognition and memory. Language was assessed using tests for verbal comprehension, production and pragmatics.

Methods: Patients were cognitively classified following the Revised Consensus Criteria and divided in three groups showing different levels of language deficits: group 1 - no language deficit; group 2 - one language deficit; group 3 - two or more language deficits. Chi-square for independence and non-parametric measures to compare groups were applied.

Results and Discussion: Nearly half of ALS-CN patients (48%) reported one language test under the clinical cut-off, and only 13% of patents classified as ALS-CI showed no language deficits, while the rest 87% of ALS-CI reported two or more language deficits. ALS-BI and ALS-CBI cases all reported two or more language deficits. Deficits in production and in comprehension appeared more frequent in ALS-CI patients ($p=0.011$, $p=0.003$ respectively), with a higher percentage of comprehension deficits (83%). Nearly all ALS-CI reported at least one deficit in pragmatic abilities (96%) and all ALS-BI and ALS-CBI patients showed pragmatic deficits. Males showed higher percentage of pragmatic deficits (97%, $p=0.007$). No significant differences on language deficits have been found between bulbar and spinal onset. Months from onset and level of impairment at testing (ALS-FRS total score) were not significantly different between levels and type of language impairment. Comparing performances at neuropsychological tests among the three levels of language deficits, no significant differences in neuropsychological performances were found between group 1 and 2.

Conclusions: Language deficits have found to be spread in our sample, encompassing verbal comprehension, production and pragmatics. Our study reveals that also cognitive intact patients (ALS-CN) showed at least one language deficit in 48% of cases. Pragmatic domain is the most compromised (84% of the total sample), present in nearly all ALS-CI (96%), likely due to the influence of executive impairment. Lower age and higher education seem to preserve comprehension, pragmatics and presence of language deficits. Finally, executive functions, verbal/visuospatial learning and social cognition differentiate the group with no language deficits from the group with a clinical language impairment,

while attention and working memory differentiate the group with one language deficit from the clinical impaired group.
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QUANTITATIVE SUSCEPTIBILITY IMAGING IN AMYOTROPHIC LATERAL SCLEROSIS

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Objectives: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease characterized by the degeneration of Upper (UMN) and Lower Motor Neurons. Previous QSM-based studies revealed higher susceptibility values in PreCentral Gyrus's (PrCG) of ALS patients [1,2], but also in extra-motor cortical areas as compared to heathy controls (HCs) [3]. We aimed to study the susceptibility-based and structural properties of multiple cortical gyri in ALS patients as compared to HCs and patients with other neurodegenerative diseases (NDs).

Methods: 49 ALS, 40 NDs (17 hereditary spastic paraparesis, 6 REM sleep behavior disorder, 17 parkinsonism), and 29 HCs were prospectively enrolled. We collected: ALS Functional Rating Scale (ALSFRS-R), disease duration (from clinical onset to MR), PENN UMN Score, and disease progression rate (DPR), calculated as 48-ALSFRS-R/disease duration. MR protocol included MPRAGE and QSM. We focused on: PrCG, caudal middle frontal, paracentral gyri and pars-triangularis in the frontal lobe, postcentral, inferior parietal and supramarginal gyri in the parietal lobe, transverse temporal gyrus in the temporal lobe and posterior and isthmus of the cingulate gyrus in cingulate cortex. Median susceptibility values of each gyrus were extracted and ROI-based analysis was performed, comparing age- and sex- matched subgroups of the three popoluation (Bonferroni-corrected Kruskal-Wallis test) and testing those values for potential correlations with clinical data (Spearman's test).

Results: Disease duration of ALS patients was quite short (~50% < 1 year and ~75% < 2 years). Susceptibility values were significantly higher in PrCG, caudal middle frontal and paracentral gyri, pars triangularis, supramarginal and posterior cingulate gyri of ALS patients compared to HCs. No significant differences were found between ALS and NDs. Cortical thickness was significantly reduced in the inferior parietal and posterior cingulate gyrus, while volume measurements were significantly decreased in supramarginal gyrus of ALS compared to HCs. In ALS patients, we found a significant correlation between susceptibility values in caudal middle frontal gyrus and PENN UMN score (Rho=0.325, p=0.024). A significant correlation was also found between DPR and the cortical thickness in the precentral gyrus (Rho=-0.306; p=0.035), and between DPR and volume of the paracentral gyrus (Rho=-0.326; p=0.024).

Conclusions: Susceptibility-based analysis confirmed the iron accumulation in several cortical areas of ALS patients even in the early phase of the disease. The pathological role of iron deposition in other neurodegenerative diseases remains to be elucidated. Susceptibility and structural measurements correlated with clinical scores of UMN involvement and disease progression, suggesting the possible prognostic value of these imaging biomarkers.
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PRESYMPTOMATIC GEOGRAPHICAL DISTRIBUTION OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS: A POPULATION-BASED CLUSTER ANALYSIS

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Aim: Environmental factors have been hypothesized to play a role in the etiology of most ALS cases [1]. Clusters in the spatial distributions of patients could underlie the role of environmental factors. However, the degeneration in ALS is thought to start many years before the disease onset [2] and most geoepidemiological studies used the position of patients at the time of their diagnosis. The aim of the study was to investigate the geographical distribution of ALS patients before the disease onset.

Methods: Data from the Piemonte and Valle d'Aosta Register for ALS (PARALS) were used. Patients who were resident in Piemonte at the time of the diagnosis and who received an ALS diagnosis during the 2007-2014 period were considered. The residence address was used to geolocalize each patient. A cluster analysis was performed using the Kulldorff statistics [3] and considering the position of patients at the time of onset and at 1-year intervals until 50 years before the onset. All analyses using the population from 2014 to 1982 were sex- and age-adjusted; the remaining analyses were not adjusted based on the data unavailability.

Results: A total of 995 patients were included. The analysis revealed a higher-incidence cluster in the Western area of Piemonte, 3 to 6 years before the disease onset interval. Four years before the onset, in an area including 67 communalities, 94 ALS cases were expected while 138 were

observed (Relative Risk = 1.54, p = 0.04). No low-incidence clusters were revealed.

Discussion: We could not find a univocal factor able to justify our results. Multiple hypotheses (industrialization, soil components) will be explored with ad hoc studies. More importantly, we showed that analyses focused on the time of diagnosis could miss previous geographical clusters of patients.

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RELATIONSHIP BETWEEN CEREBROSPINAL FLUID/SERUM ALBUMIN QUOTIENT AND PHENOTYPE IN AMYOTROPHIC LATERAL SCLEROSIS

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Objectives: To analyze the relationships between CSF/serum albumin quotient (Q-Alb) and phenotype in a large ALS cohort.

Materials: 328 consecutive patients who were diagnosed with ALS in our Department between 2002 and 2022 and underwent CSF analysis.

Methods: Q-Alb was calculated as follows: CSF albumin concentration/serum albumin concentration*10^3. The following features were considered: 1) sex; 2) age at onset; 3) site of onset; 4) ALS family history; 5) age at lumbar puncture (LP); 6) disease duration at LP; 7) motor phenotype (classic, bulbar, flail arm, flail leg, UMN-predominant, respiratory, pure LMN, pure UMN); 8) Cognitive and Behavioural ALS Screen (ECAS); 9) ALSFRS-R; 10) disease progression rate (DPR); 11) clinical staging (King's College and Milano-Torino staging (MiToS) systems); 12) Penn Upper Motor Neuron Score (PUMNS); 13) Lower Motor Neuron Score (LMNS); 14) composite MRC strength score; 15) index of active denervation on EMG; 16) transcranial magnetic stimulation (TMS) measures; 17) presence of a pathogenic gene mutation; 18) total disease duration.

Results: Q-Alb did not correlate with age at LP but was independently associated with sex, with male patients displaying higher levels than female ones. Although spinal-onset patients had a higher median Q-Alb compared to bulbar-onset ones, site of onset was not independently associated with Q-Alb. Q-Alb did not differ between ALS motor phenotypes or between purely motor ALS and ALS with cognitive and/or behavioural impairment. Q-Alb was not associated with disease stage and did not correlate with disease duration at LP, ALSFRS-R, DPR, PUMNS, LMNS, composite MRC score, or TMS measures. However, Q-Alb had a weak positive correlation with active denervation score (rS = 0.179, p = 0.004). Q-Alb was not associated with specific genetic forms of ALS. Finally, Q-Alb was not associated with survival.

Discussion: Q-Alb reflects the function of the blood-CSF barrier (BCSFB) or of the blood-brain and blood-spinal cord barriers (BBB and BSCB, respectively). Previous work has documented increased Q-Alb in ALS compared to unaffected individuals. This, together with the absence of associations with nearly all ALS phenotypic features in our cohort, suggests dysfunction of the CNS barriers as a shared, phenotype-independent, element in ALS pathophysiology. However, the correlation with active denervation index could point to barrier dysfunction as local driver of LMN degeneration.

Conclusions: Dysfunction of CNS barriers could play a role in ALS pathophysiology. Future multimodal and longitudinal investigations could contribute to elucidate the mechanistic role of this dysfunction in ALS pathogenesis, anatomical spreading and progression.

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SERUM LEVELS OF NEUROFILAMENT LIGHT CHAIN (NFL) IN A LARGE COHORT OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

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Objectives: To compare serum NFL (sNFL) levels in ALS patients and controls and to investigate associations of sNFL with ALS phenotype.

Materials: 209 ALS patients from our Department (2015-2022); 46 neurologically healthy controls (2020-2021).

Methods: sNFL was measured by Simoa on the Quanterix SR-X instrument.

Results: sNFL was higher in ALS patients compared to controls ($p < 0.0001$). Among ALS patients, sNFL negatively correlated with estimated glomerular filtration rate (eGFR; r = -0.163, p = 0.018). Even after correcting for eGFR, sNFL positively correlated with age at onset (r = 0.170, p = 0.014) and age at sampling (r = 0.135, p = 0.0496), while it did not differ between male (n = 123) and female patients (n = 86) and was not associated with site of onset (bulbar, n = 50; spinal, n = 159) or ALS gene mutations. sNFL was associated with motor phenotype, with disease subclasses characterized by prominent UMN impairment, either predominant or associated with significant LMN dysfunction, showing higher levels compared to LMN subclasses (p = 0.051 and p = 0.005, respectively). sNFL correlated with Penn UMN Score (r = 0.259, $p < 0.001$), MRC muscle strength score (r = -0.332, $p < 0.001$) and an EMG score of active denervation (p = 0.232, p = 0.013). sNFL was not associated with Strong categories of cognitive/behavioural phenotype and did not correlate with cognitive scores on ECAS. Likewise, it was not associated with

oculomotor abnormalities after correction for eGFR. On the contrary, sNFL correlated positively with disease progression rate ($r = 0.468$, $p < 0.001$) and negatively with time from symptom onset to sampling ($r = -0.201$, $p = 0.004$) and ALSFRS-R score ($r = -0.398$, $p < 0.001$). Accordingly, sNFL was also associated with MiToS ($p < 0.0001$) and King's staging ($p = 0.01$), as well as with survival (HR = 4.033 for patients with levels above vs below the median, $p = 0.0002$).

Discussion: Our results confirm the main findings of previous studies in a large cohort. sNFL seems to be a maker of both UMN and LMN impairment and is associated with disease progression rate and survival. On the contrary, sNFL is not associated with extra-motor, namely cognitive, features.

Conclusions: Our study supports the validity of sNFL as ALS biomarker; at the same time, the negative correlation with renal function, albeit weak, should be taken into account in the future.

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SERUM LEVELS OF GLIAL FIBRILLARY ACIDIC PROTEIN (GFAP) IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

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Objectives: To compare serum levels of GFAP (sGFAP) in ALS patients and controls and to investigate associations of sGFAP with ALS phenotype.

Materials: 114 ALS patients from our department (2015-2022); 38 neurologically healthy controls (2020-2021).

Methods: sGFAP was measured by Simoa on the Quanterix SR-X instrument.

Results: sGFAP was higher in ALS patients compared to controls ($p = 0.0269$). Among ALS patients, sGFAP negatively correlated with estimated glomerular filtration rate (eGFR; $r = -0.350$, $p = 0.0001$). Even after correcting for eGFR, sGFAP positively correlated with age at onset/sampling ($r = 0.410$, $p = 0.00001$), while it did not differ between male ($n = 71$) and female patients ($n = 43$) and was not associated with site of onset (bulbar, $n = 27$; spinal, $n = 87$), motor phenotype, survival, or ALS gene mutations. While sGFAP did not correlate with Penn UMN Score, after correction for eGFR it negatively correlated with MRC muscle strength score ($r = -0.228$, $p = 0.031$). Remarkably, patients with oculomotor abnormalities had higher sGFAP levels compared to those with normal ocular movements ($p = 0.019$), and, although sGFAP was not associated with Strong classification of cognitive/behavioural phenotype, it negatively correlated with performance in memory ($r = -0.194$, $p = 0.038$) and in non-ALS-specific domains ($r = -0.192$, $p = 0.041$) on the ECAS, as well as with MoCA score ($r = -0.309$, $p = 0.003$). After correction for eGFR, sGFAP negatively correlated with ALSFRS-R score ($r = -0.295$, $p = 0.003$), whereas it did not correlate with disease progression rate or MiToS or King's stages. There were no significant correlations with neurophysiological UMN or LMN indices. After correction for eGFR, sGFAP negatively correlated with pulmonary forced vital capacity (FVC) ($r = -0.415$, $p = 0.013$), as well as with serum protein ($r = -0.284$, $p = 0.010$) and albumin levels ($r = -0.437$, $p < 0.001$).

Discussion: Increased levels of sGFAP in ALS patients are in agreement with a role of astrocytes in ALS. Our analyses suggest that astroglial pathology could modulate ALS phenotype, especially non-motor/non-typical aspects (cognition, and particularly memory, and ocular movements). Negative correlations with FVC and serum protein/albumin suggest an association of astrogliosis with impairment of ventilation and nutrition, whose directionality deserves investigation.

Conclusions: sGFAP might serve as peripheral biomarker of astroglial pathology in ALS. Additional studies are warranted; at the same time, the negative correlation with renal function cannot be disregarded.

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NEUROMUSCULAR DISEASES

ATYPICAL PRESENTATION OF COQ4-RELATED MITOCHONDRIAL DISEASE WITH STROKE-LIKE EPISODES AND ANTI-PHOSPHOLIPID ANTIBODIES: AN OVERLAP SYNDROME?

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Objectives: Coenzyme Q10 (CoQ10), also known as ubiquinone, is a lipophilic component of all cellular membranes and has multiple metabolic functions. It has central role in the mitochondrial respiratory chain (OXPHOS) as an electron carrier, but also plays a role as an antioxidant in the cell membrane and may modulate apoptosis. Diseases associated with CoQ10 deficiency are phenotypically heterogeneous. Five major clinical phenotypes have been described [1], none of them have been associated whit stroke-like episodes. Here we report the case of a baby with early onset of stroke affected by CoQ10 deficiency and antiphospholipid syndrome (APS).

Materials: A 2-month-old baby female went to Emergency Department for onset of fever and seizures. She was born in term, from

non-consanguineous parents. Familial history was negative for neurological diseases.

Methods: She underwent to a clinical, biochemical, and instrumental protocol for neuromuscular disorders including muscle biopsy.
Results: Blood test revealed hyperCKemia and the presence of IgM and IgG antibodies anti-Cardiolipin, also detected in her mother blood. Cardiac assessment was normal. Chet-Xray showed interstitial pneumonia. Brain MRI revealed two ischemic areas in both occipital lobes with peak of lactate at spectroscopy. Electroencephalogram confirmed focal epileptic anomalies. Due to finding of IgM anti-Cardiolipin antibodies and the stroke event anticoagulant therapy was started. Needle myography and muscle biopsy revealed a myopathic pattern with global reduction of oxidative enzymes and thrombosis of the muscle arteriole. Genetic test revealed two novel compound heterozygous variants in COQ4 gene, mtDNA was negative.

Discussion: Neonatal APS is a rare condition, which may depend on the passage of antibodies through the placenta or by the production of de novo antibodies by the fetus. Laboratory findings includes high titers of IgM anticardiolipin antibodies and moderate titers of IgG isotype and negative antinuclear antibody associated with thrombotic events [2]. In our case, at first assessment, laboratory tests and symptoms could be ascribed to APS. In addition, in APS was reported a secondary mitochondrial disfunction, involving CoQ10 [3]. However, in our patient neuroimaging and muscle biopsy suggested a primary mitochondrial disfunction. After two years the baby developed a severe epileptic encephalopathy, two novel stroke-like episodes occurred involving basal ganglia and diencephalic structures. IgG anti-Cardiolipin antibodies were normalized, no thrombotic events were registered therefore anticoagulant therapy was discontinued.

Conclusions: This case illustrates how diagnosing mitochondrial diseases represent a challenge in emergency setting. It also represents the first report of COQ4-related disorder with clinical manifestations like MELAS syndrome.
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PREVALENCE AND CHARACTERISTICS OF PERIPHERAL NEUROPATHY IN PATIENTS WITH PSORIASIS AND PSORIATIC ARTHRITIS

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Introduction: Different laboratory and clinical data suggest a link between neurogenic inflammation and pathogenesis of psoriasis. [1,2]. There is also evidence of an abnormal function of small cutaneous nerve fibres and a few reports of peripheral neuropathy in patients with psoriasis [3].
Objective: To assess the prevalence and clinical features of peripheral neuropathy in patients with psoriasis and psoriatic arthritis with and without treatment with TNF-alpha inhibitors (drugs that are known to increase the risk of neuropathy).

Methods: One hundred patients with psoriasis or psoriatic arthritis and 100 controls (partners of the patients) were consecutively enrolled. Eligible patients were evaluated by an expert neurologist and underwent a detailed medical history and neurological visit. Patients with a clinical suspicious of neuropathy underwent laboratory, electrophysiological and ultrasound investigations.

Results: Forty control subjects were enrolled so far. Mean age at study inclusion was 57 years (24-79), 50% were male. None of the control subjects had polyneuropathy, while 4 patients had carpal tunnel syndrome. Out of a total of 100 patients, 33 (33%) had psoriasis, 13 (13%) psoriatic arthritis and 54 (54%) patients had both. Mean age at study inclusion was 56 years (range 24-85), 56% of patients were male. Twenty-eight (28%) patients had a history of therapy or were in maintenance treatment with TNF-α inhibitors, 31 (31%) with other biologics (brodalumab, ustekinumab, ixekizumab, tildrakizumab, guselkumab, secukinumab) and the rest of the patients (41%) with conventional therapy (i.e. corticosteroids, methotrexate). Nine patients (4 with psoriasis, 2 with psoriatic arthritis and 3 with both) were found to have polyneuropathy (p= 0.0599, versus controls), which in all was axonal, length-dependent, symmetric, purely or predominantly sensory. Symptoms included distal lower limbs paraesthesia, impairment of vibration, joint position, touch and pressure sensations and absent or diminished deep tendon reflexes mainly in the lower limbs. None of the patients had walking impairment. All these patients were found to have an alternative cause for the polyneuropathy, including type 2 diabetes mellitus (6 patients), MGUS (2 patients), HCV or HBV chronic infection (3 patients), and an exposure to chemotherapy (3 patients). Four patients were diagnosed with carpal tunnel syndrome (p= 0.2749, versus controls).

Discussion and Conclusion: Preliminary results of our study suggest that psoriasis and psoriatic arthritis are associated with a small increased risk of polyneuropathy. This risk seems to be secondary to the comorbidities that are frequently present in patients with psoriasis and psoriatic arthritis, particularly diabetes.
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TREATMENT OF REFRACTORY GMG PATIENTS WITH ECULIZUMAB AND EFGARTIGIMOD: A CASE SERIES

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Objectives: Myasthenia Gravis (MG) is an autoimmune disease affecting the neuromuscular junction and causing disability. Apart from symptomatic use of cholinesterase inhibitors (pyridostigmine), treatment includes corticosteroids and/or nonsteroidal immunosuppressants, pulsed immunosuppressive therapy (i.e. intravenous immunoglobulins, plasmapheresis). 10-35% of MG patients are thought to be refractory, and frequently disease control comes at a high price of adverse events and comorbidities.

Two novel FDA and EMA approved agents are available in Italy for compassionate use: Eculizumab, an anti-C5 monoclonal antibody, and Efgartigimod, an antibody fragment targeting the FcRn. Here we discuss our clinical experience in a small series of refractory gMG patients.

Materials and methods: We treated 6 refractory gMG patients (2 males, 4 females, age 44 – 79). They were previously treated, or had contraindications to, prednisone, azathioprine, mycophenolate mofetil, rituximab, plasmapheresis and IVIg, in variable combination or order, with either a poor response and/or intolerable side effects. Three patients were treated with Efgartigimod, two were anti-AChR positive, one was anti-Musk positive. Three patients were treated with Eculizumab, all anti-AChR positive. We measured gMG impact at baseline and after treatment with the MG Activities of Daily Living (MG-ADL).

Results and discussion: At baseline, Eculizumab treated patients were all on treatment with pyridostigmine (mean dose 340mg), two with prednisone (mean dose 13.75mg), and two with azathioprine (mean dose 75mg). All had previous failures to IVIg, one had previous history of plasmapheresis. Baseline mean MG-ADL was 11 and decreased to 4 (mean scale reduction 6). One patient was able to interrupt treatment with pyridostigmine, prednisone and azathioprine while on Eculizumab. At baseline, Efgartigimod treated patients were all treated with pyridostigmine (average dose 250mg), two with prednisone (average dose 15mg). Baseline mean MG-ADL was 13 and decreased to 2 at the end of the first cycle (four weekly infusions), we observed a marked improvement with an average reduction of 11 points at the MG-ADL score. The benefit was clear after the first week of treatment and was stable during the first period after the end of the cycle. For all time to re-treatment was 4 weeks after the last infusion. No adverse events were reported with both treatments.

Conclusions: Eculizumab and Efgartigimod treatment rapidly improved measures of disability in our case series. Considering the excellent tolerability, we consider them a great therapeutic opportunity for patients experiencing disability despite treatment.

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ATYPICAL CLINICAL AND NEUROPSYCOLOGICAL FINDINGS IN CONGENITAL MYASTHENIC SYNDROME DUE TO RAPSN MUTATION

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Objectives: Congenital myasthenic syndromes (CMSs) are a genotypically and phenotypically heterogeneous group of neuromuscular disorders, which have in common an impaired neuromuscular transmission. Rapsyn (RAPSN) mutations are a common cause of postsynaptic congenital myasthenic syndromes. We here report clinical and neuropsychological findings of a patient affected with an atypical presentation of RAPSN-related CMS.

Patient and Methods: A 5-years-old girl presented with speech and behavioral disorders since infancy. No respiratory failure was reported. Since the age of 4 she presents eyelid ptosis and easy fatigue appearing the afternoon and worsen during the day. Clinically she has mild hypotonia, facial weakness with open mouth and bilateral eyelid ptosis. Neuropsychological tests, array-CGH, Magnetic Resonance Imaging (MRI), karyotype, neurophysiological examination and clinical exome analysis were conducted in order to achieve a diagnosis.

Results: Array-CGH, MRI and karyotype yielded normal findings; neuropsychological tests showed intellectual disability (ID) while neurophysiological examination including repetitive stimulation was normal. Clinical exome showed the presence of the c.264C>A homozygte variant in the RAPSN gene which causes the p.N88K amino acid change in the protein. Treatment with cholinesterase inhibitors results in significant clinical benefit on myastenic symptoms.

Discussion: Rapsyn p.N88K mutation is known to cause congenital myasthenic syndromes 11 (CSM11) which is usually characterized by a relatively homogeneous early onset phenotype with fluctuating eyelid ptosis, occasional bulbar symptoms, mild proximal muscle weakness and exacerbations precipitated by minor infections. To date, about 60 cases were reported all over the world and cognitive involvement has not been described so far. Our patient presented with early onset global psychomotor retardation, speech and behavioral disturbance for which no other specific causes were found by extensive genetic analysis.

Conclusion: Considering the rarity of CMS11, the paucity of cases in the literature, the absence of other genetic abnormalities potentially related to intellective disability, our study suggests that psychomotor abnormalities may be an early atypical presentation of CMS11, thus possibly expanding the phenotype of RAPSN-related disease. Our study warns physicians to be wary of this diagnostic possibility in their clinical practice.

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EXTENSIVE CLINICAL AND NEUROPHISIOLOGICAL ASSESSMENTS OF A CMT2 FAMILY WITH A NOVEL KIF5A VARIANT

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Charcot–Marie–Tooth disease (CMT) is the most frequent form of inherited chronic motor and sensory polyneuropathies and one of the most frequent genetic neuromuscular disorders, with a prevalence of 1:2500. Over 100 CMT causative genes have been identified. Almost 90% of CMT patients harbor a mutation in PMP22, GJB1, MPZ, MFN2 or, in the Mediterranean area, GDAP1 and HSPB1 genes. Other genes, especially that related with CMT2 phenotype, are less frequently

found. Among these, KIF5A encodes the heavy chain of Kinesin I, a heterotetrameric complex consisting of two light chains and two heavy chains. Kinesin I, located in central and peripheral nervous system, is involved in the anterograde transport of various cargoes (RNA, mitochondria, neurofilaments) along microtubules in neurons. KIF5A variants were described as causing rare form of Hereditary-Spastic-Paraplegia type, Charcot-Marie-Tooth type 2 disease (CMT2), a severe neonatal neurological syndrome called NEIMY (Neonatal-Intractable-MYoclonus), Amyotrophic-Lateral-Sclerosis, and recently, in Distal Spinal Muscular Atrophy. We present here three siblings (2 males and 1 female) harboring a c.587 C>A p.Thr196Asn KIF5A variant, that has never been described before. They present with a prevalent sensory polineuropathy, more severe at lower limbs, associated with pyramidal signs. They all underwent screening laboratory exams, brain MRI, cardiological evaluation and neurophysiological tests (nerve conduction studies, motor evoked potential, nerve ultrasound) that showed an increase of central motor way conduction time, an axonal sensori-motor neuropathy, and an increase in nerve size at brachial plexus and at lower limbs proximal sites.

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MUSCLE MANIFESTATIONS AND CK LEVELS IN COVID INFECTION: RESULTS OF A LARGE COHORT OF PATIENTS INSIDE A PANDEMIC COVID-19 AREA

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Objective: To investigate both muscular manifestations and CK levels in a large cohort of patients with COVID-19 infection and to determine whether hyperckemia is associated with morbidity and mortality.

Materials and methods: Data of 615 patients discharged from ASST Ovest Milanese (Milan, Lombardy, Italy) with final diagnosis of COVID-19 infection were retrospectively extracted from electronical medical records from 21 February to 1 May 2020. Patients were descriptively analyzed with respect to the following variables: sex, age, muscular manifestations (myalgia and/or arthralgia), fatigue, respiratory involvement (SARS pneumonia or respiratory failure) and history of falls. Association between patients' characteristics and CK levels was investigated. In addition, the proportion of patients who died following access to the ER was calculated. Finally, the effect of CK levels and other patients' features on mortality was estimated using a logistic regression model.

Results: 176 (28.6%) patients had raised serum CK levels. CK levels were significantly associated with history of falls, male gender, SARS pneumonia, respiratory failure and in-hospital death. No correlation was found between hyperckemia and muscular manifestations.

Discussion and conclusions: Our study provides preliminary evidence that hyperckemia is associated with respiratory failure and fatal outcome in patients with COVID-19 infection.

In these patients, among other testing, CK dosage is recommended.

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ANTI-HMGCR MYOPATHY WITH CHRONIC EVOLUTION: A DIAGNOSIS AT RISK TO BE MISSED

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A new subgroup of immune-mediated necrotizing myopathy associated with anti-3-hydroxy-3-methylglutarylcoenzyme A reductase (HMGCR) antibodies has been recently described as charac-terized by statin exposure, a subacute progressive proximal muscle weakness and highly elevated CK levels. Subsequently, the spectrum of the disease has been broadened to a minority of younger patients without statin exposure and to a chronic form with asymptomatic CK elevation even several years before developing muscle weakness. Herein, we describe three cases of anti-HMGCR myopa-thies who were admitted in Neurological Department of Imperia Hospital in the last year. The first one, female 71y, had a previous long history of statins-exposure (atorvastatin) without symptoms of intolerance. Over few months she developed progressive inability in climbing stairs with an asymmetric muscles weakness distribution. At hospital admission, seven months later, clinical picture had evolved into a severe symmetrical tetraparesis, forcing her to wheelchair. Elevated CK levels (2707 I.U./l) and positive anti-HMGCR antibodies (74.5 CU/mL, n.v. <20) were detected. IVIG (2g/kg) were discontinued for an infusion reaction; steroids were not tolerated for hyperglycaemia. The patient underwent five plasma-exchange sessions, then Methotrexate (7.5 mg/week) was added to treatment. At one year follow-up a complete remission was achieved. The second one, female 72y, was treated with statins (atorvastatin) for five years until 2021 when asymptomatic CK elevation was detected (2902 U/L). Two months later she developed proximal muscle weakness with positive Gowers sign and mild dysphagia. Anti-HMGCR tested positive (91.3 CU/mL). She was treated with prednisone (slowly tapered) and monthly IVIG; Azathioprine trial failed due to gGT elevation (995 U/L). Laboratory and clinical examination normalized respective-ly in three and five months. The third, female 57y with Parkinson disease (PD), suspended statin therapy (simvastatin) for cuta-neous manifestations. In the same period transaminases elevation was detected but CK was not test-ed. During the subsequent year and half, despite PD treatment implementation, neurological disabil-ity worsened. When she arrived to our observation she was wheelchair bound due to a mainly prox-imal asymmetrical muscular deficit; CK resulted 2741 U/L

and anti-HMGCR tested 489.4 CU/mL. She was treated with IV methylprednisolone (500 mg for 5 days) and subsequent IVIG cycles, re-gaining the ability of maintain upright position. Our cases represent a subgroup of anti-HMGCR myopathies with a long history of statin-exposure and a chronic weakness evolution, which could become evident even after statin discontinuation. The alert should be related to the clinical picture, even in the absence of clear temporal relationship.

HEREDITARY TRANSTHYRETIN AMYLOIDOSIS IN THE NEUROLOGIC CLINIC: WHEN SHOULD WE THINK ABOUT IT? THE RESULTS FROM 24 MONTHS OF SYSTEMATIC SCREENING

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Background and aims: Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv) is caused by mutations in the TTR gene, leading to misfolded monomers which aggregate generating amyloid fibrils [1]. The clinical phenotype in non-endemic areas is characterized by a late onset with a multisystemic disease affecting the sensorimotor, autonomic functions along with other organs [2]. Hence, the diagnosis may be quite difficult with a relevant misdiagnosis and high costs for the community [3]. We conducted a systematic screening in patients presenting with polyneuropathy in our Centre for Neuromuscular disease to improve recognition and early diagnosis.

Methods: A genetic screening for ATTRv was proposed in patients presenting with a sensory-motor idiopathic polyneuropathy and almost two or more "red flags" among the following: family history of polyneuropathy or cardiopathy; bilateral carpal tunnel syndrome, cardiac insufficiency, renal amyloidosis, lumbar tract stenosis, autonomic dysfunction, gastrointestinal idiopathic disease, amyloid deposits on biopsy, vitreous opacities, diagnosis of CIDP not-responsive to standard treatments. Non-parametric analysis has been carried out to underline differences among screened-positive versus negative patients.

Results: 235 patients underwent genetic testing for suspected for ATTRv and 39 patients resulted positive (17%). Not significant differences appeared between patients screening positive versus negative depending on age and gender. Patients with a positive genetic test presented a higher frequency of family history of polyneuropathy and ATTR ($p<0.0001$ for both) or family history of cardiopathy ($p<0.015$), but a reduced frequency of autoimmunity ($p=0.007$) and CIDP ($p=0.004$). Of interest, a previous diagnosis of motor neuron disorder was more frequent in ATTRv positive patients ($p=0.008$).

Conclusions: A systematic screening for ATTR-PN yielded an increased recognition of the disease in our neurological clinic. A positive family history has the higher predictive value in the guidance of the clinical suspicion, but some specific misdiagnoses have to be considered. A focused approach for the screening of ATTRv could lead to an earlier diagnosis and identification of asymptomatic carriers, who will be promptly treated after a strict follow-up at the clinical onset.

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COMPARISON OF THE DIAGNOSTIC ACCURACY OF THE EAN/PNS AND EFNS/PNS DIAGNOSTIC CRITERIA FOR CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

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Objectives: To compare the sensitivity and specificity of the newly published EAN/PNS criteria for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with those of the EFNS/PNS.

Materials: Patients with CIDP were included from the Italian CIDP database. Control patients suffering from sensory or sensorimotor or motor axonal peripheral neuropathy (diabetic peripheral neuropathy [n= 72], chemotherapy-induced neuropathy [n= 41], idiopathic neuropathy [n= 30], vasculitic neuropathy [n= 13], non-anti-MAG paraproteinemic neuropathy [n= 5], vitamin B12 deficiency neuropathy [n= 5]), regularly followed at our outpatient peripheral neuropathy clinic, were included.
Methods: Sensitivity and specificity of the two above-mentioned criteria were evaluated in 330 patients with CIDP and 166 controls. Comparison of the utility of nerve conduction studies of different extensiveness and of the sensitivity of the two sets of criteria in typical CIDP and its variants were also assessed.

Results: EFNS/PNS criteria had a sensitivity of 92% for possible CIDP and 85% for probable/definite CIDP, while the EAN/PNS criteria had a sensitivity of 83% for possible CIDP and 74% for CIDP. Using supportive criteria, the sensitivity of the EAN/PNS criteria for possible CIDP increased to 85% and that of CIDP to 77%, remaining lower than that of the EFNS/PNS criteria. Both sets of criteria did not show significant differences in sensitivity values among the different clinical CIDP

forms. Specificity of the EFNS/PNS criteria was 68% for possible CIDP and 84% for probable/definite CIDP, while the EAN/PNS criteria had a specificity of 88% for possible CIDP and 98% for CIDP. More extensive study increased the diagnostic sensitivity of both sets of criteria but reduced the specificity.

Discussion: The diagnostic accuracy of the EFNS/PNS criteria is similar to that of the EAN/PNS, with the EAN/PNS criteria showing an improvement in specificity with a reduction in sensitivity compared to the EFNS/PNS criteria. Using the EAN/PNS criteria, more extensive study offered the best balance between sensitivity and specificity and it is therefore recommendable. When we looked at the effect, in terms of diagnostic gain, of the individual changes that have been made in the EAN/PNS criteria from the EFNS/PNS criteria, some have proved to be disadvantageous while others to be effective.

Conclusions: In our patient populations, the EAN/PNS criteria were more specific but less sensitive than the EFNS/PNS criteria. With the EAN/PNS criteria, more extensive nerve conduction studies are recommended to obtain an acceptable sensitivity while maintaining a very high specificity.

RISK OF RELAPSE AFTER COVID-19 VACCINATION IN PATIENTS WITH CHRONIC INFLAMMATORY NEUROPATHIES AND SAFETY AND TOLERABILITY OF THE COVID-19 VACCINES

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Objectives: We performed a multicenter, prospective and retrospective, observational study, to evaluate the risk of disease relapse after COVID-19 vaccination in patients with chronic inflammatory neuropathies and the safety and tolerability of COVID-19 vaccines in these patients.

Materials: Study subjects were chosen from among patients with CIDP or MMN included in the Italian CIDP and MMN databases.

Methods: We invited to participate CIDP and MMN patients fulfilling the EFNS/PNS criteria for probable/definite diagnosis who had been in a stable maintenance treatment or in remission without ongoing active treatment in the three months prior to the commencement of the study. We assessed the relative risk (RR) of relapse associated with COVID-19 vaccination by comparing patients who underwent or did not undergo vaccination. We also compared the frequency of relapse in CIDP and MMN patients undergoing vaccination for COVID-19 in the three months prior and after vaccination and evaluated safety and tolerability of the COVID-19 vaccines. Subjects were evaluated using objective outcome measures and a specific questionnaire.

Results: A total of 336 patients were included (278 CIDP; 58 MMN). 307 (91%) patients underwent COVID-19 vaccination, including 269 (88%) with Pfizer/BioNTech, 28 (9%) with Moderna, and 10 (3%) with AstraZeneca. Twenty-nine patients (9%) did not undergo vaccination. Clinical relapse was observed in 16 (5.2%) patients (13 CIDP; 3 MMN) who underwent COVID-19 vaccination and in none of the patients who did not undergo vaccination (RR= 3.21, 95% confidence interval [CI] 0.19–52.25). Compared to the 3-month control period preceding baseline, during which 4 (1.3%) of the 307 vaccinated patients had a disease relapse, the relative risk of relapse was increased. (RR: 4.00; 95% CI, 1.35 to 11.82). The specific RR for Pfizer/BioNTech was 2.77 (95% CI, 0.16 - 45.74), and for Moderna was 9.31 (95% CI, 0.52 -165.33). None of the 10 patients who received the Astrazeneca vaccine had a relapse. The specific RR of relapse associated with COVID-19 vaccination in CIDP patients was 1.96 (95% CI, 0.12 to 31.81), while in MMN patients was 1.75 (95% CI, 0.09 - 31.64). The safety profile of the COVID-19 vaccines was similar to that observed in the general population. There were no serious adverse events.

Discussion: Vaccination for COVID-19 in patients with CIDP and MMN seems to be associated with a small increased risk of disease relapse, and with an acceptable short-term safety profile.

Conclusion: The benefits of COVID-19 vaccination in CIDP and MMN patients outweigh the risk of disease relapse.

X-LINKED EMERY-DREIFUSS MUSCOLAR DYSTROPHY: A MULTICENTER ITALIAN COHORT STUDY

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Background: X-linked Emery Dreifuss muscolar dystrophy (EDMD1) is a rare early-onset myopathy characterized by scapulohumeral weakness, contractures and cardiac involvement. EDMD1 natural history has been poorly investigated with most of the studies including only few patients. Aim of the study is to investigate the clinical and molecular features in a large cohort of EDMD1.

Methods: We retrospectively collected data of 34 affected and genetically defined males (15 members of 5 families, and 19 sporadic cases) from 11 referral neuromuscular centers in Italy. Male patients were included only if showing detectable muscle weakness or contractures at the neurological examination.

Results: The mean age of onset was 17.8 ± 6.3 years (range 2.5-63), among which 24 (70.6%) presenting with muscle weakness or contractures and 7 (29.4%) with cardiac onset. The mean follow-up period was 18.4 ± 13.06 years (range 1-59 years). Loss of walking ability was observed in 2/34 (5.9%) patients, after a disease duration of 49 and 35 years, respectively. At the last visit 27 (79.4%) out of 32 remaining patients showed a mild disease severity with Gardner-Medwin-Walton scale (GMWS) scoring 1-3, while 5 (14.7%) patients had normal motor performance (GMWS=0). Contractures were detected in 29 (85%) patients, mostly at the elbow (n=27) and ankle (n=26) sites. Heart involvement was found in 24 (72%) patients, with a mean age at onset of 29.9 years ± 18.6 (SD). The most common arrhythmias were heart block, atrial fibrillation and flutter. Eighteen out of 34 (53%) required pacemaker or implantable cardioverter defibrillator at a mean age of 30.11 years ± 15 (SD). Eight mutations resulted unreported in literature.

Conclusions: Our data provide a further insight in the field of EDMD1 and suggested that the disease natural history is dominated by the heart involvement, while the skeletal muscle weakness progressed slowly over the years.

AN ATYPICAL CASE OF ANTI JO-1 ANTISYNTHETASE SYNDROME

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Antisynthetase syndrome is an autoimmune disease characterized by the presence of antibodies against various aminoacyl transfer RNA synthetases. Most frequent clinical features are interstitial lung disease, myositis and arthritis. Other common manifestations include fever, rashes, Raynaud's syndrome and mechanic's hands. Renal involvement can be present and is myoglobin-induced or immune-mediated. A 19-year-old boy presented to our Emergency Department with fever and diarrhea. Two weeks before he had an episode of dark urine. He also reported one month of gradually progressive exercise intolerance, muscle and joint pain mainly affecting wrists and ankles and a vanishing skin rash on the face and arms. The patient had diabetes mellitus type I since age 14. Family history was positive for autoimmune diseases. On examination he presented peripheral edema and a mild waddling gait with proximal and axial weakness. Laboratory investigations revealed raised CK levels (31455 U/L) and hypoalbuminemia and urine analysis revealed proteinuria (>30 mg/dL) and myoglobinuria (9079 ng/mL). EMG was myopathic with spontaneous activity. Muscle MRI was suggestive of myositis with symmetrical bilateral involvement. He was tested with a myositis-specific antibody panel and results were positive for anti Jo-1, with a high title. He underwent HRCT to screen for interstitial lung disease but findings were non specific. Nailfold capillaroscopy showed few tortuosities, dysmorphic capillaries and microhemorrhages. A renal biopsy was performed to investigate the cause of the nephrosic syndrome. C3 deposits were found within the glomerular basement membrane, tubular basement membranes and in Bowman's capsule. These findings were consistent with the diagnosis of C3 glomerulopathy. These investigations, coupled with the clinical features, led to the final diagnosis of anti Jo-1 antisynthetase syndrome associated with C3 glomerulopathy started as rhabdomyolysis. He was given oral methylprednisolone 100 mg/day and received two doses of Rituximab 1 g/2 weeks. At 3-month follow-up the patient had an improvement of his symptoms with no weakness and pain. CK levels were 550 U/L. The present case illustrates the importance to suspect an inflammatory myopathy and to screen for highly specific autoantibodies in patients with rhabdomyolysis, especially if they are young and have other autoimmune diseases. Immune mediated renal damage in antisynthetase syndrome is rarely reported. To our best knowledge this is the first case describing a patient with anti Jo-1 antisynthetase syndrome who developed C3 glomerulopathy. The case confirms the efficacy of Rituximab in these forms.

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IMPLEMENTING SMALL FIBRE NEUROPATHY SCREENING IN CLINICAL PRACTICE. THE DIAGNOSTIC ACCURACY OF SMALL FIBRE NEUROPATHY SYMPTOMS INVENTORY QUESTIONNAIRE (SFN-SIQ) IN PURE SMALL FIBRE NEUROPATHY

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A definite diagnosis of pure small fibre neuropathy (SFN) relies on objective diagnostic testing, such as skin biopsy, quantitative sensory testing (QST), and nociceptive evoked potentials, which require high resources and have a limited availability. Accordingly, diagnostic tools with easy implementation in non-specialist centers are warranted to select patients needing second level diagnostic tests. In this study we aimed to test the accuracy of the Small Fibre Neuropathy Symptoms Inventory Questionnaire (SFN-SIQ) for diagnosing pure SFN. We enrolled 86 patients with suspected pure SFN. In these patients we calculated the SFN-SIQ diagnostic accuracy, using a combination of clinical examination, quantitative sensory testing, and skin biopsy as a reference standard. We found that SFN-SIQ showed an excellent discrimination ability between patients with and without pure SFN, with 81% sensitivity and 75% specificity in the diagnosis of pure SFN. Our study, providing the diagnostic yield of SFN-SIQ for pure SFN diagnosis, suggests that this questionnaire might be used to screen patients with suspected SFN and select those needing second level diagnostic tests such as QST, skin biopsy, or nociceptive evoked potentials.

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NEPHROPATHY IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY ASSOCIATED WITH NODAL AND PARANODAL ANTIBODIES: A SYSTEMATIC REVIEW OF THE LITERATURE

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Introduction: Antibodies against contactin-1 (CNTN-1) and neurofascin 140/186 (NF-140/186) proteins have been described in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), expanding the spectrum of Autoimmune Nodopathies [1]. In a small proportion of this patients, the presence of a concomitant nephropathy has been reported [2]. In the present study, we performed a systemic review of the literature on the concurrent presentation of CIDP and NS.
Methods: We searched Pubmed, Embase and Cochrane up to June 2022 and included all cases of CIDP and nephropathy. Data were extracted according to a predefined protocol and authors were contacted and asked to provide missing information. Included CIDP patients with nephropathy with and without antibodies against nodal-paranodal proteins were compared with 52 seronegative CIDP patients followed at our center.

Results: In literature, 70 patients with CIDP associated with nephropathy are described, of which 39 with antibodies against nodal-paranodal proteins (35 for CNTN-1, 2 for NF 140/186, 1 for NF 140 and NF 155, 1 for both CNTN-1 and NF-140, usually of IgG4 isotype). Kidney biopsy disclosed a membranous glomerulonephritis (MG) in all patients with anti-CNTN-1 antibodies and a focal segmental glomerulosclerosis (FSG) in anti-NF 140/186 positive patients. Compared to seronegative CIDP patients, those with an associated nephropathy and Ab against nodal-paranodal proteins were more frequently males, had an older age at onset, had higher CSF proteins level, more frequently reported ataxia and tremor, had a more severe disability measured with mRS at symptoms onset, showed a less frequent improvement of CIDP symptoms and signs after treatment, and more frequently required a second-line therapy. Strikingly, about 26% of those patients died during follow-up. CIDP-nephropathy patients without antibodies were similar to seropositive ones, probably because they are part of the same population but described before antibody testing was possible. Nephrotic syndrome was severe in both CIDP-nephropathy groups, with response to treatment being poor.

Conclusion: CIDP associated with nephropathy is rare. Concomitant nephropathy seems more frequent in patients with anti-CNTN-1 Ab than in those with anti NF-140/186 Ab. Histological pattern seems to correlate with the type of nodal/paranodal Ab, with anti-CNTN-1 Ab patients having a MG and those with anti NF-140/186 Ab a FSG. CIDP associated with nephropathy and nodal-paranodal Ab is a severe syndrome, with the neuropathy signs and symptoms often requiring second-line therapies and death occurring in 26% of cases.
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CHARCOT-MARIE-TOOTH DISEASE TYPE 2E PRESENTING AS SPASTIC PARAPLEGIA IN A FAMILY

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Aim: Charcot-Marie-Tooth disease (CMT) is a group of genetically and clinically heterogeneous disorders of the peripheral nervous system, with or without central nervous system involvement. The aim of this study is to describe the peculiar clinical presentation of an Italian family with a mutation in the NEFL gene (CMT2E).

Materials and Methods: Eight subjects over three generations (5 male; 3 female) have been serially evaluated beginning from the early 2000's. All subjects underwent periodic clinical examination, nerve conduction studies (NCS) and needle EMG, multimodal evoked potentials and molecular studies with NGS.

Results: The first clinical evaluation of the two probands (patients II-1 and II-2) showed a predominant involvement of the pyramidal system in the lower limbs with spastic gait, hyperexcitable deep tendon reflexes, ankle clonus, and Babinski sign. Their mother (patient I-1) reportedly suffered from similar disturbances. After several years, both sons of patient II-1 in their early 30's began to show a gait disorder. The neurological examination revealed distal muscle weakness and atrophy in upper and lower limbs, length-dependent sensory loss, pes cavus, hammertoes deformity, gait ataxia and mild pyramidal features. NCS disclosed an axonal sensorimotor polyneuropathy. Similar results were obtained in the probands at ten-year follow up. Three additional subjects were examined later, one of which also showed clinical features of peripheral sensorimotor neuropathy with pyramidal signs. Genetic testing with a NGS panel for spastic paraplegia (SPG) genes in the probands showed no abnormalities, however, a panel for hereditary neuropathies showed a heterozygous, pathogenic mutation (p.E397K) in the tail domain of the gene encoding the light chain neurofilament protein (NEFL) in all clinically affected patients but in none of the unaffected relatives.

Discussion and conclusions: Neuron-specific intermediate filaments are essential for the radial growth and maintenance of axons. NEFL mutations have been associated with different CMT phenotypes including axonal, demyelinating and intermediate CMT. Additional, pyramidal signs have been sporadically reported, but a spastic paraplegia phenotype has been described only recently, in a few patients carrying mutations in the head domain of the NEFL gene. The clinical heterogeneity within the present family indicates that NEFL integrity is essential for the maintenance of both peripheral and central axons, as described for the heavy chain neurofilament protein (NEFH) in which mutations can cause either ALS or CMT. Moreover, we show that mutations in the tail, as well as in the head, domain of NEFL can determine a SPG phenotype.
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PATISIRAN GLOBAL OPEN-LABEL EXTENSION STUDY AT 36 MONTHS: EFFECT OF LONG-TERM TREATMENT ON MORTALITY AND AMBULATORY FUNCTION IN PATIENTS WITH HATTR AMYLOIDOSIS WITH POLYNEUROPATHY

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Background & Objective: Hereditary transthyretin-mediated (hATTR) amyloidosis is a progressive and fatal disease. Without treatment, patients experience debilitating polyneuropathy with loss of ambulatory function and a median survival of 4.7 years from diagnosis. The effects of long-term treatment with patisiran, an RNAi therapeutic approved for the treatment of hATTR amyloidosis with polyneuropathy, are being assessed in the ongoing Global Open-Label Extension (OLE) study (NCT02510261).

Methods: Patients in the Global OLE study were analyzed in three groups based on enrollment in the parent studies: APOLLO-placebo, (n=49), APOLLO-patisiran, (n=137), and Phase 2 OLE patisiran (n=25). In the Global OLE, all patients received patisiran 0.3 mg/kg once every three weeks for up to 5 years. Mortality was analyzed from parent study enrollment in all patients who received ≥1 dose of patisiran in the Global OLE (n=224).

Results: At Global OLE baseline, the APOLLO-placebo group had more severe disease than the APOLLO-patisiran or Phase 2 OLE groups, reflecting disease progression while on placebo in the parent study. At data cut-off (Jan 27, 2021), the maximum duration of patisiran treatment varied by group (APOLLO-placebo, 36 months; APOLLO-patisiran, 54 months; Phase 2 OLE, 60 months), and median survival from start of parent study was not reached in any group by Month 36. Mortality was lower in patients who initiated treatment earlier in their disease course (APOLLO-patisiran, 13.5%; Phase 2 OLE, 11.1%) when compared with the APOLLO-placebo group (34.7%). In a multivariate analysis, NT–proBNP >3000 ng/L, NYHA Class >1, and placebo assignment in the parent study remained significant risk factors for mortality, whereas FAP Stage >2, non-V30M genotype, and mean left ventricular wall thickness ≥1.3 cm were not significant. At Month 36, most patients remained ambulatory (PND).

Conclusions: At Month 36 in the ongoing 5-year Global OLE, survival was greater in patients who received patisiran treatment earlier. The therapeutic benefit of patisiran on ambulatory function was sustained and was greatest in groups that initiated patisiran treatment earlier. These results highlight the substantial impact of earlier diagnosis and treatment in patients with hATTR amyloidosis with polyneuropathy.

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MYASTHENIA GRAVIS, COVID-19 AND VACCINES: EXPERIENCE FROM AN ITALIAN COHORT

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Aims: Since COVID-19 infection became a global public health problem, finding a treatment has been an emergency and vaccines are considered the only solution. In the last months, a big amount of data has been published on COVID-19 and vaccines that are currently available for the general population, but little is still known regarding patients with myasthenia gravis. The aims of this study are to evaluate the impact of COVID-19 and vaccine safety in MG patients.

Methods: We performed a retrospective study among a cohort of patients with Myasthenia gravis attending to the Neuromuscular Clinic of the University Hospital "Paolo Giaccone" of Palermo. Patients underwent a telephonic interview through a dedicated questionary about COVID-19 infection, vaccinations, and their effects on MG.

Results: In our cohort 9 patients resulted positive to SARS-COV2 infection, 4 patients died for COVID-19, a patient worsened for MG, requiring respiratory support, whereas 3 patients were asymptomatic. Among the vaccinated patients (n=53), about 45% (n = 24) experienced at least one AE, with a complete resolution within one week. No serious AEs and life-threatening conditions were observed.

Conclusions: The reduced number of adverse events in our population suggests that vaccines for SARS-cov2 are safe in myasthenic patients that could take advantage of vaccination avoiding life-threatening complications such as myasthenic crisis and COVID-19 pneumonia. The continuation of the regular and periodic clinical follow-up will provide us data on the real effectiveness of vaccine prevention.

SCREEN AND CARE IN HEREDITARY TTR-MEDIATED AMYLOIDOSIS: AN ITALIAN MULTICENTRE PROJECT

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Purpose: The goal of the project is to spread awareness of the importance of screening for hereditary transthyretin amyloidosis (hATTR) is a severe, adult-onset AD inherited systemic disease predominantly affecting the peripheral and autonomic nervous system, and heart. Considerable therapeutic advances have raised many challenges, including optimisation of diagnosis and management approaches in ATTRv.

Methods: Twenty-four physicians, referring to ten coordinators, participated in educational meetings, collected data from patients who underwent a neurologic/cardiologic examination within the past six months, described the signs/symptoms that raised suspicion of hATTR and then identified patients with confirmed hATTR. An educational form to help a common and organized data gathering was used to register: reason for referral, family history of neuropathy/cardiomyopathy; previous diagnosis/diagnostic elements; instrumental exams performed; signs/symptoms that raised the suspect of hATTR; neurophysiological examination, EKG; confirmation of hATTR and mutations. The aim of the data collection was to assess (a) The number of suspected/confirmed cases of hATTR (b) the signs/symptoms leading to the suspect of hATTR (c) The possible difference in the frequency of signs/symptoms leading to the suspect of hATTR in the populations with confirmed/not confirmed hATTR (d) The mutations observed in patients with confirmed hATTR. Results: (a) Data were collected from 10,841 patients, hATTR was suspected in 104 (0.95%) and confirmed in 15/104 (14,4%) patients. (b) The following signs/symptoms led to the suspect of hATTR: numbness/tingling; difficulty in walking; hyposthenia; balance disorders with walking difficulties; altered sensitivity to hot/cold; neuropathic pain. (c) None of the signs/symptoms described in (b) were statistically more frequent in the population with confirmed hATTR. (d) The mutations observed were: GLU109GLN; ILE88LEU; PHE84ILE; VAL50MET; HIS110ASN; VAL40ALA.

Conclusions: Once hATTR is suspected, the diagnosis is confirmed in a significant percentage of cases. Even if signs/symptoms leading to suspect of hATTR did not appear significantly more frequent in the confirmed group, probably because of the small size of confirmed group, the results outline the importance of a careful clinical evaluation and the need to always consider the possibility of hATTR in patients with neurological/cardiological symptomatology. Awareness and recognition of hATTR will help with early diagnosis, faster access to therapies, thereby slowing the progression of this devastating disease.

CLINICAL AND NEUROPHYSIOLOGICAL RECOVERY OF CHRONIC MOTOR NEUROPATHY DUE TO ACUTE INTERMITTENT PORPHYRIA AFTER GIVOSIRAN TREATMENT. THE CASE OF A 12-YEAR-OLD PATIENT WITH CHILDHOOD-ONSET DISEASE

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Objective: Patients with severe forms of Acute Intermittent Porphyria (AIP) and recurrent crisis may develop a chronic predominantly motor neuropathy which represents a major cause of disability and reduction of quality of life. Recently approved for AIP treatment, Givosiran is a new synthetic small-interference RNA (siRNA) that drastically decreases deta-aminolevulinic acid (ALA) production and reduces the recurrence of porphyric attacks. However, the effects of Givosiran on Chronic Porphyric Neuropathy (CPN) have not been unveiled yet. We describe the first case of a pediatric patient with refractory AIP and severe associated CPN followed prospectively for one year after Givosiran initiation. The objective of the study is to evaluate the effects of Givosiran treatment on AIP-associated CPN.

Materials and methods: The patient is a 12 years old male affected by refractory AIP and a severe form of CPN, causing foot deformity, plegia of ankle dorsiflexion and chronic pain since the age of 7. We followed him prospectively at Modena University Hospital for 18 months after Givosiran treatment initiation (subcutaneous administration, 2.5 mg/Kg monthly). Serial neurological evaluation including clinical scales and neurophysiological tests were performed to demonstrate improvement of neurological functioning in parallel with the monitoring of ALA urinary level. Clinical neurological scales included Medical Research Council scale, modified INCAT Sensory Sumscore, INCAT Overall Disability Score, inflammatory Rasch-built Overall Disability Scale and Norfolk Quality Of Life Diabetic Neuropathy 35 items. Neurophysiological assessments included complete nerve conduction study, electromyography and trans-cranial magnetic motor evoked potentials with measurement of central motor conduction time and cortical silent period. All evaluations were performed by the same neurologist, blinded towards the effects of Givosiran on porphyric attacks, ALA levels or adverse events.

Results: ALA urinary levels dropped drastically and the patient had no porphyric attacks during treatment. All the administered neurological evaluation scales and the serial neurophysiological assessments showed a progressive and significant improvement in all domains. Of notice, an improvement of central motor conduction parameters was noticed. At the end of follow up, our patient was able to walk unaided again after being wheelchair-bound for 5 years.

Discussion and conclusions: This is the first description of the effects of Givosiran treatment on CPN in refractory AIP. In our patient, a clear beneficial effect was demonstrated with both clinical and neurophysiologic outcome measures. Interestingly, some observations suggest a potential, previously unknown role of central motor pathway impairment in AIP.

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PRIMARY MITOCHONDRIAL MYOPATHY: 12-MONTH FOLLOW-UP RESULTS OF AN ITALIAN COHORT

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Objectives: To assess natural history and 12-month change of a series of clinical scales and outcome measures in a cohort of 117 patients with primary mitochondrial myopathy (PMM).

Material and Methods: 12 Months follow-up data of 117 patients with PMM were collected; patients are followed by centers of the Italian network for mitochondrial diseases. We analyzed the 6-Minute Walk Test (6MWT), Timed Upand-Go Test (x3) (3TUG), Five-Times Sit-To-Stand Test (5XSST), Timed Water Swallow Test (TWST), and Test of Masticating and Swallowing Solids (TOMASS) as functional outcome measures; the Fatigue Severity Scale and West Haven-Yale Multidimensional Pain Inventory as patient-reported outcome measures. PMM patients were divided into three phenotypic categories (PEO, PEO&MiMy, MiMy)

Results: At 12 months follow up, 3TUG, 5XSST and FSS were stable, and TWST and the perceived pain severity (WHYMPI) worsened. 6MWT significantly increased in the entire cohort, especially in the higher percentiles and in PEO patients, while was substantially stable in the lower percentile (<408 m) and in PEO and MiMy patients. This increase in 6MWT was considered not significant, as inferior to Minimal Clinical Important Difference MCID (33,3 m). NMDAS total score showed a slight but significant decline at 12 months (0.9 point). The perceived pain severity significantly worsened. Patients with PEO performed better in functional measures than patients with PEO&MiMy or MiMy and had lower values of NMDAS.

Conclusions: PMM patients showed a slow global decline valued by NMDAS at 12 months, and 6-MWT was a more reliable measurement below 408 m, substantially stable at 12 months. PEO patients had better motor performance and lower NMDAS than PEO&MiMy and MiMy

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ITALIAN DATABASE ON MULTIFOCAL MOTOR NEUROPATHY (IDAM): DATA FROM THE FIRST 100 INCLUDED PATIENTS

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Introduction: Multifocal motor neuropathy (MMN) is characterized by progressive, predominantly distal, multineuropathic limb weakness, usually more pronounced in the arms, minimal or no sensory loss, multifocal persistent partial motor conduction block (CB), frequent association with anti-GM1 IgM antibodies and response to IVIg. The EFNS/PNS diagnostic criteria define MMN but are often not uniformly used.

Methods: We established a Web-based database to collect the data from patients with a diagnosis of MMN (IDAM) followed by Italian centres with expertise on neuropathy in order to: 1) review the clinical and electrophysiological parameters used in the diagnosis of MMN; 2) determine the usefulness of more invasive or expensive tests in the diagnosis MMN (CSF, nerve biopsy, MRI or US); 3) determine the diagnostic relevance of antibodies to neural antigens, their association with specific clinical phenotype, progression of symptoms or response to therapy; 4) determine the response to therapy in MMN including their effect on disability and quality of life.

Results: As of May 2022, we included 104 patients with a clinical diagnosis of MMN. Eleven patients were excluded for the absence of available nerve conduction studies and 16 for the presence of objective sensory loss (4), abnormal upper limb SAP (8), bulbar impairment (3), or the presence of only cramps (1). 77 patients (53 women, 24 women, mean age 41.2 years, mean disease duration at the time of inclusion 11.7 years) fulfilled the EFNS/PNS criteria for the diagnosis of definite (10), probable (35) of possible (32) MMN. A predominant upper limb impairment was present at onset in 69% of the patients and still evident at inclusion in 39% of the patients. Anti-GM1 Ig M antibodies were present in 24/42 examined patients (59%), MRI abnormalities in 4/10 patients and abnormal US in 10/14 patients. Improvement after IVIg was observed in 53/60 treated patients (87%).

Conclusion: Almost 20% of the patients did not fulfill current EFNS/PNS diagnostic criteria for MMN. An objective sensory loss, abnormal sensory NCS or evidence of bulbar impairment were the leading causes of exclusion. CMAP area was not consistently reported by the Centers that often only reported CMAP amplitude. Patients fulfilling EFNS/PNS criteria almost invariably fulfilled typical diagnostic presentation of MMN with almost 90% of them improving after IVIg. Increased anti-GM1 IgM and US abnormalities often supported the diagnosis even if anti-GM1 IgM antibodies sometimes supported a misdiagnosis.

Supported by Baxalta US Inc, Takeda group, Investigator-Initiated Research grant no. IISR-2017-104226

REAL-WORLD IMPACT OF VITAMIN B12 DEFICIENCY IN THE CONTEXT OF NEUROPATHY: A SINGLE-CENTER RETROSPECTIVE STUDY

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Background and Aim: In the elderly, the prevalence of Vitamin B12 (B12) deficiency ranges from 6% to 40%. B12 is essential for both central and peripheral nervous system functions at all ages and peripheral neuropathy is a common but underrecognized complication of B12 deficiency, owing primarily to the poor determination of B12 level by physician and low sensitivity of B12 level determination methods. As a result, the clinical and electrophysiological characteristics of B12-deficiency associated neuropathy are still poorly understood. We conducted a retrospective study on patients with neuropathy at our Neuromuscular Disorder Clinic between 1st November 2019 and 1st June 2022 to assess the real-world impact of B12 deficiency in patients presenting with a exacerbations of neuropathy.

Results: In 27 of 260 (10.39%) patients with all-cause neuropathy, B12 levels were below the lower limit of normal. 12 of these patients presented with a predominantly sensory axonal polyneuropathy, which was classified as B12-responsive neuropathy, while in the remaining 15 the neuropathy was ascribed to other types of etiology (8 with CIDP, 1 with GBS, 1 with HNPP, 2 with MGUS/Multiple Myeloma associated neuropathy, 1 with diabetes polyneuropathy, 1 with Bell's palsy and 1 with post-chemotherapy neuropathy). In almost all of the cases described, the finding of low vitamin B12 levels was concomitant with clinical worsening of neuropathy and B12 intramuscular supplementation improved the patient's clinical condition in all reported cases.

Conclusion: Vitamin B12 depletion is an insidious condition that may be underrated especially in patient with an underlying neuropathy. This disorder is potentially reversible if therapy is initiated promptly, raising the importance of early diagnosis.

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HELIOS-A: STUDY OF VUTRISIRAN IN PATIENTS WITH HATTR AMYLOIDOSIS

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Introduction: Hereditary transthyretin-mediated amyloidosis (hATTR) is a fatal, multisystem disease. Vutrisiran, an investigational RNA interference therapeutic that targets variant and wild-type TTR, was assessed in the Phase 3, HELIOS-A study (NCT03759379).

Methods: Patients with hATTR amyloidosis with polyneuropathy were randomized (3:1) to vutrisiran (25 mg subcutaneous injection every 3 months) or patisiran (0.3 mg/kg intravenous infusion every 3 weeks), a reference comparator. The placebo group (n=77) from the APOLLO study was the external control. The primary endpoint: change from baseline in neuropathy (mNIS+7) at Month 9, versus external placebo.

Results: 164 patients randomized (vutrisiran, n=122; patisiran, n=42). As reported previously, at 9 months vutrisiran significantly improved mNIS+7 versus external placebo (Figure); improvement was maintained until 18 months (secondary endpoint). Vutrisiran met all other secondary endpoints, with significant improvements in quality of life (Norfolk QOL-DN) and gait speed (10-meter walk test) at Months 9 and 18, and in nutritional status (mBMI) and disability (R-ODS) at Month 18, versus external placebo. Vutrisiran achieved robust, sustained TTR reduction across 18 months, which was non-inferior to patisiran. Most adverse events with vutrisiran were mild or moderate, with no drug-related discontinuations or deaths.

Discussion: Vutrisiran significantly improved multiple important disease-relevant endpoints, versus external placebo, and demonstrated an acceptable safety profile.

Conclusion: Vutrisiran may provide benefit across important hATTR amyloidosis disease manifestations.

PATISIRAN IN HATTRE89Q AMYLOIDOSIS. EFFICACY IN A POPULATION WITH A PROMINENT CARDIAC MUTATION

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ATTRm amyloidosis is a progressive disease clinically heterogeneous that is in part determined by the genotype. Carpal tunnel syndrome (CTS) can be the initial symptom in up to one third of patients. In the course of the disease, patients then usually develop a peripheral and autonomic neuropathy and/or a restrictive cardiomyopathy. New therapies, in particular TTR gene silencing drugs such as patisiran, can slow down and in some cases reverse the polyneuropathy progression. A clinical trial is currently ongoing with the purpose to evaluate the efficacy and safety of patisiran in patients with ATTR Amyloidosis with cardiomyopathy. About a quarter of the patients treated at our center have the E89Q mutation, which is primarily associated with cardiomyopathy and prevalent in Italy (especially Sicily and Bulgaria). More than half of them are on patisiran. The objective of our study is to describe the characteristics and clinical response of this genetically homogeneous cohort. Fourteen patients (8 m and 6 f) underwent a complete follow-up that encompasses: neurological (NIS), autonomic (Compass-31) and cardiological (NYHA) function scales, blood analyses, nutritional status evaluation (mBMI) and some instrumental investigations such as nerve conduction studies, sudoscan, lying to standing test, electrocardiogram, echocardiogram and whole body bone scan with TC99. During the period under review, most patients showed no signs of disease progression. These data encourage us to starts patisiran even when sensorimotor polyneuropathy is minimally symptomatic but initial signs of autonomic or cardiac dysfunction are present. The study also confirms how an accurate multisystem screening is mandatory in carriers who reach a potentially risky age of onset.

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BENIGN MONOMELIC AMYOTROPHY OF LOWER LIMB: AN ITALIAN CASE SERIES

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Benign monomelic amyotrophy of the lower limb (BMALL) is a rare neurogenic syndrome of unknown aetiology clinically characterized by weakness and atrophy restricted to a single lower limb. It presents an insidious onset, slow progression and later stabilization, even if some deteriorating cases have bene described [1]. Most cases are found in Asian countries and affect males in the second or third decade of life. [2] We describe an Italian population of BMALL, consisting of 18 patients diagnosed at our Regional Center for Neuromuscular Diseases by electrophysiological studies, MRI or muscle CT and, in some cases, by muscle biopsy. Consistent with literature data, males were more affected than females (M:F 3,5:1) and the left lower limb was more frequently involved (3:2). All cases were sporadic. The onset, between 10-65 years in our population, was difficult to set precisely. The disease has a very slow course and long phases of stationarity without clinical involvement of other limbs (mean disease duration=25years; range [6-60years]). Motor and sensory conduction velocities were within the normal range in the affected limb. Both electromyography (EMG) and muscle biopsy analysis showed neurogenic findings in the involved limb. In some cases, EMG revealed neurogenic features also in clinically unaffected limbs. Muscle MRI or CT scan showed consistent involvement of the posterior muscles of the leg and, less frequently, the thigh and gluteus (insert percentages with new pts). Lumbosacral MRI excluded intraspinal pathologies and root compression and Survival Motor Neuron (SMN)-gene analysis showed no deletions. Our case series demonstrates the same clinical features of BMALL found in Asian populations. [3] We highlight the mismatch between the extent of atrophy and the functional deficit, which in many cases was minimal or absent. According to our results, BMALL shows a fair frequency even in Western countries and it should be considered in the differential diagnosis of motor neuron disease and radiculopathies.

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IMAGING OF NEURALGIC AMYOTROPHY IN THE ACUTE PHASE

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Introduction: This study describes imaging findings of peripheral nerves and muscles affected by neuralgic amyotrophy (NA) in the acute phase.
Methods: MRN and high-resolution US examinations were performed at 5 sites in 40 patients total with acute NA within 31 days of symptom onset. Correlation between imaging and EMG findings was measured.

Results: US was obtained in 30 patients and MRN in 23; 17 patients underwent US only, 10 MRN only, and 13 had both. US and MRN showed nerve abnormalities within 1 month from NA onset in 36/40 (90%) of patients. Hourglass-like constrictions (HGCs) were found in 29/40 (72%) patients and were detected in 4 patients within 1 week, 8 patients within 2 weeks, 5 patients within 3 weeks, and 12 patients within 4 weeks. The earliest HGC on US was found within 12 hours and on MRN within 3 days from symptom onset. MRN demonstrated denervation edema pattern of clinically affected muscles in 21/23 (91%) patients. The shortest time to observe edema pattern on MRN was 8 days from onset. EMG was performed in 30 patients and revealed fibrillation potentials of affected muscles in 22/30 (73%) cases. Denervation edema pattern on MRN was significantly associated with the presence of HGCs on MRN and on US, and with the presence of fibrillation potentials on EMG.

Conclusion: US and MRN are both valuable diagnostic modalities to demonstrate nerve abnormalities (especially HGCs) that appear early in the disease course and correlate with muscle denervation, demonstrated either by MRN or EMG.

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ELEVATED SERUM NEUROFILAMENT LIGHT CHAIN (NFL) AS A POTENTIAL BIOMARKER OF NEUROLOGICAL INVOLVEMENT IN MYOTONIC DYSTROPHY TYPE 1 (DM1)

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Objective: Cognitive and behavioural symptoms due to involvement of the central nervous system (CNS) are among the main clinical manifestations of Myotonic Dystrophy type 1 (DM1). Such symptoms affect patients' quality of life and disease awareness, impacting on disease prognosis by reducing compliance to medical treatments. Therefore, CNS is a key therapeutic target in DM1. Deeper knowledge of DM1 pathogenesis is prompting development of potential disease-modifying therapies: as DM1 is a rare, multisystem and slowly progressive disease, there is need of sensitive, tissue-specific prognostic and monitoring biomarkers in view of forthcoming clinical trials. As circulating Neurofilament light chain (NfL) levels have been recognized as a sensitive prognostic and monitoring biomarker of neuroaxonal damage in various CNS disorders, we conducted a study aiming to investigate the role of serum NfL as a potential biomarker of CNS involvement also in DM1.

Materials and Methods: We performed a cross-sectional study in a cohort of 40 adult DM1 patients vs a cohort of sex and age-matched controls (n=22). We collected sera from DM1 patients and controls to quantify levels of NfL. Moreover, we collected cognitive data, brain MRI, and other DM1-related diagnostic findings for correlation studies.

Results: Mean serum NfL levels resulted significantly higher in DM1 (25.32 ± 28.12 pg/ml) vs healthy controls (6.235 ± 0.4809 pg/ml, p = 0.0024). Their levels positively correlated with age (p = 0.049, 4 = 0.314), and inversely with the Rey's Auditory Verbal learning task (RAVLT) cognitive test (immediate recall, p=0.019 r=-0.413, and forced-choice recognition, p=0.001 r=-0.549). No correlations were found either with other cognitive data or diagnostic parameters in the DM1 cohort.

Discussion: Our results show that serum NfL levels are significantly higher in DM1 patients, with mean values four times more elevated than healthy controls. Given the relatively young mean age of the DM1 cohort (47.7±10.8 years), the contribute of physiological aging or vascular damage to NfL release was ruled out. NfL levels inversely correlated with the scores at RAVLT's immediate recall and recognition tasks, while no correlation was observed with performances at delayed recall of the RAVLT: these findings may depend on the fact that in DM1 patients episodic memory impairment is mainly related to attentional and executive alterations during the learning and recognition phases.

Conclusions: Our findings support serum NfL as a potential biomarker of CNS damage in DM1, which deserves further evaluation on larger cross-sectional and longitudinal studies to test its ability in assessing brain disease severity and/or progression.

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ARG143SER IS THE MOST FREQUENT VARIANT IN LIMB GIRDLE MUSCULAR DYSTROPHY-R9 IN SOUTHERN ITALY

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Background and Objective: Fukutin related protein (FKRP) is a glycosyltransferase involved in the glycosylation of α-dystroglycan essential component in linking the intracellular cytoskeleton with the extracellular matrix. Recessive mutations in the FKRP gene are associated with a broad range of dystroglycanopathies, from severe forms of Congenital Muscular Dystrophy (MDCIC) to Limb Girdle Muscular Dystrophy-R9 (LGMDR9, previously known as LGMD2I). IperCKmia, cardiomyopathy, proximal muscles weakness and atrophy, calf hypertrophy, respiratory failure are common clinical features in the LGMDR9 as well in the dystrophinopathies. Several LGMDR9 patients follow a mild Becker-like course without showing severe gait impairment until late in their adulthood. The most frequently reported FKRP mutation in LGMDR9 is 826C>A (L276I), especially in western and northern Europe. We decided to perform mutation screening of FKRP gene in patients from southern Italy with a Duchenne (DMD)/Becker (BMD) like phenotype of unknown genetic etiology.

Materials and methods: The study was performed on 110 sporadic cases resulted negative for exonic deletion/duplication of the DMD gene. The molecular analysis of the entire 1.5-kilobase coding sequence of the FKRP gene was conducted by PCR and direct sequencing.

Results: The mutational screening revealed seven patients heterozygous for 427C>A (Arg143Ser) (6,3%) and four patients homozygous or compound heterozygous for L276I (3,6%). Finally, four patients were compound heterozygous for Ala114Gly (3,6%).

Discussion and conclusions: Mutations in the FKRP gene have been identified in patients with Duchenne/Becker like phenotype and dystrophin reduction on muscle biopsy. Mutational screening of the FKRP gene was conducted on 110 DMD/BMD like phenotype sporadic patients from south Italy with no rearrangement of the dystrophin gene. Arg143Ser was the most frequent mutation identified in heterozygosity in seven patients, only in one patient was identified the second mutated allele. Our data are in agreement with what reported in the literature. In fact the Arg143Ser was previously identified in six Italian patients with clinical presentation consistent of LGMDR9 but only in one patient was identified the second mutated allele [1,2]. Arg143Ser mutation was validated in 200 control chromosome. This variant involves an evolutionary conserved residue and the loss of a positively charged amino acid in the mutated protein could have a dramatic effect on protein function. Manifesting carriers of FKRP mutation seem to be common among patients with LGMDR9. This finding suggests the possibility that Arg143Ser mutation on one allele is sufficient for the onset of the pathology or that the second mutation falls outside the FKRP gene.

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ADMISSIONS FROM EMERGENCY DEPARTMENT OF ADULT PATIENTS AFFECTED BY MUSCLE DISORDERS: A REAL-WORD EXPERIENCE FROM A REFERRAL CENTER

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Background and aims: Muscle disorders are generally treated in an outpatient setting; however, such diseases may be characterized by an abrupt onset and a rapidly worsening course or even by life threatening complications, which need medical care in an emergency department (ED) and hospitalization. In this retrospective study, we have analyzed the presentation, management, in-hospital flow and outcomes of a population of adult myopathic patients admitted from the ED.

Methods: We analyzed demographic and clinical data collected from adult subjects hospitalized from the ED of a large tertiary referral center in Italy between 2014 and 2018. Information was extracted from the computerized clinical record database using the "International Classification of Diseases, Ninth Revision" (ICD-9) codes at discharge, using all the codes related to muscular diseases for the query. For each identified case, the complete electronic medical record related to the ED visit and subsequent hospitalization were analyzed.

Results: A total of 406 patients had an ICD-9 code at discharge suggestive of a muscle disorder. After removal of subjects who met the exclusion criteria (wrong ICD-9 code; myalgias not associated with a myopathy; crush syndrome; sarcopenia and/or critical illness myopathy occurred as a complication during hospitalization; planned hospitalization via ED), the final number of patients included was 244 (137 males and 107 females; mean age 54.9 ± 19.2 years, range 18-89 years). 124 subjects (51%) had already an established diagnosis of a specified myopathy, while 40 (16%) patients received a new diagnosis of a muscle disorder during hospitalization. Among patients with a known muscle disorder, 53 (43%) had a muscular dystrophy, 33 (27%) were affected by inflammatory myopathies and 8 (6%) by a mitochondrial myopathy. In the group of newly diagnosed, acquired inflammatory myopathies were the most frequent diseases (23 patients, 58% of this group). Rhabdomyolysis was detected in 71 patients (29%), and in 9 patients it represented the symptom of onset of a muscle disorder. In 15 subjects (6%) the hospitalization was due to an acute relevant heart disease, while in 23 patients (9%) the cause was acute respiratory failure. A total of 26 patients (11%) died, mainly for respiratory failure and sepsis.

Conclusions: The picture provided by our study can be relevant to raise ER personnel's awareness on the special needs that patients affected by muscle disorders have, in order to timely treat acute conditions like inflammatory myopathies and address potentially life-threatening complications like the respiratory and cardiac ones.

GENETIC AND INFLAMMATORY MYOPATHIES: THE "EYE OF THE NEUROLOGIST" IN A DOUBLE-TROUBLE CASE SERIES

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Differential diagnosis is seldom easy to perform in the field of myopathies, especially between some inherited forms and secondary ones. We present a case series of 4 patients with a possible double diagnosis of an autoimmune systemic disease with muscular involvement plus a genetically determined myopathy. Each patient was evaluated in variable order by both our Neuromuscular Clinic neurologists, and the rheumatologists. They underwent muscle MRI, muscle biopsy, autoimmune screening and genetic testing for specific hereditary myopathies. For each patient a double diagnosis was reached: in the first case, a 60 years old woman with an evident Facioscapulohumeral muscular Dystrophy (FSHD) phenotype, a reduced D4Z4 allele was found, along with an anti-synthetase syndrome with pulmonary involvement; in the second case a patient already diagnosed with Sjogren's syndrome and undetermined connectivitis, complaining for fatigue and walking difficulties, displayed a double-heterozygous mutation on the GAA gene and was diagnosed with Pompe disease; the third case is that of a young woman with a known Carnitine palmitoyltransferase II (CPT II) deficiency experiencing a rhabdomyolysis episode during and infectious disease (that could be linked to her genetic metabolic myopathy) that underwent a rheumatologic screening and displayed high titer of anti-Mi2 antibodies, strongly associated to dermatomyositis; the last case involves a 60-years old man coming to our clinic for exercise intolerance, myalgia and cramps, in whom we found both a STIM1 mutation, consistent, along with his symptoms and findings, with a tubular-aggregate myopathy, but also a rheumatologic panel finding anti-synthetase antibodies with muscular and pulmonary involvement. While some forms of inherited or secondary myopathies tend to display rather specific clinical, laboratory or histopathological features that may aid diagnosis, in a quite high percentage of cases differential diagnosis remains a goal which may need third level investigations, such as NGS panels or other genetic techniques, muscle biopsy and its examination both at optic and electron microscopy; in the search for differential diagnosis – which is crucial in order to establish prognosis, set up follow-up and multidisciplinary management, refer patients to genetic and procreative counselling - such analyses require evaluation from the neurologist's point of view, in collaboration with other specialists, in order to interpret them in the clinical setting, including personal and family medical history and multisystem involvement.

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MUSCLE MRI OF LOWER LIMBS IN DIFFERENT FSHD CLINICAL CATEGORIES

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As a highly heterogenous muscular dystrophy in terms of phenotype and progression, the correct phenotypic classification of patients with facioscapulohumeral muscular dystrophy (FSHD) is crucial for directing genetic diagnosis and for the definition of outcome measures in clinical trials. In recent years, the Comprehensive Clinical Evaluation Form (CCEF) was proposed by the Italian Clinical Network for FSHD, defining various clinical categories by the combination of different features: subjects presenting facial and scapular girdle muscle weakness typical of FSHD (category A, subcategories A1-A3), subjects with muscle weakness limited to scapular girdle or facial muscles (category B),

asymptomatic subjects (category C), subjects with myopathic phenotype presenting clinical features not consistent with FSHD canonical phenotype (D). Whilst some studies evaluated muscular MRI pattern involvement in FSHD in general, to our knowledge the possibility of different patterns among the various aforementioned clinical categories has not been explored yet. We retrospectively analyzed muscular MRIs performed for routine follow-up on a cohort of 32 adult FSHD patients (19 category A, 11 category B, 2 category D). Dimension of the genetic defect (the D4Z4 allele length), age at evaluation, disease duration and clinical examination (including MRC strength testing and timed motor tests as 6MWT) were considered and correlated to muscle MRI results. Variability in the MRI results was found, according to the clinical classification. In the era of new treatments, including gene therapy, undergoing clinical trials for muscular dystrophies, profound understanding of FSHD pathophysiology and natural history is mandatory along with the need to assess and prove the possible presence of different disease phenotypes, in order to identify the most suitable outcome measures and refine diagnosis.

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COEXISTENCE OF SCN4A AND CLCN1 MUTATIONS IN A FAMILY WITH MYOTONIA: A CLINICAL AND FUNCTIONAL STUDY

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Background: Non-dystrophic myotonias (NDM) are rare neuromuscular diseases, including myotonia congenital (MC) caused by CLCN1 gene variants, paramyotonia congenita and sodium channel myotonia (SCM), caused by SCN4A mutations. NDM may clinically overlap, making it difficult to define genotype-phenotype correlations. We describe the clinical findings of five relatives, affected by myotonia and concomitantly harbouring single heterozygous mutations in SCN4A and CLCN1 genes. We also performed a functional characterization of both mutations.

Clinical cases: A 58-years-old woman reported a clinical history of painful muscular cramps in her legs worsened by cold temperature, and poor resistance to physical exercise since her adolescence. She also experienced difficulty in relaxing hands after the handgrip and leg stiffness when climbing stairs. Neurological examination revealed handgrip myotonia with warm-up phenomenon. Electromyography (EMG) confirmed the presence of myotonic discharges without myopathic signs. Her sons (29 and 25-years old) reported a history of legs stiffness and starting blocks during running since their adolescence. Neurological examination showed handgrip myotonia with negative warm-up phenomenon. EMG confirmed the myotonic discharges. Next-generation sequencing allowed the identification of the novel p.K1302R variant in SCN4A gene and the p.H838P variant in CLCN1 gene. We extended the genetic studies to other family members, showing the segregation with myotonic phenotype and discovering other two affected relatives carrying both mutations. Patch clamp experiments: The mutations were introduced into the pRc/CMV plasmid containing the cDNA encoding wild-type (WT) human Nav1.4 and human ClC-1 channels. Sodium and chloride currents were recorded with whole-cell patch-clamp technique in HEK293 cells transfected with p.K1302R or p.H838P and compared to relative WT currents. Sodium currents generated by p.K1302R and WT hNav1.4 were very similar. Kinetics and voltage dependences of fast and slow inactivation were superimposed. The mutant channel showed a small negative shift (3 mV) in the voltage-dependence of activation, which increased the likelihood of the channel to open at more negative voltages. The p.H838P mutation caused a reduction in chloride current density and a small voltage-dependence shift towards less negative potentials, in agreement with the location of the mutation into the CBS2 domain of the C-terminus.

Conclusions: Previous studies have proposed that SCN4A and CLCN1 mutations may act synergistically to increase the propensity for myotonic discharges, thereby influencing clinical and neurophysiological phenotype [1,2]. Our functional results suggest that the mild functional alterations induced by p.K1302R and p.H838P may be asymptomatic when expressed alone, while their combination is likely responsible for mixed myotonic phenotypes.

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NUCLEAR ENVELOPE DISORDERS: A STUDY OF PHENOTYPIC VARIABILITY IN A COHORT OF PATIENTS WITH MUSCLE LAMINOPATHY

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The epidemiology of muscle laminopathies is complex and remains not well defined; the prevalence of LGMDs is estimated to be approximately 1 in 20000, while LGMD1B makes up 5% to 10% of LGMD cases. The aim of the present study is to evaluate the natural history of disease in a cohort of neuromuscular patients with mutations in the LMNA gene or in genes coding proteins structurally and/or functionally related to the lamin A/C and to characterize the phenotypic aspects of these patients. The study, which enrolled ten patients, also involved a systematic retrospective collection of data for each patient for an overall follow-up period of five years. We aim to re-evaluate patients within this year so as to obtain an additional 2-years period of prospective assessment. Currently, evidence concerning the natural history of disease is scarce and mostly refer to cross-sectional characterizations or single case reports; this study offers disease progression data for an observation period of five years showing how neuromuscular involvement tends to remain substantially stable in

patients with a prevalent cardiological phenotype, while in patients with a prevalent muscle phenotype it is possible to observe a worsening of the motor functions. Thus, the present study highlights the need to stratify patients and to choose outcome measures on the basis of phenotypic characterization.

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A CASE OF LATE-ONSET CONGENITAL MYASTHENIC SYNDROME ASSOCIATED WITH PREPL HETEROZYGOUS MUTATION

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Aims: We report the first case of a late-onset Congenital Myasthenic Syndrome (CMS) associated with a heterozygous missense variant in Prolyl Endopeptidase-Like (PREPL) gene.

Materials and Methods: Biochemical tests, muscle magnetic resonance (MRI), electrodiagnostic testing, muscle biopsy and next generation sequencing (NGS).

Results: A short 52-years-old Italian male with clinical onset in the first decade with impaired ocular motility and diplopia. From third decade he developed bilateral eyelid ptosis, slowly progressive fatigability and weakness in the upper and lower limbs. Neurological examination showed bilateral ophthalmoparesis, shoulder-girdle hypotrophy and weakness, mild bilateral weakness of iliopsoas, rectus femoris and hamstring muscles, Gowers' sign positivity and reduced triceps ROTs. Fatigability tests were positive. CPK was normal. Electrodiagnostic testing showed a neuromuscular junction impairment with pathological repetitive nerve stimulation and a pathological single fiber EMG findings, associated with a myopathic pattern on EMG and a normal nerve conduction study. So, we performed dosage of Anti-AChR-Abs, anti-MuSK-Abs and anti-LRP4-Abs that resulted negative and also the chest CT. Lower limbs muscle MRI showed no significant changes in thigh and leg muscles. Muscle biopsy excluded a mitochondrial disease in fact we did not find ragged red fibers and COX and SDH activity was normal. However, we found slight myopathic changes (marked variability in size, nuclear centralizations, increase in connective tissue and a prevalence of type I fibers). Overall, we suspected a CMS and we started Pyridostigmine 240mg/die with benefit. To identify the genetic cause of the disease, we performed whole-exome sequencing and found a rare heterozygous missense variant in the PREPL gene, namely c.473T>C (p.Ile158Thr).

Discussion: PREPL deficiency (MIM# 616224) is a rare usually autosomal recessive inherited congenital myasthenic syndrome characterized by neonatal hypotonia, feeding problems, mild dysmorphism, neuromuscular symptoms and some patients also exhibit growth deficits [1-2]. In almost all cases this syndrome is caused by biallelic deletion/duplication in the PREPL gene but recently, some point mutations has been reported [3]. However, the function of this gene remains largely unknown. In our patient we found only one PREPL mutation, which might explain his clinical picture of CMS with a milder and later clinical expression than previously described [3].

Conclusion: The clinical and the genetic spectrum of CMSs is very wide and complex and our case could provide new information regarding the correlation between genotype and phenotype.

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MOVEMENT DISORDERS

IMPLEMENTATION OF WEARABLE SENSORS FOR EVALUATION OF DISEASE SEVERITY IN PROGRESSIVE SUPRANUCLEAR PALSY

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Objective: Progressive supranuclear palsy (PSP) is an atypical parkinsonism characterized by prominent motor and postural impairments (1). The PSP rating scale (PSPrs) is a validated tool to evaluate disease severity (2). More recently, wearable sensors such as APDM opal technologies have been used to investigate gait and related parameters in movement disorders (3). Aim of this study is to explore the relationship between a gait protocol using wearable sensors and the PSPrs.

Materials: PSP patients were evaluated with the PSPrs as well as with the gait protocol with wearable sensors based on 2-minute walking, sway and 360 degree turning tests.

Methods: Several parameters were extracted from the sensors. A Spearman rho correlation coefficient was calculated for the relationship between PSPrs (sub- and total scores) and sensor measurements. The sensors variables showing a significant correlation with PSPrs were subsequently included as independent variables in a multiple linear regression model in order to assess the sensors ability to predict PSPrs scores. The significance level in both analyses was set at ≤ 0.05.

Results: Sixty-one evaluations from 33 patients were analyzed, with 27 patients being tested twice (at baseline and at 3-months follow-up). Gait, sway and turning parameters measured with sensors showed multiple significant correlations with the PSPrs total- and sub-scores (rho between $\pm$ 0.3 and 0.7; $p<0.05$). All linear regressions built thereafter were significant ($p<0.05$) with adjusted R Square always > 0.7, indicating a strong relationship between the sensors parameters and the PSPrs. The strongest relationship was observed between PSPrs total score and turning velocity and mean stance time (R Square 0.976, $p <0.001$).

Discussion: Our clinic-based protocol evaluating gait and related parameters using wearable sensors has a strong relationship with the PSPrs

and could provide an objective evaluation to detect subtle clinical changes.

Conclusion: Wearable sensors could be easily introduced in clinical practice as well as in research settings as a tool to objectively evaluate disease severity in PSP.

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WEARABLE MOTION SENSORS TO TRACK TREMOR CHANGES AFTER NEUROSURGICAL THALAMOTOMY

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Objective: The quantitative characterization of tremor changes after neurosurgical treatment is crucial for understanding the efficacy of surgery in Parkinson's disease (PD) and essential tremor (ET). The aim of this single-case pilot study is to test inertial sensors effectiveness and usefulness in the assessment of tremor improvement after radiosurgical thalamotomy.

Materials: A wearable system was designed to measure motion signals before and after Gamma Knife radiosurgery (GKRS) thalamotomy in a PD patient with medication-resistant tremor.

Methods: The system consists of three inertial sensors per arm measuring their motion signals. Five tasks of 15 seconds' duration each were chosen to assess rest, postural and action tremor. Data captured by the sensors were wirelessly transferred in real time to an appropriate software and then analyzed obtaining (i) amplitude, (ii) angular velocity, and (iii) mean frequency of tremor. The patient was assessed by clinical evaluation and sensors measurement the day of GKRS and thereafter at 3, 6 and 12 months after treatment.

Results: A 76-year-old right-handed woman with a 13-year history of PD was deemed to be a candidate for GKRS left Vim thalamotomy for treatment of severe refractory tremor in the dominant hand. We observed a tremor improvement over time in all three inertial parameters, reaching their best outcome after 6-12 months from treatment. The amplitude of tremor was the most improved measurement. Patient showed 89%, 52% and 21% improvement of action, postural and rest tremor, respectively, between baseline and 12 months after treatment. Although these results are in line with clinical scales for tremor evaluation, they allowed to better identify which tremor features change after treatment. No bothersome ailments were report by the patient during sensors evaluation.

Discussion: The preoperative and postoperative evaluation of tremor with sensors not only allows to assess the tremor frequency, the amount of oscillations per second and the variation measured in cycles per second (Hz), but also to evaluate the degree of linear or angular displacement of the upper limb (tremor amplitude, measured in millimeters or degrees) and the angular velocity, therefore providing a more complete representation of human movement.

Conclusions: Our results demonstrated that this multi-sensor wearable system can be utilized to objectively characterize and monitor tremor changes after radiosurgical thalamotomy.

CORRELATES OF THE DISCREPANCY BETWEEN OBJECTIVE AND SUBJECTIVE COGNITIVE FUNCTIONING IN NON-DEMENTED PATIENTS WITH PARKINSON'S DISEASE

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Objectives: Subjective complaints of cognitive deficits are not necessarily consistent with objective evidence of cognitive impairment in Parkinson's disease (PD). Here we examined the demographic, clinical, and behavioral factors associated with the objective-subjective cognitive discrepancy.

Materials: We consecutively enrolled 90 non-demented patients with PD who completed the Parkinson's Disease Cognitive Functional Rating Scale (subjective cognitive measure) and the Montreal Cognitive Assessment (MoCA; objective cognitive measure).

Methods: The patients were classified as "Overestimators", "Accurate estimators" and "Underestimators" on the basis of the discrepancy between the objective vs. subjective cognitive measures. To identify the factors distinguishing these groups from each other, we used chi-square tests or one way analyses of variance, completed by logistic and linear regression analyses.

Results: Forty-nine patients (54.45%) were classifed as "Accurate estimators", twenty-nine (32.22%) as "Underestimators", and twelve (13.33%) as "Overestimators". Relative to the other groups, the "Underestimators" scored higher on the Fatigue Severity Scale (FSS), Beck Depression Inventory (BDI), and Parkinson Anxiety Scale ($p<0.01$). Logistic regression confirmed that FSS and BDI scores distinguished the "Underestimators" group from the others ($p<0.05$). Linear regression analyses also indicated that FSS and BDI scores positively related to objective-subjective cognitive discrepancy ($p<0.01$). "Overestimators" scored lower than other groups on the MoCA's total score and attention and working memory subscores ($p<0.01$).

Discussion: In more than 45% of consecutive non-demented patients with PD, we found a 'mismatch' between objective and subjective measures of cognitive functioning. Such discrepancy has been found to be associated to the presence of fatigue, depressive symptoms and frontal executive impairment. This suggests caution in relying on patients' subjective reports, especially in the absence of objective testing.

Conclusion: Our findings highlight the importance of assessing and monitoring fatigue and depressive symptoms in PD, especially when patients' complaints of cognitive impairment are used as prognostic indicators of future objective cognitive deterioration.

ASYMMETRY AND SIDE CONCORDANCE OF REST TREMOR AND BRADYKINESIA IN PATIENTS WITH ESSENTIAL TREMOR

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Objective: Subtle parkinsonian signs, i.e., rest tremor and bradykinesia (movement slowness), can occur in patients with essential tremor (ET) and can be considered soft signs for the definition of ET-plus. The aim of the present study was to investigate in a broad sample of ET patients the clinical and kinematic features of rest tremor and bradykinesia with particular attention to their body distribution and side concordance.

Materials: Standardized clinical scales and a kinematic system for movement analysis were used for the assessment of tremor and repetitive finger movements in our sample.

Methods: Eighty ET patients were enrolled. Upper limb action (postural and kinetic) tremor, rest tremor, and bradykinesia during finger tapping data were collected. We then investigated tremor asymmetry and side concordance between motor symptoms in ET patients.

Results: Thirty-one out of 80 patients (38.75%) had clinically detectable upper limb rest tremor. In 21 of them (67.74%), rest tremor was clearly asymmetric. In patients with rest tremor, the kinematic analysis of finger tapping revealed an asymmetry of the movement velocity in 17 cases (54.84%). However, in most patients (10 out of 17, 58.82%), there was no side concordance between rest tremor and bradykinesia. Conversely, in our sample, we observed a side concordance between asymmetric postural tremor amplitude and bradykinesia in a high percentage of cases (9 out of 11 patients, 81.82%: p=0.01).

Discussion: Rest tremor and bradykinesia are relatively frequent features in patients with a clinical diagnosis of ET. Our findings suggest that rest tremor and subtle bradykinesia (movement slowness) in ET possibly reflect different pathophysiological mechanisms. Conversely, the side concordance between postural tremor and bradykinesia in ET suggests that these two motor alterations may have a common pathophysiological basis, possibly reflecting the prominent cerebellar involvement in this condition.

Conclusions: Our results provide new insights on the pathophysiological basis of rest tremor and bradykinesia in ET.

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LONGITUDINAL STUDY OF CLINICAL AND NEUROPHYSIOLOGICAL FEATURES IN ESSENTIAL TREMOR

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Objectives: Essential tremor (ET) is a common and heterogeneous disorder characterized by postural/kinetic tremor of the upper limbs and other body segments and by non-motor symptoms, including cognitive and psychiatric abnormalities. Only a limited number of longitudinal studies have comprehensively and simultaneously investigated motor and non-motor symptom progression in ET. Possible soft sign changes that configure the ET-plus diagnosis are also underinvestigated. The aim of the present study was to longitudinally investigate the progression of motor and non-motor manifestations of ET.

Materials: The assessment included the clinical and kinematic evaluation of tremor and voluntary movement execution, as well as the investigation of cognitive and psychiatric disorders by means of clinical scales.

Methods: Thirty-seven ET patients underwent evaluation at baseline (T0) and at follow-up (T1) (mean interval ± standard deviation: 39.89 ± 9.83 months). Comparison of clinical and kinematic data in the two evaluations, subgroup and regression analysis were performed.

Results: A higher percentage of patients showed tremor in multiple body segments and rest tremor at T1 as compared to T0 (all p values <0.01). At T1, the kinematic analysis revealed reduced finger-tapping movement amplitude and velocity as compared to T0 (both p values <0.001). The prevalence of cognitive and psychiatric disorders did not change. Female sex, absence of family history, early tremor onset, and the presence of rest tremor at baseline were identified as predictive factors of worse disease progression.

Discussion: ET progression is characterized by the spread of tremor in multiple body segments over time and by the emergence of soft signs, including rest tremor and subtle bradykinesia. Progressive involvement of the cerebellum and its connections may play a primary role in ET progression. Furthermore, ET-plus may be considered an advanced stage of the disease rather than a distinct entity.

Conclusions: Our results provide novel information about ET progression and predictive factors of disease worsening and contribute to the debate regarding ET classification and pathophysiology.

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A PRELIMINARY REPORT ABOUT THE ROLE OF CONTINUOUS THETA BURST STIMULATION AS A POTENTIAL BIOMARKER OF LEVODOPA-INDUCED DYSKINESIAS IN PATIENTS WITH PARKINSON'S DISEASE

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Introduction: Levodopa is currently the most effective therapy in the symptomatic treatment of Parkinson's disease (PD). However, a long-term treatment is associated with complications such as motor

fluctuations and levodopa-induced dyskinesias (LIDs). Neurophysiological studies using TMS have documented an alteration of the physiological processes of LTP and LTD in M1 of patients with LIDs. We propose this prospective cross-sectional study aimed at evaluating the difference in terms cortical plasticity at the level of the M1 between PD patients with and without LIDs. The evaluation of the cortical plasticity will allow to correlate the neurophysiological alterations with the severity of the LIDs and to identify a neurophysiological biomarker predicting their severity.

Methods: Sixty patients will undergo a preliminary visit in which MMSE; UPDRS; UDyRS will be administered. The neurophysiological evaluation – using continuous theta-burst stimulation (cTBS) – is aimed at testing the presence of alterations in the LTP and LDP processes at the level of M1. Two stimulation paradigms will be used. In the first paradigm ("potentiation session"), a train of cTBS will be delivered to the motor cortex of the patients followed by the 1-min voluntary contraction of the target muscle: this procedure induces a significant increase of motor evoked potential (MEP) amplitude. In the second paradigm ("depotentiation session"), the potentiation session will be followed by the delivery of a train of cTBS lasting 10 sec: this stimulation sequence induces a significant decrease of the motor evoked potential (MEP) amplitude. The clinical follow-up will continue for 3 years.

Results: To date we have recruited 14 PD patients, 9 without LIDs and 5 with LIDS. We found a significant depotentiation in the group of non-dyskinetic patients and a not significant depotentiation in the group of dyskinetic patients. We found a significant correlation between % of depotentiation and UDyRS III.

Conclusion: Our preliminary results show that PD patients with LIDs are unresponsive to the depotentiation protocol and that impairment in depotentiation correlates with dyskinesia severity. The lack of control of synaptic plasticity in this group of patients could be one factor responsible for appearance of LIDs. Our research could help in better understanding the neurophysiological characteristics underlying the development of LIDs in patients with PD.

CORRELATION OF OBJECTIVE GAIT AND BALANCE MEASURES WITH COGNITIVE PERFORMANCE IN PARKINSON'S DISEASE

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Objective: To analyze the correlation between gait and balance kinematic features obtained by wearable motion sensors in Off and On therapeutic conditions and cognitive performances, divided into five cognitive domains.

Materials and Methods: Forty consecutive patients with Parkinson's disease (PD) candidates for device-aided therapies underwent an extensive neuropsychological assessment investigating reasoning, memory, language, frontal executive functions, and visual-spatial abilities. Domain scores were obtained as the average equivalent scores of single tests, calculated according to normative data [1]. Gait and balance parameters were acquired in both Off (a night after withdrawal of dopaminergic therapy) and On (about 45 minutes after levodopa intake) therapeutic condition by means of the Opal (APDM)™ motion sensors during a battery of tests: Two-minute walk test (2MWT); Timed-up and go test (TUG test); Sway test; 360 degrees Turn Test. Spearman correlation analyses were performed to explore correlations between kinematic and cognitive features. We considered only strong correlations ($p<0.01$) given the multiple analyses.

Results: Strong correlations were found between stride length in Off and memory (0.334; p:0.006), TUG turn velocity in Off and memory (0.405; $p<0.001$), TUG duration in Off and language (-0.425; p:0.001), double support in On and frontal executive functions (-0.209; p:0.009), Off vs. On difference in TUG duration and both memory (-0.348; p: 0.003) and language (-0.527; $p<0.001$), and Off vs. On difference in step duration and reasoning (0.366; p:0.006).

Discussion: Cognitive deficits are among the most disabling features of PD and involve dopaminergic and non-dopaminergic (i.e., noradrenergic and cholinergic) brain networks [2]. Preliminary evidence indicates an overlap between the presence and extent of cognitive decline, mainly frontal executive functions, and gait parameters; however, a comprehensive analysis of the association between a wide range of kinematic parameters in Off and On therapeutic conditions and neuropsychological tests assessing different cognitive domains has never been performed [3]. In our exploratory study, we found that features of gait impairment (especially in Off) and their response to levodopa are correlated with distinct patterns of cognitive impairment in PD.

Conclusions: The importance of kinematic features, in particular when assessed in both Off and On therapeutic conditions, emerged as potential markers of the underlying pathophysiology. Measures of brain connectivity based on functional MRI data from these patients might contribute to clarifying specific patterns of abnormal neurotransmission.

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HANDWRITING ABNORMALITIES IN PARKINSON'S DISEASE: A MACHINE-LEARNING STUDY

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Objectives: Handwriting abnormalities, including micrographia, have been reported since the onset of Parkinson's disease (PD). Also, handwriting abilities progressively decline over the course of PD, showing a suboptimal response to L-Dopa therapy [1,2]. Machine learning would represent an ideal tool for the objective detection of parkinsonian micrographia, as suggested by a recent study in healthy subjects [3]. The aim of this study is to improve the clinical ability to recognize PD, track the disease progression and evaluate the symptomatic response to dopaminergic replacement treatment, through the machine learning analysis of handwritings.

Materials: Seventy-three patients with PD (45 males; 71±11 years) and 63 healthy subjects (21 males; 71±7 years) were enrolled to participate in this study. PD patients were further divided into 51 early-stage (H&Y<2.5; 31 males; 69.2±12.3 years) and 22 advanced-stage patients (H&Y>=2.5; 14 males; 71.9±13.7 years). Patients with PD were studied both in OFF (i.e., at least 12 hours after the last L-Dopa intake) (36 males; 70.1 ±11.6 years) and ON therapy (i.e., 30-60 minutes after L-Dopa administration) (31 males; 72.0±11.0 years).

Methods: Participants performed a standardized handwriting task that was digitalized through specific electronic devices (i.e., smartphones). Then, the DBNet algorithm was used to measure and compare the average stroke sizes from handwriting samples. Also, a convolutional neural network (CNN) was applied to classify handwritings from controls and PD patients, OFF and ON therapy. Finally, receiver operating characteristic (ROC) curves were calculated to report the diagnostic performance of the algorithm.

Results: Stroke sizes were significantly smaller in PD patients than in controls. Also, handwriting strokes were smaller in advanced-stage than in early-stage PD. Finally, handwritings were comparable in OFF and ON PD patients. The CNN classifier objectively discriminated between controls and PD (accuracy=87%). Also, handwriting analysis distinguished early-stage and advanced-stage patients (accuracy=89%). Lastly, machine learning was not able to discriminate between OFF and ON therapy patients (accuracy=50%).

Discussion: Handwriting abilities decline in PD manifesting with micrographia. Handwriting abnormalities can be detected since the early stages of PD and progressively degrade in more advanced stages of the disease. Dopaminergic replacement therapy does not improve significantly handwriting abilities, including micrographia, in PD patients.

Conclusions: Machine learning analysis of handwriting samples in PD allows to objectively and automatically detect the disease, track the disease progression, and recognize the effect of L-Dopa. Therefore, advanced handwriting analysis would represent a novel biomarker of PD.

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EXPLORING THE PROGNOSTIC ROLE OF GBA VARIANTS ON THE CLINICAL OUTCOME OF DEEP BRAIN STIMULATION IN PARKINSON DISEASE PATIENTS

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Background: Parkinson disease (PD) represents a heterogeneous syndrome with a widely variable clinical course, both in terms of progression and occurrence of non-motor symptoms. GBA heterozygous variants are a well-known genetic risk factor for PD and result in earlier disease onset and more malignant phenotype, with a greater burden of non-motor signs compared to non-carriers. Thus, GBA-PD patients are more likely to undergo deep brain stimulation (DBS), yet the impact of this genetic factor on the long-term outcome of DBS remains unclear.

Aims: To explore the prognostic role of GBA variants on the clinical progression of PD patients after DBS surgery.

Methods: We retrospectively analysed genetic and clinical data from our cohort of DBS-PD patients upon stratification for the presence/absence of GBA variants. All patients underwent pre-DBS evaluation and had a regular follow-up visit after surgery. Clinical assessment included: MDS-UPDRS in both ON and OFF state, cognitive evaluation and levodopa equivalent daily dose (LEDD).

Results: 84 DBS-PD patients were genotyped, of whom 16 (19%) carried GBA variants (9F/7M, age at onset: 57.1±7.4yrs; disease duration 13,9±5.8 yrs; target DBS: 13 STN/3 GPI). Among GBA-PD, 7 carried severe variants, 4 had mild variants, and 5 presented risk alleles. After surgery, all GBA-PD showed persistent motor improvement, with satisfactory control of motor fluctuations and dyskinesias. LEDD was also significantly reduced by 30%. Four patients developed postural instability; five patients, all with disease duration >10 years, manifested dementia within 5 years from surgery.

Conclusion: Determining the impact of prevalent genetic mutations on PD phenotype is a key step towards a personalised medicine approach, in order to improve prognostic assessment and better guide therapeutic choices. This study addresses the impact of GBA variants on the clinical outcome of DBS. Although preliminary, our data suggest that GBA mutations do not seem to negatively influence the motor and non-motor outcome of DBS patients. Further studies on larger PD cohort with a longer follow-up are needed to further explore this important issue, as this could open new perspectives for customized DBS implantation protocols and stimulation paradigms.

NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH PARKINSON'S DISEASE WITH AND WITHOUT MILD COGNITIVE IMPAIRMENT: FREQUENCY, CLUSTERS, AND ASSOCIATED FACTORS. THE PARKINSON'S DISEASE COGNITIVE IMPAIRMENT STUDY

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Background and Objectives: Neuropsychiatric symptoms (NPS) can co-occur in definite clusters during Parkinson's disease (PD) with dementia and these patterns of symptoms could have relevant therapeutic and prognostic implications. However, very few data have explored the relationships between specific clusters of NPS in non-demented PD individuals with and without Mild Cognitive Impairment (PD-MCI). To identify NPS clusters in a large hospital-based sample of mild-moderate, non-demented PD patients and to evaluate the putative associations between clinical parameters and NPS clusters.

Methods: 429 nondemented PD patients (PD-NC 264 [62%] and PD-MCI 165 [38%]) from the PACOS cohort were included [1]. PD-MCI was diagnosed according to the MDS, Level II criteria for MCI [2]. NPS and their severity were assessed using the Neuropsychiatric Inventory (NPI) [3]. Cluster analysis was used to investigate the interrelationship of NPI items. Multinomial logistic regression was carried out to assess to the effect of clinical and cognitive features on the allocation of a patient to a particular cluster.

Results: The most common NPS reported by the total PD sample were depression (62%), sleep disturbance (61%), anxiety (60%), and apathy (44%). PD-MCI patients had statistically significant higher mean NPI composite scores than PD-NC in all NPS examined (p-values from 0.005 to p= <0.001). Cluster analysis identified 4 symptom clusters, as follows: 1) No symptom (60%); 2. Hallucination (5%); 3. Depression (23%), and 5. Irritability/Anxiety (12%). After multinomial logistic regression analysis and compared with the No symptom cluster, a low score

on the adjusted MMSE predicted allocation to the Hallucination (OR= 0.81, 95% CI=0.73-0.91) and Irritability/Anxiety clusters (OR= 0.82, 95% CI=0.75-0.91); furthermore, the risk to belong to the latter cluster was significantly increased for woman than men (OR= 2.96, 95%CI= 1.37-6.40). The use of antipsychotic (OR= 4.88, 95% CI= 1.56-15.27) and antidepressant drugs (OR= 2.41, 95% CI= 1.38-4.22) was associated with a higher likelihood of being placed in the Depression cluster. Similarly, the use of anxiolytic (OR= 2.48, 95% CI= 1.22-5.04) and antidepressant drugs (OR= 2.70, 95% CI= 1.29-5.64) was associated with a significantly higher likelihood of belonging to the Irritability/Anxiety cluster.

Discussion and Conclusions: NPS are common in non-demented PD patients; the severity of these symptoms significantly differs in PD patients with and without MCI. Female gender, low MMSE, and psychotropic drug use were found to be factors associated with specific NPI clusters. Prospective data relating to large populations are required to confirm and extend these findings.

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PERAMPANEL AS A NOVEL TREATMENT FOR MYOCLONUS IN MYOCLONUS-DYSTONIA SYNDROME

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Background: Myoclonus-dystonia (MD) is a heterogeneous genetic group of disorders characterized by subcortical myoclonus and mild to moderate dystonia. The main causative gene is the epsilon sarcoglycan gene (SGCE) but genetic background can be heterogeneus. Response to medications is variable, with poor tolerability limiting their use [1].

Case presentation: We present the case of a patient with involuntary movements since childhood. Symptoms progressed gradually over the years, involving neck, shoulders and upper limbs and causing disability in everyday life. She referred to a neurologist at the age of 46y, and myoclonus-dystonia was diagnosed. Genetic testing identified a novel mutation in SGCE gene (c.907delC) in heterozygosis. Her parents were dead; thus, no genetic analysis was possible. However, none of her relatives reported neurological disturbances. Clinically, she presented brief myoclonic jerks predominating in the upper limbs and neck, mild at rest and elicited by action, posture and tactile stimulus. Myoclonus was accompanied by mild neck and right arm dystonia. Over time she assumed a large variety of antiepileptics without beneficial effect on myoclonus and low tolerability. Treatment with Perampanel at 4 mg/day was started, with a beneficial effect on myoclonus and reduced disability. No adverse events were reported.

Discussion: Perampanel is the first selective non-competitive AMPA receptor antagonist approved in add-on for focal and generalized tonic-clonic seizures. It has been used to treat myoclonus in a few patients with Progressive myoclonic epilepsies and Lance Adams syndrome with beneficial effects [2,3] but no reports are available in literature in MD. To our knowledge this is the first trial of perampanel in MD.

Conclusions: We presented the case of a patient with MD due to SGCE mutation who was treated with Perampanel with beneficial effects. We propose Perampanel as a novel treatment for myoclonus in MD.

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LATE-ONSET CEREBELLAR ATAXIA: CLINICAL, INSTRUMENTAL AND GENETIC DESCRIPTION OF FLORENTINE CASES

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Objective: The aim of this retrospective study is to analyse clinical, laboratory and genetic elements of ataxic patients monitored in the Ambulatory of the Florence area, trying to improve the flow-chart used to diagnose this rare and complex disease.

Materials and Methods: This retrospective study included 71 patients followed by "Malattie Rare" Ambulatory of the department of Neurologia 1 in the AOU-Careggi during the period from January 2013 to December 2018, who were diagnosed with ataxia on the basis of clinical criteria. All patients underwent a diagnostic pathway made by: medical history, neurological examination, blood tests, cardiological, urological and in Sincope Unit examinations, neuroimaging, neurophysiological studies and genetic testing performed in the Neurogenetic Laboratory of this AOU and of Istituto Neurologico Carlo Besta, in Milan.

Results: 12 patients (17%) were diagnosed with Friedreich ataxia, 10 of them (14%) with some inherited subtypes of ataxia, other 10 (14%) with MSA, 36 (51%) with ILOCA and 3 (4,2%) with secondary ataxias. Frequencies of FRDA, inherited subtypes of ataxia and MSA appeared in accordance with the literature. ILOCA's group, surprisingly the biggest one, was composed of some inherited-like (31%) and MSA-like (8,3%) subspecies. 2 genetic mutations causing ataxia were founded in 2 ILOCA's group patients.

Discussion: Data suggest that ILOCA's group is very frequent, therefore a lot of effort is still needed to identify its diagnosis, which is the first step in developing effective treatments.

We found out that the majority of this class resemble inherited and MSA ataxias. Supporting this, finding 2 genetic mutations during the follow-up of ILOCA's group has been of great importance.

Conclusions: On the basis of these results and the analysis of diagnostic approaches used, we suggest a new flow-chart to improve the diagnosis of ataxia in outpatient care.

NEUROPHYSIOLOGICAL CHANGES OF PRIMARY MOTOR CORTEX IN PATIENTS WITH ESSENTIAL TREMOR-PLUS

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Introduction: Essential tremor-plus (ET-plus) represents a recently introduced entity indicating ET patients with additional neurological signs of uncertain significance, including rest tremor, bradykinesia and mild cognitive impairment (MCI). The concept of ET-plus, however, is still controversial and only few studies investigated the neurophysiological mechanisms underlying this condition.

Aims: To investigate possible neurophysiological changes of the primary motor cortex (M1) and their relationship with soft signs in patients with ET-plus.

Materials and Methods: Thirteen ET-plus patients were enrolled (5 females, 70±7.97 years). Most patients had rest tremor, subtle bradykinesia, MCI and only 3 of them had impaired tandem gait. No patients had dystonia. Patients were evaluated by standardized clinical scales. Objective measurements of rest tremor and bradykinesia (during finger tapping) were obtained by kinematic analysis. M1 excitability was assessed by the recordings of resting motor thresholds (RMTs), input/output curve of the motor-evoked potentials (MEPs) and using a conditioning-test paradigm for the assessment of short-interval intracortical inhibition (SICI) and short-latency afferent inhibition (SAI). Plasticity-like mechanisms were indexed according to MEPs amplitude changes after intermittent theta-burst stimulation (iTBS). Data were compared to those from 16 healthy controls (HCs). Correlations between clinical, kinematic, and neurophysiological data were assessed in patients.

Results: Compared to HCs, ET-plus patients had higher RMTs (P=0.019), indicating a lower corticospinal excitability and a lower MEPs facilitation after iTBS (P=0.032), reflecting a lower cortical plasticity. ET patients were slower than HCs during finger tapping (P=0.03). No correlations, however, was found between neurophysiological, clinic and kinematic. In particular, there was no significant relationships between neurophysiological changes of M1 and the type or severity of soft signs in patients.

Conclusion: We here provided novel information on excitability and plasticity abnormalities of M1 in patients with ET-plus. The lack of correlation between clinical and neurophysiological data suggests that various ET-plus forms do not represent entities with a specific pathophysiological background.

ORTHOSTATIC HYPOTENSION IN VASCULAR PARKINSONISM: THE IMPACT ON NON-MOTOR SYMPTOMS

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Objective: Orthostatic hypotension (OH) occurs in up to 26% patients with Vascular Parkinsonism (VP), but its impact on other non-motor symptoms in patients with VP is still unknown. Therefore, the aim of our study was to assess the impact of OH on other non-motor symptoms in patients with VP with OH (OH+) and in patients with VP without OH (OH-).

Materials and methods: The study included 11 patients with VP (OH+) and 11 patients without VP (OH-). All subjects underwent a complete clinical, neuropsychiatric and neuropsychological assessment. Clinical evaluation included full neurological examination, the Non Motor Symptom Scale (NMSS), to assess non-motor symptoms and a standard Tilt-test protocol. Neuropsychiatric evaluation assessed: depression, anxiety, apathy, anhedonia and alexithymia. Neuropsychological battery included evaluation of: global index of cognitive impairment, short- and long-term verbal memory, long-term visual-spatial memory, immediate visual memory, language abilities, complex constructional praxis, attention and executive functions.

Results: The result of NMSS indicated that patients with VP (OH+) experienced more "excessive sweating" (Domain 9, item 30) than VP (OH-) (36,40% vs. 0,0%; p=0.027). No significant neuropsychiatric and neuropsychological differences were found between groups.

Discussion: Our results suggest that patients with VP (OH+) have excessive sweating. If this relationship is causative or associative remains unclear. Possible explanations are that excessive sweating is driven by hypovolemia, one cause of OH, or that OH and excessive sweating are both consequences of autonomic nervous system dysfunction. We hypothesize that neuropsychiatric symptoms and neuropsychological deficits may not emerge in patients with VP (OH+) because compensatory mechanisms of cerebral vasoregulation and homeostatic autoregulation in VP may be already impaired.

Conclusion: There are still gaps in knowledge about autonomic nervous system dysfunction in patients with VP. In particular, OH in VP needs to be further investigated as it is an important risk factor for falls and heavily contributes to the disease burden. Longitudinal studies and larger samples of patients with VP are needed to assess the long-term impact of OH on other non-motor symptoms.

Funding: This work was supported by grant from Ministero della Salute [GR-2016-02361783] to Francesca Assogna and Clelia Pellicano.

DYSPHAGIA AND FIBEROPTIC ENDOSCOPIC EVALUATION OF SWALLOWING IN EARLY TO ADVANCED STAGE HUNTINGTON'S DISEASE

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Aims: Huntington's disease (HD) is a neurodegenerative disorder characterized by motor disturbances, cognitive decline, and behavioral changes. A well-recognized feature of advanced HD is dysphagia, which leads to malnutrition and aspiration pneumonia, the main cause of death in HD. Previous studies have evaluated the importance of dysphagia in HD patients with moderate-to-advanced stage disease, but it is unclear whether dysphagia affects patients already at an early stage of disease and whether genetic or clinical factors can predict its severity.

Methods: We performed fiberoptic endoscopic evaluation of swallowing (FEES) in a cohort of 61 HD patients with early-to-advanced disease and in a control group of 31 healthy subjects. Dysphagia severity, swallowing safety, and swallowing efficacy were rated with validated ordinal scales (DOSS, PAS, YALE). Eight patients were also evaluated after 7-10 months.

Results: Dysphagia was found in 35% of early-stage, 94% of moderate-stage, and 100% of advanced-stage HD. Silent aspiration was found in 7.7% of early-stage, 11.8% of moderate-stage, and 27.8% of advanced-stage HD. A strong correlation was observed between disease progression and dysphagia severity: dysphagia severity, as assessed by DOSS, strongly correlated with the Total Motor Score (TMS) and a TMS > 36.5 predicted swallowing dysfunction (81% sensitivity and 83% specificity), suggesting that motor impairment could be predictive of dysphagia onset. Analysis after 7-10 months in a limited number of patients (n=8) has shown a worsening of swallowing capacity for liquids.

Discussion: Dysphagia severely reduces the quality of life of HD patients and increases the risk of malnutrition [1], [2]. An accurate swallowing assessment is essential for correct management of HD patients [2]. FEES is a validated and widely used technique to assess the pharyngeal phase of swallowing [1]. Dysphagia is known to be frequent in patients with moderate- and advanced-stage HD. These findings show that abnormal swallowing can be already observed in early-stage HD patients and well detected by FEES; the risk of lower airway invasion increases with disease progression. We found that worse dysphagia is associated with worsening of motor symptoms. Dysphagia features may serve as a marker of disease progression. Dysphagia can be characterized as a disorder of communication between sensory and motor networks involved in swallowing [3].

Conclusions: This is the first study based on FEES to describe swallowing alterations in HD patients with early-stage disease. Our data improve knowledge about dysphagia onset and progression. A better understanding of this topic may inform guidelines for dysphagia early recognition and appropriate management.

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YOUNG-ONSET PARKINSON'S DISEASE: REAL DATA FROM A SINGLE-CENTRE LONGITUDINAL COHORT

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Objective: Parkinson disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons of substantia nigra pars compacta (SNc) and the accumulation of alpha synuclein in several brain regions. Young-onset Parkinson's disease (YOPD) is defined by an age of onset before 50 years. Both pathology and phenotype of YOPD seem to differ from those of typical, Late-onset PD [1]. However, available data are still scarce and almost anecdotal. Accordingly, an in-depth analysis is needed. To retrospectively analyse and shape the course of a YOPD single-centre cohort.

Materials: A longitudinal cohort of 193 YOPD patients was selected from a population of 2000 PD patients followed up from 2000 to 2021 at Tor Vergata University Hospital (Rome, Italy).

Methods: For each patient data regarding main demographic and clinical features were collected at onset and at follow up time. Descriptive statistics was run on qualitative and quantitative variables. The course of disease from onset to ten years later in terms of both Hoehn and Yahr (H&Y) stage and levodopa equivalent daily dose (LEDD) was then estimated.

Results: YOPD had a prevalence of 9.7%, with a genetic origin in 9.3% of cases. It mostly presented as a mainly motor, asymmetric rigid-akinetic syndrome. Motor progression in terms of H&Y showed a linear increase of 0.92 points/10 years, whereas the flow of LEDD showed a non-linear trend, with an increase of 526.90 mg/day in the first five years, and of 166.83 mg/day from five to ten years. Motor fluctuations affected up to 80% of the cohort, starting after 6.5±3.2 years from disease onset. Neuropsychiatric troubles affected the 50% whereas sexual difficulties the 12%. After levodopa initiation, female patients presented levodopa-induced dyskinesias earlier than males (2.71 ± 1.73 years vs 3.46 ± 2.73 years, p=0.003). Three female patients (3.4%) reported worsening of motor features during menses.

Discussion: The analysis of the YOPD cohort showed a "brain-first" PD subtype [2], characterized by slow, linear motor progression, with non-linear dopaminergic requirements. Major burden resulted from motor fluctuations, neuropsychiatric complications and marital issues. Gender-specific motor disturbances emerged.

Conclusion: This study analysed main features of a large, single-centre, longitudinal cohort, to shape YOPD and detect those elements that might be helpful to develop a tailored approach for such a burdening condition.

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CLINICAL UTILITY AND VALIDATION OF A VISUAL QUALITY SCALE FOR CINGULATE ISLAND SIGN IN THE DIAGNOSIS OF LEWY BODIES DISEASE AND ALZHEIMER DISEASE: A FDG-PET/MRI STUDY

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Background: Brain 18F-FDG-PET is proposed as supportive biomarker in the diagnosis of dementia with Lewy bodies (DLB), showing reduced occipital metabolism and presence of the cingulate island sign (CIS), a relative preservation of the metabolism in the posterior cingulate cortex (PCC) compared with the precuneus and cuneus.

Objective: To assess clinical utility, validation and reproducibility of a visual qualitative CIS scale in diagnosis of DLB and Alzheimer's disease (AD) at different stages of disease and various phenotypes.

Materials and methods: Patients with a diagnosis in the spectrum of Lewy bodies disease (DLB and MCI-LB) and with AD (typical and atypical variants) who underwent FDG-PET/MRI during the diagnostic work-up were recruited. Clinical data at time-point of PET scan and in the follow-up assessments at least for 24 months were retrospectively collected. FDG-PET/MRI images were independently evaluated by a nuclear medicine and a neurologist specialist assessing the presence of hypometabolism in PCC, precuneus, and cuneus in each hemisphere and applying a visual rating of CIS with specific reading criteria [1]. Validation of qualitative CIS scores was made with ROI-based semi-quantitative analysis of metabolism of PCC, cuneus and precuneus.

Results: 36 patients with LBD (30 DLB 6 and MCI-LBD) and 31 patients with AD (20 typical and 11 atypical presentations, including 6 visuo-spatial variants) were recruited. Mean CIS score was 0,59±1,24 for the AD patients, and 1.84±1.69 for DLB ones (p=0.001). Hypometabolism of the right cuneus was more frequent in DLB (p=0.001). With a defined cut-off CIS score > 2, sensitivity and specificity were 0,56 and 0,81, respectively (accuracy 0,67). Presence of CIS was rated for 6 patients with biological diagnosis of AD, 5 of them with atypical presentation. Absence of CIS was found in 16/36 DLB: 9 with absent hypometabolism in both cingulate cortex and precuneus and 7 with hypometabolism in both regions. The former group consisted of 6/9 MCI-LBD (5 with stable cognitive impairment over a period of 3 years) and the latter 7 patients with dementia. Scores of qualitative CIS rating correlated with semiquantitative uptake of FDG tracer (r=0.45; p=0.001). Ratings of nuclear medicine and neurologist had high concordance (p=.0001).

Discussion: A qualitative scoring of CIS on FDG-PET images is specific of DLB for higher values. Lower sensitivity is expected for cases of MCI-LB or dementia due to mixed DLB/AD changes. Specificity may be influenced by inclusion of atypical AD cases, mostly young-onset cases with atypical cortical presentation.

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NEUROIMAGING AS A POTENTIAL TOOL FOR DRIVING DBS STIMULATION IN PD

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Objectives: To identify the best site of DBS stimulation within or nearby the subthalamic nucleus of patients with advanced PD, to maximize the clinical motor outcome.

Materials and Methods: Twenty-five patients treated with bilateral STN-DBS were enrolled in the study. They all received a comprehensive clinical evaluation by means of the MDS Unified Parkinson Disease Rating Scale (MDS-UPDRS) before (baseline) and 1 year after (follow-up) DBS surgery. Presurgical MRI scan including conventional images (i.e., T1-weighted volumes, fluid-attenuated inversion recovery and T2-weighted scans) and post-surgical CT scan images were combined for the identification of the volume of tissue activated (VTA), using Lead-dbs software [1]. Using Voxel-based Lesion-Symptom mapping [2], individual VTAs were modelled to identify possible associations between follow-up subsets at the MDS-UPDRS and voxels belonging to VTAs. Age, disease duration and VTA volumes were entered as covariates of no interest. This use of VLSM allows to identify VTA subfields accounting for specific measures of positive/negative outcome.

Results: A significant sweetspot (p=0.043) accounting for patient improvement in bradykinesia was found covering the left dorso-lateral border of STN and extending to the surrounding white matter within the zona incerta and the most anterior portion of ansa lenticularis (peak coordinates: x=16; y=-13; z=-8). No associations were identified with rigidity and tremor UPDRS subscores.

Discussion and Conclusions: This study points out the usefulness of neuroimaging for predicting DBS positive and negative outcomes, and its possible translation to clinical settings. From a speculative perspective our finding suggests the importance of zona incerta and fibers surrounding the lateral-posterior part of STN as a potential key target for patients with remarkable bradykinesia. Future studies based on brain connectivity might clarify the underlying mechanisms.

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KINEMATIC ANALYSIS OF MILD BRADYKINESIA FEATURES IN FRAIL ELDERLY PEOPLE

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Objective: Mild Parkinsonian signs, including bradykinesia, commonly occur in elderly people with a prevalence ranging from 15% to 95%. To kinematically characterize the possible bradykinesia features in elderly people in relation to their overall frailty.

Methods: We enrolled 41 healthy subjects (25 F, mean age ± 1 SD: 63.9±8.91, range 46-83 years). The kinematic analysis of bradykinesia included repetitive finger-tapping analysis. We measured the number of movements, as well as rhythm (coefficient of variation - CV), amplitude, velocity, and amplitude decrement (sequence effect) of repetitive movements. Along with demographic and clinical data collection, including the Mini-Mental State Examination (MMSE) and the Frontal Assessment Battery (FAB), we evaluated the frailty status of all participants using a 40-item Frailty Index (FI). The possible relationships between demographic and clinical data and kinematic movement features were assessed by Spearman's correlation test.

Results: First, we found a significant positive correlation between the CV and the FI (r= 0.42, p<0.01), i.e. the higher the CV (more altered movement rhythm) the higher the subject frailty. Second, we found that the sequence effect positively correlated with the age of subjects (r=-0.34, p<0.05), i.e. the greater the sequence effect during finger-tapping, the older the subject.

Discussion: The kinematic analysis of finger tapping allows an objective assessment of bradykinesia features in frail elderly people. The correlation between altered movement rhythm and the overall frailty of the subject possibly reflects a frontal dysfunction (given previous studies suggesting a relationship between altered movement rhythm and executive dysfunction as well as between executive dysfunction and frailty). The correlation between the sequence effect and the age of the subject possibly reflects altered network dynamic and synaptic plasticity alterations primarily due to aging.

Conclusions: The preliminary data emphasize the importance of the quantitative assessment of bradykinesia features in the frail elderly population, which are possibly underestimated and likely reflect distinct pathophysiological mechanisms. The present results require confirmation on a larger sample of healthy subjects.

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DIGITAL LITERACY IN PARKINSON'S DISEASE

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Objectives: The increased use of telemedicine has highlighted the presence of a "digital divide" among internet users, but there are no available data in Parkinson's Disease (PD) [1,2]. We therefore aimed to: (1) compare digital literacy between PD patients and healthy controls (HC) and (2) determine the influence of disease features on digital inclusion.

Materials: A modified version of the Internet Skills Scale (ISS) evaluating three main domains (operational, information navigation, and mobile) [3] was administered to consecutive PD patients from five Italian centers. Clinical (MDS-UPDRS-III, Hoen & Yahr (HY), presence of depression and cognitive decline) and demographic informations (age, sex, education, job status, family income, housing context) were concomitantly registered.

Methods: We used Mann-Whitney U-Test to check for group differences and linear regression model to further determine the possible predictive value of age-corrected MDS-UPDRS-III and HY on ISS score.

Results: 270 PD patients and 49 HC, matched for age and sex, were enrolled. No significant differences were found regarding ISS global score, but PD patients performed significantly worse in the "Information Navigation" domain than HC (p=0,006). PD patients with possible/mild cognitive decline had worse ISS global score (p=0,035) as well as worse Information Navigation (p=0,025) and Operational (p=0,035) skills than those without. No significant differences were found comparing patients stratified by the presence of depression/apathy. Age-corrected MDS-UPDRS-III and H&Y were independent predictors of ISS global score (for both p<0.001).

Discussion: Global "digital performances" in PD patients do not differ from healthy subjects of the same age-group. Nevertheless, they experienced worse abilities in the "Information Navigation" domain, which is more cognitively demanding and might indicate an early cognitive dysfunction in these subjects. Moreover, worse digital performances were predicted by higher motor disability and disease burden.

Conclusions: Higher motor disability and presence of cognitive dysfunction might impair the use of telemedicine services in a disease stage when theoretically more needed. Further studies should also evaluate other factors (i.e. digital inclusion) which might preclude a widespread use of telemedicine services.

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NEUROIMAGING CORRELATES OF TREMOR AND BRADYKINESIA IN PATIENTS WITH ESSENTIAL TREMOR

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Introduction: Essential tremor (ET) is a neurological condition characterized by postural and kinetic tremor of the upper limbs. Moreover, it has been recently pointed out that bradykinesia may be a relatively common motor feature in ET. Despite the well-known role of the cerebellum in ET pathophysiology, the possible involvement of other brain areas remains unclear.

Aims: To investigate structural damage and resting-state functional alteration of the cerebral cortex, basal ganglia, and the cerebellum in ET. Moreover, we aimed to assess possible correlations between magnetic resonance imaging (MRI) findings and bradykinesia.

Methods: Twenty patients with ET and 17 healthy subjects (HS) underwent multimodal 3T-MRI, including 3D-T1 and blood oxygen-level dependent (BOLD) sequences at rest. MRI structural analysis was performed on 3D-T1 images. A seed-based analysis was performed to study resting-state functional connectivity (rsFC) of the dentate nucleus and globus pallidus. Postural and kinetic tremor and bradykinesia during repetitive finger tapping were kinematically recorded via an optoelectronic system. We then analysed: tremor amplitude (GRMS^2) and frequency (Hz) and various movement parameters, e.g., movement velocity and amplitude and sequence effect. Finally, we assessed possible correlations between neuroimaging, clinical scores and kinematic parameters.

Results: Compared to HS, ET patients showed a higher dentate FC with cerebellum, and a lower FC with precentral and frontal areas. Furthermore, ET patients showed a higher pallidal FC with cerebellum and sensorimotor areas, and a lower FC with crus II and superior frontal gyrus. Confirming previous findings, ET patients showed lower movement velocity of finger tapping, compared to HS. Pallidal and dentate rsFC negatively correlated with tremor severity, however, they both positively correlated with movement velocity during finger tapping.

Conclusion: We here provided novel pathophysiological information in ET. The data suggest a role of both basal ganglia and cerebellar nuclei in generating either postural tremor or bradykinesia in ET.

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FUNCTIONAL CONNECTIVITY IN EARLY STAGES OF PARKINSON'S DISEASE: AN EEG STUDY

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Objective: Parkinson's disease (PD) is a neurodegenerative disorder, characterized by the degeneration of dopaminergic neurons of substantia nigra. Nevertheless, it is now well known that PD is a multisystem disease, involving several brain structures, reflecting an ascending progression of synucleopathy [1], even if a top-down cortical pathogenesis of PD was recently proposed [2]. In accordance, previous studies have reported abnormal functional connectivity in PD at different stages. Scarce are, instead, studies examining brain connectivity in patients at early stages of PD. For this aim, we analyzed differences in functional connectivity

between de novo PD patients and healthy controls by means of high-density EEG.

Materials and Methods: Data were recorded with a 64-channels EEG system. Source reconstruction method was used to identify brain regions activity. We analyzed power spectral density and functional cortical connectivity, based on imaginary part of coherency (iCOH) [3], in four frequency bands (θ-α-β-γ). Finally, we compared spectral density and functional connectivity matrices between healthy controls and de novo PD patients through T-test. The analyses were based upon custom written Matlab scripts, combined with Brainstorm and Brain Connectivity toolboxes functions.

Results: 11 de novo PD patients and 10 healthy subjects were studied. No differences were observed in spectral analysis between the two groups, except for the γ band where a significant increase in power density was found in PD patients. A reduced connectivity in the main EEG frequency bands (α-β frequency bands) was observed in PD patients compared to controls, while a hyperconnectivity was found in PD patients γ in band.

Discussion: We found that de novo PD patients have a reduced connectivity in the main EEG frequency bands (α-β). In first hypothesis, the dysfunction we observed in EEG functional connectivity may be related to downstream effects through striatal-thalamocortical circuit, although a cortical involvement since the early stages of PD cannot be excluded. A further result of our research is that PD patients showed a hyperconnectivity in γ frequency, when compared to other frequencies. γ cortical oscillations have been associated with execution and planning of movements. In our opinion, the observed γ hyperconnectivity may be interpreted as a compensatory mechanism performed by cortical neurons still not affected by synucleinopathy, that can be lost as the disease progresses.

Conclusion: Functional connectivity analysis may ease a better understanding of the complexity of PD physiopathology, from the earliest stages of disease. Future studies are needed to confirm these data.

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EXPOSURE TO AMANTADINE AND OUTCOMES OF COVID-19 IN PATIENTS WITH PARKINSON'S DISEASE: PRELIMINARY FINDINGS FROM AN EARLY OBSERVATIONAL STUDY

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Background: Despite the increased vulnerability suggested by their demographic and clinical profile, patients with Parkinson's Disease (PD) do not show an increased prevalence nor mortality from SARS-CoV-2 infection. Amantadine is often prescribed for the symptomatic management of PD for both antiparkinsonian and anti-dyskinetic effects. In addition, amantadine has long been used as an antiviral compound (it was approved for influenza-A prophylaxis), and experimental evidence suggests potential antiviral effects against SARS-CoV-2, including a high affinity for the alpha-helical pentameric bundle of CoV E peptide which may interfere with viral entry and replication. We hypothesized that incidental exposure to amantadine may confer protection against the development of SARS-CoV-2 infection in patients with PD.

Methods: Observational study in patients with PD participating in the Parkinson's Disease Outcome Project in early 2021 in two centers (New York University - USA, and Villa Margherita - Italy). Since the availability of specific tests for COVID-19 was very limited at that time, we developed a 13-item questionnaire to retrospectively assess the prevalence of variables linked to SARS-CoV-2 exposure and COVID-19 severity during the 6 months prior to the survey, including symptoms of infection (i.e. fever, dry cough, and sudden onset hyposmia), and indicators of clinical severity (i.e. hospitalization, oxygen support, and radiological findings). Patients were grouped based on amantadine status (On/Off amantadine), and likelihood of COVID-19 infection (none, intermediate, of high) based on our questionnaire. Between group differences were analyzed by Student t-test, chi-square test, and Fisher exact test depending on variable distribution.

Results: Of the 184 surveyed patients, 37 were receiving amantadine whereas 147 were off-amantadine. Subjects on amantadine were younger (age 67.1 Vs 77.8, p=0.006) and more likely to receive group support than those off amantadine. An increased frequency of conjunctivitis (p = 0.04) and an almost significant increased frequency of affected family members (p = 0.058) were found in subjects on amantadine. Pair-wise comparison between groups with none (n = 122), intermediate (n=62), or high (n=11) likelihood of COVID-19 showed no significant differences of amantadine exposure and no differences of other demographic features.

Conclusions: No significant differences in SARS-CoV-2 exposure and COVID-19 clinical outcome emerged between PD patients with and without amantadine as part of their usual PD regimen, failing to support a protective effect from this compound. The retrospective nature of the study, the lack of a confirmed diagnosis in most cases, and the small size of patients deemed at high risk of COVID-19 (11) prevent definitive conclusions. Prospective and properly powered studies are needed.

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CLINICAL CHARACTERIZATION OF TREMOR DURING WALKING IN PARKINSON'S DISEASE

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Introduction: In patients with Parkinson's disease, hands tremor can be observed in different conditions, including rest, posturing (re-emergent tremor, postural tremor) and motor execution (kinetic tremor). In PD, tremor of the hands is also frequently observed during walking. The occurrence and clinical features of Tremor During Walking (TDW) in PD have not been fully addressed. It is, therefore, unknown whether

TDW is akin to other PD forms of tremor or exhibits specific features with respect to severity, site of distribution and response to treatment.

Objectives: The aim of this study was to perform a clinical characterization of TDW in PD patients. The clinical features of TDW were compared with those of other PD tremors either in off and on condition.

Methods: Fifty-one patients with PD and resting tremor participated to the study. Each patient underwent a full clinical examination and a standardized video recording of tremor, during different conditions including rest, maintenance of a posture, finger-nose maneuver, and walking. We measured the severity of tremor through the item 3.17 of the MDS-UPDRS part III, the latency of onset and the body distribution of tremor. Patients were clinically evaluated off and on treatment (60 minutes after taking their usual dopaminergic treatment).

Results: In the off-treatment evaluation TDW was present in 79% of the patients enrolled. The mean severity of TDW was similar to that of rest tremor but significantly higher than those of other tremors, i.e. re-emergent (p= 0,003), postural (p= 0,001) and kinetic tremor (p= 0,001). The mean latency of onset of TDW was 6 ± 4 seconds. The body distribution of TDW overlapped that of rest tremor and re-emergent tremor. Dopaminergic treatment induced a significant and similar improvement of TDW (p=0.0001), rest tremor (p=0.00001) and re-emergent tremor (p=0.0001). Conversely postural and kinetic tremor were unchanged after therapy (p values >0.05).

Discussion: The similarity of clinical characteristics of TDW and resting tremor suggests that TDW may represent a continuation of resting tremor during the maintenance of a stable motor plan and that these tremors may share similar pathophysiological mechanisms. The significant improvement induced by dopaminergic treatment suggests that dopaminergic loss may be involved in the pathophysiology of TDW.

Conclusion: TDW is present in most PD patients with resting tremor and is similar to resting tremor in terms of severity, body distribution and response to dopaminergic treatment. Future neurophysiological studies are needed to clarify the pathophysiological substrate of TDW in PD.

CORRELATES OF PSYCHOLOGICAL DISTRESS IN PATIENTS WITH PARKINSON'S DISEASE DURING THE COVID-19 OUTBREAK

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Aims: following the severe consequences of the COVID-19 outbreak, on March 9, 2020, the Italian government implemented extraordinary measures to limit viral transmission, including restrictive quarantine measures. This resulted in a rapid and profound change of people's daily lives. Aims of this study were: 1) to assess the psychological impact of the 40-day quarantine in a large cohort of patients with Parkinson's disease (PD) and in their caregivers; 2) to analyze whether prelockdown clinical features may predispose to this subjective response.

Materials: The study sample was recruited from an ongoing longitudinal study. Therefore, an extensive prelockdown motor, non-motor and cognitive evaluation were performed. From this cohort, we selected a subset of 94 patients with PD.

Methods: After 40 days of lockdown, the Impact of Event Scale-Revised, the Kessler Psychological Distress Scale, and the 12-item Zarit Burden Inventory were obtained from PD patients and their caregivers by email. A multivariate regression analysis was performed to determine whether prelockdown clinical features were associated with the psychological impact of lockdown.

Results: Regression analyses showed that prelockdown levels of anxiety, treatment-related motor complications, patients' quality of life, and lockdown hours per day were significantly associated with psychological impact measures of the 40-day quarantine. We also showed that caregiver burden was correlated with overall patient autonomy and attention/memory impairment.

Discussion: Dopaminergic as well as serotoninergic and adrenergic pathways have been involved in both anxiety symptoms in PD and stress-related responses. Similarly, converging evidence supports the presence of high synaptic dopaminergic concentrations before and after levodopa administration in PD patients with treatment-related motor complications. This may support the presence of a link between PD-related pathophysiological mechanisms and dopaminergic-driven maladaptive processing of traumatic events.

Conclusions: We identified specific PD motor and nonmotor features potentially predisposing to higher psychological impact of stressful situations, such as quarantine. Our observations provide crucial insights about potential determinants of post-traumatic stress in patients with PD during the COVID-19 outbreak. Results of the present study may help guide postpandemic interventions and preventive strategies to avoid further impairment of psychological well-being in patients with PD.

RISK AND PROTECTION FACTORS IN PARKINSON'S DISEASE: A PROSPECTIVE POPULATION STUDY

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Background: Several environmental and lifestyle factors have been independently investigated in previous studies on Parkinson's disease (PD) with controversial results, which likely depend on limitations intrinsic to the study design [1,2]. No study has so far prospectively investigated potential risk/protection factors for PD using both linear and nonlinear statistical approaches; the latter may reveal more complex associations and new risk/protection PD factors undetected with linear models.

Objectives: To assess a simultaneous investigation of potential risk/protection factors involved in PD in a large prospective population study, using both classical statistical analyses and machine learning approaches.

Materials and Methods: Participants to the Moli-sani Study were enrolled between 2005 and 2010 and followed-up until December 2018. Incident PD cases were obtained by individual-level record linkage to the Regional Hospital Discharge Forms, the Italian register of deaths (both through ICD-9 code = 332) and the Regional Register Prescribing System (through the ATC classification = N04XX; anti-Parkinson drugs). Exposure to potential risk/protection factors were assessed at baseline and during the follow-up. Multivariable Cox PH regressions and survival random forests were built to identify the most influential factors.

Results: 213 PD incident cases were identified out of 23,901 adult subjects (median (IQR) follow-up 11.18 (2.02) years). Linear association models revealed that age, sex, dysthyroidism, type 2 diabetes and marginally exposure to paints were associated with an increased risk to develop PD, whereas coffee intake predicted a lower PD risk. Both hyper- and hypothyroidism were independently associated with PD risk. A Survival Random Forest showed that age was by far the most influential feature on PD risk, followed by coffee intake, daily physical activity and high blood pressure.

Discussion: This is the first prospective study with a simultaneous assessment of potential protection/risk factors associated with PD through

complementary statistical approaches. The study provided novel insights into potential protection/risk factors influencing PD incidence, shading light on the role of dysthyroidism, diabetes, and high blood pressure, which so far showed uncertain relationships with PD, and confirming the relevance of most factors (age, sex, coffe intake and daily physical activity) known to be associated with PD from previous evidence [1,2,3].

Conclusion: Our study provided novel insights into the investigation of protection/risk factors associated with PD, opening new strategies to prevent the development of PD.

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CLINICAL FEATURES OF PARKINSON'S DISEASE IN RELATION TO DIFFERENT AGES AT ONSET: A RETROSPECTIVE STUDY

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Introduction: Age at onset of Parkinson's disease (PD) symptoms influences the disease course and long-term therapeutic response. Studies on the prevalence and initial course of symptoms in PD patients with different age at onset are scarce.

Objective: To evaluate the prevalence and progression of motor and non-motor symptoms over the first 5 years of illness in PD patients with different age at onset.

Materials & Methods: We retrospectively collected data on motor, non-motor and therapeutic features during the first 5 years of illness in 82 PD patients referred to our PD Center. Subjects evaluated at the time of diagnosis (T0) and followed-up for 5 years (T1) were included. They were divided into 3 groups according to age at onset of motor symptoms as follows: ≤55 years old (29 patients, group A), 56-69 years old (20 patients, group B), and ≥70 years old (33 patients, group C). Motor symptoms were evaluated by the MDS-UPDRS-III scale, non-motor features by the NMSS and therapeutic regimen was expressed as LEDD.

Results: At T0, gastrointestinal symptoms were significantly more frequent in group B patients (35%, p=0.01). At T1, postural instability (36%, p=0.008) gait disturbances (73%, p=0.002), and attention/memory symptoms (33%, p=0.001) were significantly more prevalent in group C patients, whereas miscellaneous symptoms domain was more frequent in group B patients (65%, p=0.001). In the whole population, there were significant increases in the prevalence of gait disorders (p=0.001), postural instability (p=0.001) and several NMSS domains between T0 and T1. Within-group analysis showed that gait disorders significantly increased in B (p=0.031) and C (p=0.001) groups, and postural instability significantly increased in group C solely (p=0.004).

Discussion: Regarding the prevalence of motor and non-motor symptoms at the time of diagnosis (T0), group B patients complained of significantly more gastrointestinal symptoms than others; considering the first five years of the disease (T1), postural instability, gait disturbances and attention/memory symptoms were more prevalent in group C patients. During the first five years of the illness since the diagnosis, in the general group of patients we observed a significant increase of gait disorders, postural instability and different NMSS domains. During this period, gait disorders significantly increased in group B and C patients, whereas postural instability increased only in the latter group.

Conclusion: These results suggest that different age at onset of PD symptoms may be associated with a different motor and non-motor feature prevalence and progression in the first 5 years.

ASYMMETRY OF BRADYKINESIA FEATURES IN PARKINSON'S AND INTERHEMISPHERIC INHIBITION IMBALANCE

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Introduction: Bradykinesia and other motor symptoms in Parkinson's disease (PD) are predominantly asymmetric. An asymmetrical reorganization and an altered connectivity between the two primary motor cortices (M1) have previously been demonstrated in PD. Whether the asymmetry of motor manifestations relates to the imbalance of the inhibitory interhemispheric connections, however, is still unknown.

Aims: To investigate the relationship between the asymmetry of bradykinesia, quantified by kinematic analysis of finger tapping, and the asymmetry of the interhemispheric inhibitory connections in PD, tested by transcranial magnetic stimulation (TMS).

Methods: Twelve PD patients (1 female, 69.75±9.9 years) and 10 age- and gender-matched healthy controls (HCs) were enrolled. Objective bradykinesia measurements during finger tapping were obtained using a motion analysis system from both sides. Paired-pulse TMS was used to measure the interhemispheric inhibition (IHI) between the hand areas of the two M1, with an interstimulus interval (ISI) between the conditioning (CS) and the test stimulus (TS) of 10 ms (short-latency IHI, sIHI) and 40 ms (long-latency IHI, lIHI). Asymmetry indices (AI) were calculated for all neurophysiological data. We then tested possible relationship between kinematic and TMS data in patients.

Results: PD patient were slower than in HCs during finger tapping (p=0.01). In PD there was a more severe progressive reduction of movement amplitude during movement repetition, i.e., sequence effect (p=0.04). When testing IHI (from the most affected to the less affected hemisphere), we found a reduced sIHI in patients. The amount interhemispheric disinhibition, i.e., interhemispheric imbalance quantified by the sIHI-AI, correlated with the sequence effect of the less affected side (p<0.001).

Conclusions: We here provided novel evidence on the role of interhemispheric disinhibition in the pathophysiology of bradykinesia asymmetry in PD. The results support the hypothesis that the sequence effect has pathophysiology mechanisms distinct from those underlying other bradykinesia features.

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NEURODEGENERATION AND INFLAMMATION IN PARKINSON'S DISEASE: AN INSIGHT FROM BLOOD BIOMARKERS

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Background and aim of the study: Parkinson's disease (PD) is the second most frequent neurodegenerative disorder and is characterized by a great phenotypical heterogeneity. A-synuclein deposition plays a crucial role in PD development but also other mechanisms, including inflammation, seem to underlie PD pathogenesis and progression. Recently, great attention has been put on biomarkers which could follow disease initiation and progression to both monitor disease progression and understand underlying pathophysiological mechanisms. Our aim was to measure blood levels of neurodegeneration and inflammation biomarkers and correlate them with clinical and demographic data.

Materials and Methods: We consecutively enrolled PD patients and evaluated them by means of validated clinical scales (UPDRS, Hoehn and Yahr staging, MMSE, NMSQ). Then, serum levels of selected biomarkers (Neurofilament light chain, BDNF, IL-1β, IL5, IL-6, IFN, TNF-a, IL4 and IL10) were essayed using commercially available kits on an ELLA™ automated immunoassay system (Bio-Techne, San Jose, CA, USA). Descriptive statistics, parametric and non-parametric tests were used when necessary. Spearman correlation test was used to correlate clinical-demographical data and biological measures.

Results: 104 patients were enrolled with a mean age of 66.55 years and disease duration ranging from 0 to 29 years, with a mean of 8 +/-5 years. NfL levels showed a positive correlation with disease duration and UPDRS III score (respectively rho 0,348, p=0.014 and rho 0,258 and p=0.047). A correlation analysis between inflammatory markers and disease duration showed a trend in increase of pro-inflammatory citokynes in the first years, with a tendency to peak at 5 years from diagnosis and then a decrease. No differences were found in biomarkers levels considering the presence/absence of motor fluctuations.

Discussion: In this study we confirm the role of NfL as a marker of disease progression, confirming its reliability also if measured in the serum of PD patients. If combined with more specific markers, it could play a significant role in monitoring disease progression and also be predictive of conversion to a clinical manifest phase in prodromal patients. Moreover, we also found an interesting trend showing an increase of pro-inflammatory cytokines in the earliest phases of the disease, followed by a decrease in the following years.

Conclusion: This study shows the association between serum NfL and disease burden and the tendency to manifest a pro-inflammatory status in patients in the earliest phases of the disease.

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AXIAL FEATURES IN STN-DBS-TREATED ADVANCED PD PATIENTS: STANDARDIZED CLINICAL-INSTRUMENTAL APPROACH FOR A LONG-TERM POSTOPERATIVE FOLLOW-UP.

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Objective: To examine the long-term effects of dopaminergic treatment and bilateral subthalamic nucleus deep brain stimulation (STN-DBS) on axial features in advanced Parkinson's Disease (PD) patients. Possible correlations between speech and gait parameters were evaluated as well. Background: STN-DBS is an effective long-term treatment in PD, improving a broad spectrum of symptoms, including tremor, rigidity and bradykinesia. Axial symptoms are very common in PD, including gait and speech disorders. To date, only few studies have instrumentally tested these alterations together, suggesting the presence of similarities between spatial-temporal gait and perceptual-acoustic speech parameters.

Methods: This long-term observational study included 25 consecutive STN-DBS treated PD patients with a five-year postoperative follow-up. Axial symptoms have been assessed in the long-term after surgery using a standardized clinical-instrumental approach. Speech was assessed by perceptual and acoustic analysis, while gait by means of the instrumented timed up and go test (iTUG). Disease motor severity was evaluated applying the Unified Parkinson's Disease Rating Scale (UPDRS) part III. This study considered three different stimulation and drug conditions for each patient: on-stimulation/off-medication, off-stimulation/off-medication, on-stimulation/on-medication conditions (single and dual task).

Results: Both on-stimulation/off-medication and on-stimulation/on-medication conditions resulted in an improvement of motor scores and most of gait variables, while their effect on speech parameters was heterogenous. In the on-stimulation/on-medication condition patients with a poorer voice quality performed worse the sit to stand and gait phases of the iTUG. Conversely, patients with a higher speech rate performed well

the turning and walking phases of the iTUG. These data suggested that levodopa treatment and DBS stimulation may influence in the same way specific speech and gait parameters.

Conclusions: Our results suggest that STN-DBS and dopaminergic treatment could improve gait parameters in the long-term after surgery, while they had heterogenous effect on speech variables. Moreover, several correlations between speech and gait parameters were identified, allowing to deepen the common pathophysiological basis of these alterations.

POSSIBLE CORRELATIONS BETWEEN SPEECH ACOUSTIC PARAMETERS, AXIAL MOTOR SYMPTOMS AND DISEASE SEVERITY IN ADVANCED PARKINSON'S DISEASE PATIENTS: A CLINICAL-INSTRUMENTAL ASSESSMENT

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Background: Speech alterations are frequently observed in Parkinson's Disease (PD) patients. However, the relationship between speech acoustic parameters, axial features and PD motor severity is still debated. Furthermore, chronic dopaminergic treatment effects on speech parameters are unclear.

Objective: The aim of this study was to evaluate possible correlations between axial motor symptoms, disease severity and speech parameters in advanced PD patients and to examine the effects of stable dopaminergic treatment on speech disturbances.

Methods: In this study data from 50 advanced PD patients in OFF- and ON-states were retrospectively evaluated. We performed a perceptual and acoustic analysis of spontaneous monologue and sustained phonation. Particularly, quantitative parameters and speech intelligibility rate were evaluated either in the OFF and ON-medication conditions. The Unified Parkinson's Disease Rating Scale (UPDRS) part III score and subscores, including Postural Instability Gait Disorder (PIGD) composite subscore, and Hoehn and Yahr scale (H&Y) were calculated as well. Statistical analysis was performed using Spearman correlation coefficient and Mann-Whitney test to compare groups.

Results: In the ON-state PIGD subscore correlated positively with dysfluency score ($p=0.04$) and negatively with speech intelligibility rate ($p=0.00$). Furthermore, patients presenting freezing of gait (FOG) had lower speech intelligibility rate compared to patients without FOG ($p=0.05$). This means that patients with higher axial impairment after levodopa intake were more disfluent and less intelligible. As regards disease severity, in the OFF-state H&Y score correlated negatively with maximum phonation time (MPT) of sustained phonation and speech intelligibility rate ($p=0.01$ and $p=0.04$ respectively), meaning that more severe PD patients had poorer speech quality. In the OFF- and ON-conditions, patients with speech dysfluencies had longer levodopa treatment duration than patient without speech dysfluencies (OFF: $p=0.03$; ON: $p=0.04$), regardless of levodopa equivalent dose (LED) and disease duration.

Conclusions: Our study confirm the possible correlation between speech and axial symptoms in advanced PD patients. Furthermore, MPT and speech intelligibility rate correlated with disease severity, so that they could represent possible markers of disease severity. Patients with speech disfluencies had longer history of dopaminergic treatment, but not necessarily longer disease duration or higher LED compared to patients without disfluencies.

SPEECH DISORDERS IN PARKINSON'S DISEASE: LONG-TERM EFFECTS OF BILATERAL STN-DBS

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Objective: To examine the long-term effects of bilateral subthalamic nucleus Deep Brain Stimulation (STN-DBS) on speech in advanced Parkinson's disease (PD) patients.

Background: Speech disturbances are very common and often disabling in PD. However, mixed and debated results have been reported regarding the effects of STN-DBS on speech parameters, particularly about long-term follow-up.

Methods: This observational study included 25 consecutive advanced PD patients treated with bilateral STN-DBS with a five years follow-up. We collected all available demographic variables, clinical characteristics and neuroimaging data. Each patient underwent a neurological evaluation and a perceptual-acoustic analysis of speech in both OFF- and ON-therapy conditions before surgery. The clinical assessment was performed using the Unified Parkinson's Disease Rating Scale (UPDRS) part III score and subscores. Subsequently, in the long-term postoperative follow up, each patient has been reevaluated with the same protocol in three different stimulation and drug conditions: on-stimulation/off-medication; off-stimulation/off-medication; on-stimulation/on-medication. The percentage change of speech intelligibility was evaluated by comparing preoperative off-medication condition with postoperative on-stimulation/off-medication condition. According to the presence/absence of postoperative worsening of speech intelligibility, PD patients were classified into two groups ("stable" versus "worsened") that were compared to find significant differences in demographic, clinical and speech variables.

Results: After surgery, speech intelligibility did not worsen in comparison to preoperative values. Bilateral STN-DBS resulted in a significant acute improvement of speech intelligibility ($p<0.005$) in the postoperative follow-up by comparing the on-stimulation/off-medication and off-stimulation/off-medication conditions. The "worsened" PD patients' group (n=9) before surgery had a greater severity of motor symptoms, while after surgery they had a lower intensity of spontaneous speech and

sustained phonation, higher shimmer of sustained phonation and worse speech intelligibility.

Conclusions: This study highlights the possible beneficial long-term effects of STN-DBS on speech intelligibility. Moreover, a better understanding of PD characteristics associated with long-term speech worsening after STN-DBS may be useful to achieve a greater prognostic accuracy and to employ early speech interventions, when necessary.

PHOSPHORYLATED A-SYNUCLEIN IN SKIN NON-MYELINATING SCHWANN CELLS: A NEW BIOMARKER FOR MULTIPLE SYSTEM ATROPHY

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Aim: A biomarker for multiple system atrophy (MSA) is urgently needed. MSA is characterized by the accumulation of phosphorylated α-synuclein (p-syn) as glial cytoplasmic inclusions (GCIs) in the brain. We aimed at investigating if p-syn can also be detected in skin Remak non-myelinating Schwann cells (RSCs) and may represent a reliable clinical biomarker for MSA.

Materials and methods: We included 96 patients: 46 with probable MSA (29 MSA-P and 17 MSA-C), 34 with Parkinson's disease (PD) and 16 with dementia with Lewy bodies (DLB). We also included 50 healthy control subjects. P-syn aggregates in skin sections were stained by immunofluorescence, followed by analyses with confocal microscopy (IFC) and immuno-electron microscopy (IEM). All analyses were performed in a blinded fashion.

Results: Overall, p-syn aggregates were found in 78% of MSA patients and 100% of patients with PD/DLB, whereas they could not be detected in controls. As for neuronal aggregates 78% of MSA patients were positive for p-syn in somatic neurons, whereas all PD/DLB patients were positive in autonomic neurons. When analyzing the presence of p-syn in RSCs, 74% of MSA patients were positive, whereas no such GCIs could be observed in PD/DLB patients. Analyses by IEM confirmed that GCIs were only found in cases with MSA and absent in those with PD/DLB.

Discussion: A specific biomarker for MSA would be valuable for clinical practice. The advent of techniques to detect abnormal α-syn may represent an important step forward for the identification of such a biomarker. Our current data based on a large cohort of MSA patients demonstrate that the detection of GCIs in RSCs of the upper derma yields a much better capacity than p-syn in skin neurons to discriminate MSA from other synucleinopathies, as no such deposits could be found in neither PD nor DLB.

Conclusions: 1) fibrillar p-syn in RSCs is a pathological hallmark of MSA and may be used as a specific and sensitive disease biomarker; 2) in Lewy body synucleinopathies (PD/DLB) only neurons contain p-syn deposits; 3) the cell-specific deposition of p-syn in the skin thus mirrors that of the brain in many aspects and suggests that also non-myelinated glial cells are involved in the MSA pathogenesis.

CORTICOBASAL SYNDROME AND PARKINSON'S DISEASE AT THE BEGINNING: USEFULNESS OF DIFFERENT ASYMMETRICAL PATTERNS FOR EARLY DIAGNOSIS

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Objectives: Differential diagnosis between Parkinson's Disease (PD) and Cortico-basal syndrome (CBS) could be challenging, especially at the early stage, due to the asymmetric onset of the diseases [1]. Despite the clinical overlap, the anatomical circuits involved in the occurrence of these disorders are different. Aim of the present study is to evaluate R2 Blink Reflex Recovery Cycle (R2BRRC) and cortical thickness in drug-naïve PD patients and in CBS patients for characterizing pathophysiological mechanisms underlying these conditions.

Materials & Methods: Patients with diagnosis of PD and CBS were recruited. R2BRRC was evaluated bilaterally at interstimulus intervals (ISIs) of 100-150-200-300-400-500-750 ms. Asymmetry index (AI) of R2BRRC for each ISI was computed [2]. Patients underwent a structural brain MRI using a 3-D T1-weighted and cortical thickness and MRI-AI was calculated.

Results: Fourteen drug-naïve PD patients and 10 patients with early CBS diagnosis were enrolled. R2BRRC of PD patients showed an increased brainstem excitability for less affected side (LAS) stimulation at ISIs of 100 and 150 ms ($p<0.001$) compared to most affected side (MAS), whereas no differences between LAS and MAS were found in CBS. R2BRRC-AI at ISI of 100 ms showed significant difference between groups, being higher in PD. Cortical thickness analysis showed significant differences between groups in left medialorbitofrontal, superiorfrontal and superiorparietal gyri and in total hemisphere cortical volume contralateral to MAS, and conversely, MRI-AI was significantly higher in CBS group.

Discussion & Conclusion: Drug-naïve PD patients exhibited an asymmetric pattern of brainstem excitability, compared to CBS. Conversely, CBS patients showed an asymmetric pattern of cortical atrophy. This opposite pattern of neurophysiological and structural abnormalities involving cortical and subcortical brain structures could highlight the different pathophysiological mechanisms underlying these neurodegenerative disorders.

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DUODENAL ALPHA-SYNUCLEIN PATHOLOGY AND ENTERIC GLIOSIS IN ADVANCED PD PATIENTS

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Objectives: In Parkinson's Disease (PD), the role of the gut-brain axis has been greatly highlighted by recent developments in both clinical and preclinical research. Considering the involvement of the enteric nervous system (ENS) in the prodromal stages of PD and its relationship with gut motility, the detection of αSyn aggregation and its deposition in gut tissues appears to be of great relevance. In the present study we aim to investigate the histopathological changes in the enteric nervous system by characterizing both αSyn aggregates and enteric glial responses in duodenum biopsies of advanced PD patients with extensive clinical and demographical documentation.

Materials: Fourteen patients with advanced PD who required initiation of Levodopa Carbidopa Intestinal Gel (LCIG) infusion and 10 control subjects comparable for age- and sex- undergoing screening diagnostic endoscopy were included in the study. Four 3 mm3 duodenal-wall biopsies were sampled in a topographically unrelated district to PEG-J placement for histopathological and immunohistochemical analyses.

Methods: Biopsies were fixed, paraffin-embedded, and microtome sectioned. Immunoperoxidase and immunofluorescent staining was performed for aggregated αSyn (Clone 5G4), Glial Fibrillary Acidic Protein (GFAP) and Beta-III Tubulin. Sections were evaluated by experienced morphologists and underwent morphometrical analyses for the quantification of immunoreactivites.

Results: Duodenal samples collected from PD patients were characterized by marked immunoreactivity for aggregated αSyn (14/14; 100%), while absent (2/10) or barely detectable (8/10) immunoreactivity was found in controls. Semi-automatic morphometrical quantification for aggregated αSyn revealed statistically significant higher immunoreactive tissue area in PD patients compared to controls (****$p<0.0001$). Thread-like aggregated αSyn reactivites were detected exclusively in PD patients, and colocalized with pan-neuronal maker Beta-III Tubulin, indicating aggregated αSyn deposits in duodenal nerve fibers. Morphometrical analyses revealed both increased EGC density and increased cell size when compared to controls (***$p = 0.0002$), suggesting for local reactive gliosis.

Discussion: In the present study, we documented marked immunoreactivity for aggregated αSyn and morphological changes in EGC suggestive of reactive gliosis in the duodenum of advanced PD patients. These findings expand our knowledge on the involvement of the enteric nervous system in PD and suggest the duodenum as possible target for early disease detection.

Conclusions: In conclusion, our data suggest that duodenal biopsy may represent a safe, feasible and useful tool for characterizing PD pathology in the GI tract and discerning patients from controls. Future studies will be required to confirm these findings in a prodromal or early PD phase.

CORRELATION BETWEEN COGNITIVE IMPAIRMENT AND OLFACTORY DISORDER IN PATIENTS WITH PARKINSON'S DISEASE

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Objectives: Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms (such as bradykinesia, tremor, rigidity, and postural instability). Moreover, PD is usually associated with non-motor symptoms (NMSs) such as olfactory dysfunction, sleep disorders, autonomic dysregulation, cognitive impairment and neuropsychiatric symptoms, (including apathy, and anxiety) [1]. Association between cognitive impairment and olfactory dysfunction in PD patients is still unclear. The aim of this study was to evaluate correlations between the role of each single cognitive domain and the olfactory function in PD patients.

Material: One hundred eighty-two PD patients (105 men and 77 women with a mean age of 70.2 ± 9.3) were included in this study. Patients with cognitive impairment were excluded. Methods. Olfactory function was assessed with the Sniffin' Sticks Extended Test (SSET) which evaluated Olfactory Threshold (OT), Discrimination (OD), Identification (OI) and their sum Threshold-Discrimination-Identification (TDI) scores [2]. The cognitive ability was evaluated by the Montreal Cognitive Assessment (MoCA). Significant correlations between the role of each single cognitive domain and the olfactory function in PD patients were calculated.

Results: Significant correlation was observed between odor threshold versus naming ($r = 0.183$, $p<0.05$) and attention ($r = 0.225$, $p<0.01$), as well as between odor discrimination versus executive function ($r = 0.164$, $p<0.05$) and abstraction ($r = 0.188$, $p<0.05$).

Discussion and Conclusion: The impairment of executive domain, abstraction and attention were significantly associated to worst scores in olfactory functions. These findings suggest common pathways between cognitive decline and olfactory dysfunction in PD. Moreover, specific cognitive impairment in single domain were also related to particular subtests, suggesting distinctive patterns related to different type of odor dysfunctions.

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THE PHENOMENON OF SPREAD TO AN ADDITIONAL BODY SITE IN PATIENTS WITH FUNCTIONAL MOTOR DISORDERS

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Objective: Functional motor disorders (FMDs) manifest with involuntary movements, weakness or gait disorders, which are typically inconsistent and incongruent with recognized neurological diseases [1]. FMD pattern my change over time in terms of body distribution and semiology of core functional motor symptoms. These changes may contribute to an apparently unpredictable clinical heterogeneity that may render it difficult to track disease pathways. The aim of this study is to assess changes in the body distribution and the semeiology of functional motor disorder in patients who reported only one or more than one body site affected at FMD onset.

Material and Methods: Data were obtained from the Italian Registry of Functional Motor Disorders, which included patients with a diagnosis of clinically definite FMDs [2]. The relationship between FMD features and spread to other body sites was estimated by multivariable Cox regression analysis.

Results: We identified 201 (49%) patients who reported only one body site affected at FMD onset and 209 (51%) who reported multiple body sites affected at onset. FMD spread from the initial site to another site in 43/201 (21.4%) patients over 5.7 +7.1 years in those with only one site affected at FMD onset; FMD spread to another body site in 29/209 (13.8%) over 5.5 + 6.5 years. The spread of FMD was associated with non-motor functional symptoms and psychiatric comorbidities only in the patients with one body site affected at FMD onset.

Discussion: The spread of FMD was significantly associated with other non-motor functional symptoms and psychiatric comorbidities in the patients who reported it starting at one body site, whereas none of the variables was closely associated with the risk of spread in the patients who reported multiple body sites affected at FMD onset. Our patients also experienced changes in FMD semeiology over time. This phenomenon was consistently more frequent among those who experienced spread to an additional body site, regardless of the number of body sites affected at onset.

Conclusion: Our findings provide novel insight into the natural history of FMD. The number of body sites affected at onset does not seem to have a consistent influence on the risk of spread. Furthermore, our findings suggest that psychiatric comorbidities and non-motor functional symptoms may predict the spread of FMD symptoms, at least in patients with one body site affected at onset.

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RIGIDITY IN PARKINSON'S DISEASE: THE VELOCITY-DEPENDENT FEATURE EVIDENCED FROM A NEUROPHYSIOLOGICAL STUDY

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Objectives: Seminal studies have demonstrated increased neural component (NC) of muscle tone and long-latency reflexes (LLRs) in patients with Parkinson's disease (PD) with rigidity. [1–3] However, the role of individual muscle components (i.e., NC, viscose component - VC and elastic component - EC) in determining the 'objective rigidity' in PD is still a matter of debate. Moreover, in PD patients, the putative velocity-dependent feature of neurophysiologic and biomechanical measures has never been assessed. Therefore, the aim of this study is to probe the velocity dependency of rigidity in PD, by simultaneously recording specific components of muscle tone, during robot-assisted wrist extensions, at various angular velocities.

Materials: We recruited 16 PD patients and 25 age- and sex-matched healthy subjects (HS). We used a robot-assisted device able to deliver controlled wrist extensions at six different angular velocities. All PD patients were evaluated in OFF therapy with L-Dopa.

Methods: All the participants underwent an experimental paradigm consisting of robot-assisted controlled wrist extensions at 50, 100, 150, 200, 236 and finally 280°/sec. For each value of angular velocity, we collected all the biomechanical components of muscle tone (i.e., NC, VC and EC). Also, we recorded the EMG activity from the right flexor carpi radialis (FCR) muscle which allowed to extract the short-latency reflexes (SLRs) and LLRs.

Results: We found that the NC and the amplitude and the AUC of LLRs were significantly higher in PD patients than in HS. Also, the higher the velocity, the greater the NC and the amplitude and the AUC of LLRs in PD patients, particularly from 200°/sec to 280°/sec. We also found a significant correlation between amplitude vs. AUC of the LLRs, NC vs. amplitude of the LLRs and NC vs. AUC of the LLRs.

Discussion: We demonstrated that parkinsonian rigidity is related to increased NC and LLRs. Also, for the first time, we demonstrated that objective rigidity in PD is dependent on the angular velocity of the muscle stretch.

Conclusions: Overall our findings suggest that NC and LLRs are the major contributors to the velocity-dependent objective rigidity in PD.

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THE ROLE OF DYSPHAGIA AS A POOR OUTCOME PREDICTOR IN ADVANCED PARKINSON'S DISEASE PATIENTS TREATED WITH LEVODOPA-CARBIDOPA INTESTINAL GEL

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Introduction: Dysphagia is a swallowing disturbance that can occur in every stage of Parkinson's disease (PD), worsening with disease progression and appearing more frequent in advanced and late PD stages. Dysphagia is known to affect quality of life (QoL), leading to malnutrition and representing an important risk factor for the development of aspiration pneumonia. Some studies have highlighted the pivotal role of dysphagia in predicting disease progression; however, no one involved advanced PD patients treated with levodopa-carbidopa intestinal gel (LCIG).

Objective: To evaluate the impact of dysphagia on the occurrence of poor outcome measure in advanced PD patients under LCIG treatment.
Methods: In this retrospective study, we considered 32 PD patients referring to our Movement Disorder Center who had started LCIG treatment between 2012 and 2022. Following medical records were collected: (I) demographic and clinical features; (II) detailed pharmacological therapy including LCIG dosage; (III) self-reported dysphagia; (IV) clinical outcome measures (H&Y, hospitalization, death). We considered a primary composed endpoint, including the outcomes of "death", "HY=5" and "hospitalization". Secondary endpoints were the outcomes of "death" and "HY=5".

Results: Among thirty-two advanced PD patients under LCIG treatment, "dysphagic" patients were 17 (53%) and "non-dysphagic" patients were 15 (47%). These two groups were similar in terms of age, gender, disease duration, age and H&Y at LCIG implantation, time of LCIG, presence of cognitive impairment and visual hallucinations. 10/17 dysphagic patients (59%) and 2/15 non-dysphagic patients (13%) met the primary endpoint ($p = 0.022$, LogOR 2.228). 8/17 dysphagic patients (47%) and 1/15 non-dysphagic patients (7%) met the secondary endpoint of "death" ($p = 0.032$, LogOR 2.521). 7/17 dysphagic patients (41%) and 1/15 non-dysphagic patients (7%) met the secondary endpoint of "H&Y=5" ($p = 0.066$, LogOR 4.529). 5/7 dysphagic patients (71%) who present H&Y=5, have presented an H&Y score <5 before the occurrence of dysphagia.

Discussion: The role of dysphagia in predicting the progression of PD in advances stage is well known, but data on PD patients under LCIG treatment are lacking. Our results show that in this population of PD patients, those with dysphagia presents a worst progression in term of occurring of death, hospitalization and high functional impairment.

Conclusion: Our study demonstrates that dysphagia represents a poor outcome predictor in terms of occurrence of death, high functional impairment, and hospitalization in advanced PD patients treated with LCIG, highlighting the importance of prioritizing its management.

DECREASE OF LEVODOPA EQUIVALENT DAILY DOSE IN PARKINSON PATIENTS TREATED WITH SAFINAMIDE: A THREE-YEARS' RETROSPECTIVE STUDY

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Objectives: Safinamide is a reversible monoaminoxidase B inhibitor used in the treatment of motor and non-motor fluctuations in Parkinson's disease (PD). A previous retrospective study demonstrated a significant reduction of levodopa equivalent daily dose (LEDD) in patients treated with safinamide after one year of follow-up. In this retrospective study, we aim to evaluate whether total LEDD reduction persists even after 3 years of follow-up and if there is a possible correlation with clinical phenotype.

Material and methods: Twenty-eight PD patients were evaluated at different time points: at the time of Safinamide prescription (T0), after one (T1), two (T2), and three years (T3). We collected data about clinical phenotype, disease duration, mean daily dose of LD, and LEDD of other PD drugs.

Results: We stratified the patients depending on clinical phenotype and disease duration (0-6 years or more than 7 years). The repeated-measures ANOVA showed in the akinetic-rigid group (9 patients) a significant constant decrease of the total LEDD in the following three years (T0-T1 p=0,003; T0-T2 p=0,013; T0-T3 p=0,040) with a mean decrease of 16% from baseline to T3. A slight though not significant LEDD increase was observed in patients with tremor dominant PD. Furthermore, the group with more than seven years of disease duration (15 patients) demonstrated a decreasing trend in total LEDD (-7% comparing T0 to T3) while in the other group (13 patients) we observed a growth in total LEDD (+8% comparing T0 to T3).

Conclusions: In conclusion, these results support the LD-sparing role of Safinamide even 3 years after its introduction. To the best of our knowledge, our study also highlights for the first time that this benefit is more relevant in PD patients with an akinetic-rigid phenotype and longer disease duration.
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PARKINSON'S DISEASE SUBTYPES AND EXTENSION OF NIGRAL DEGENERATION: EVIDENCE FROM A SCINTIGRAPHIC STUDY

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Objective: Parkinson's disease (PD) is highly heterogenous: considering motor symptoms, it can manifest as tremor-dominant (TDT), akinetic-rigid (ART) and mixed type (MT). The aim of this study was to evaluate the extension of nigrostriatal degeneration, investigated through 123I-FP-CIT single-photon emission tomography (SPECT), among these three clinical subtypes of PD. A supposed difference in striatal dopamine uptake may indicate different pathophysiology of this heterogenous disease.

Materials: We selected 57 patients (32 females, 25 males, mean age 59 ±9) with a diagnosis of idiopathic PD who performed 123I-FP-CIT SPECT, followed at Parkinson Centre of Tor Vergata University Hospital. We excluded any subject with cognitive impairment or suspect of atypical Parkinsonism.

Methods: Disease severity was evaluated through the Unified Parkinson's Disease Rating Scale (UPDRS) motor score and H&Y staging. Based on predominant motor features on UPDRS they were subtyped into 19 TDT, 23 ART and 15 MT. Quantitative SPECT analysis of ipsilateral and contralateral subregions of putamen and caudate were taken into consideration. We used one-way ANOVA to explore possible differences of age, UPDRS motor score, H&Y staging and disease duration between groups. We used Student t test to compare dopaminergic uptake between each phenotype.

Results: TDT, ART and MT were similar in matter of demographic and clinical variables (UPDRS III, H&Y, disease duration), whereas they

were significantly different in nigrostriatal uptake: in particular, in TDT patients, the 123I-FP-CIT uptake was higher in both caudate and putamen subregions compared to ART, but no compared to MT. Moreover, 123I-FP-CIT uptake in ART patients was significantly lower compared to MT in each striatal subregion explored.

Discussion: Dopamine active transporter (DAT) SPECT is a reliable tool in the diagnose of PD, whereas his association with clinical features and his role as a prognostic value of disease is still debated [1]. Our results, showing patients with tremor having less severe dopaminergic defect compared to patients without tremor, consist with the hypothesis that tremor in PD is generated by mixed mechanism that may involve cerebellothalamocortical circuits [2], other than nigrostriatal impairment. Besides, we supported the idea that neuroimaging can be useful to better clarify some aspects of pathophysiology in PD.

Conclusion: Identifying different PD subtypes is important for predicting, better profiling and managing the heterogeneity of PD: molecular imaging may have a role in early identification of different patient subtypes.

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A TWO-YEAR LONGITUDINAL STUDY OF COGNITIVE AND NEUROPSYCHIATRIC PROFILES OF VASCULAR PARKINSONISM

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Objective: Despite their high impact on quality of life, cognitive and neuropsychiatric profiles of vascular parkinsonism (VP) have not been fully elucidated and longitudinal data are lacking. Therefore, the aim of our study is to identify specific cognitive and neuropsychiatric profiles characterizing VP and compare them to patients with vascular dementia (VD), arteriosclerotic encephalopathy without or with minimal cognitive and motor impairment (AEWCM) and healthy controls (HC), at baseline (T0), 12 (T1) and 24 months (T2).

Materials and methods: Twenty patients with VP, 20 with VD, 20 with AEWCM and 20 HC were enrolled. All participants underwent a complete clinical, functional, neuropsychological, and neuropsychiatric assessment. Clinical and functional evaluation assessed motor and non-motor symptoms, and ability to perform activities of daily living. Neuropsychological battery included evaluation of global index of cognitive impairment, short- and long-term verbal memory, long-term visual-spatial memory, language abilities, complex constructional praxis, attention and executive functions. Neuropsychiatric evaluation assessed severities of anxiety, depression, apathy, alexithymia and anhedonia.

Results: Patients with VP scored significantly worse than HC at T1 and T2 in long-term verbal memory and at T2 in short-term verbal memory. VP group had increased impairment in the instrumental activities of daily living scale (IADL) at T1 and T2 respect to HC. Although no significant neuropsychiatric differences were found among groups, patients with VP exhibit higher total scores in the Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HARS) at T0, T1 and T2.

Discussion: Verbal memory impairment found in VP is consistent with some previous studies. We hypothesize that memory deficit can be related to subclinical depressive and anxiety symptoms detected, which are known to affect memory efficiency and, more specifically, the encoding memory processes. The reduced independence in IADL in VP may depend on memory impairment and motor difficulties. Other differences may not emerge because our patients with VP are younger and more educated than patients described in the current literature.

Conclusion: Our results suggest that VP is characterized by cognitive impairment and subclinical psychiatric symptoms. These findings emphasize the importance to follow longitudinally these symptoms in patients with VP to optimize the management of cognitive dysfunction and to promptly identify potential progression of neuropsychiatric symptoms from subclinical to clinical disorder. Further longitudinal studies and larger VP cohorts are needed to confirm our results.

Funding: This work was supported by grant from Ministero della Salute [GR-2016-02361783] to Francesca Assogna and Clelia Pellicano.

CSF BIOMARKERS IN PREDICTING MOTOR AND COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

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Introduction: Despite the urge of reliable diagnostic and prognostic biomarkers, no definitive biomarker for Parkinson's disease (PD) has been identified so far. Because of the complexity of the multifactorial pathophysiological processes underlying the disease, it has been hypothesised that a combination of multiple CSF biomarkers reflecting different pathological processes could represent the most suitable approach for providing an accurate diagnostic and prognostic model. The main purpose of this pilot study is to highlight the association between different CSF biomarkers and the magnitude of the clinical impact of PD, considering both motor and non-motor impairment, with special focus on cognitive impairment.

Methods: Twenty-seven patients with idiopathic PD with disease history of 4–10 years from the onset of symptoms and under medication with Levodopa for at least 3 years were included. Subjects with MoCA scoring ≤ 24 were excluded. All patients underwent an extensive neurological evaluation, comprehensive of UPDRS and neuropsychological assessments, and CSF collection. Quantifications of CSF biomarkers (α-synuclein, neurogranin, Aβ42, p-tau181, total-tau, YKL40, sTREM2, NfL) were conducted by automated assays. Correlations between continuous variables were investigated by means of Spearman's correlation coefficients; a linear regression model was built in order to study the impact of CSF biomarkers in predicting motor impairment as defined by UPDRS III.

Results: Significant correlations were found between levels of each CSF biomarker taken into examination, with the exception of Aβ42 and NfL. Considering neuropsychological measures, Aβ42 levels positively correlated with Mini-Mental State Examination (MMSE; $\rho=0{,}610$; $p<0{,}005$) and Semantic-Phonological Delta (SPD; $\rho=0{,}486$; $p<0{,}05$). Although no significant correlations were found between clinical scales and single CSF biomarkers, a multiple linear regression model including α-synuclein, Aβ42 and neurogranin showed an adequate statistical significance in predicting clinical motor impairment as defined by UPDRS III ($R2=0{,}489$; $p<0{,}005$); the inclusion of clinical variables such as age, disease duration and LEDD proved to be irrelevant.

Discussion & Conclusion: The evidence of numerous significant correlations among CSF biomarkers of neuroinflammation and neurodegeneration exploit the large complexity of PD pathogenetic mechanisms, in which different pathways contribute to its clinical manifestations. Furthermore, these results yield further support to the importance of the

role of Alzheimer's type pathology in PD clinical heterogeneity and corroborate the hypothesis that, despite no singular CSF biomarker being actually able to predict PD clinical status, the use of combinations of multiple biomarkers reflecting different pathological processes could improve diagnostic and prognostic accuracy.

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LONGITUDINAL EVALUATION OF PATIENTS WITH DYSTONIC AND ESSENTIAL TREMOR TREATED WITH MRGFUS THALAMOTOMY: ONE YEAR OUTCOME AND ADVERSE EVENTS PROFILE

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Objectives: MRgFUS thalamotomy is increasingly recognized as a safe and effective procedure for drug-resistant tremor in Parkinson's Disease and Essential Tremor (ET) [1]. On the contrary, data on its effectiveness and tolerability on patients with Dystonic Tremor (DT) are still scarce [2]. The primary aim of this project is to report our preliminary clinical findings on patients with DT treated with MRgFUS thalamotomy and to compare the effectiveness, radiological features and adverse events profile with patients with ET.

Materials: Between January 2019 and November 2021, 51 patients with ET and 9 with DT underwent MRgFUS thalamotomy in our Institute.

Methods: Patients were evaluated before surgery and 1-, 6- and 12-months after unilateral thalamotomy with The Essential Tremor Rating Assessment Scale (TETRAS). The position of the lesion was calculated on T1-weighted MRI one day and one month after thalamotomy.

Results: 9 patients with DT and 42 with ET reached the 6-months follow-up and were included in the analysis. In both groups, we found a similar and significant improvement in Activities of Daily Living (ADL) and in the clinical severity of tremor. At 12 months ADL improved by a median of 51.5% in DT and 47.0% in ET patients (p=0.268 between groups). At the same timepoint, tremor score for the treated side significantly dropped by a median of 64.1% in DT and 50.1% in ET (p=0.247 between groups). The analysis of the position of the final lesion revealed that in DT it was positioned a median of 1.5 mm anterior to the initial target, probably in the VoA/VoP complex. No adverse effects were reported in the DT group during the follow-up. Conversely, in the ET group we observed persistent, albeit mild and uncommon, adverse effects.

Discussion: We confirm the effectiveness and overall tolerability profile of thalamotomy in ET patients that has been already reported in the literature [1]. We report a series of DT patients in which we found a similar improvement in tremor score and ADL (compared to ET patients) but without any persistent adverse effect. A more anterior (compared to the VIM) thalamic target to treat dystonic tremor has already been suggested by others [3] in a series of DT patients treated with deep brain stimulation.

Conclusion: MRgFUS Thalamotomy may be an effective and particularly safe treatment for dystonic tremor. Studies with larger sample sizes are needed to confirm our preliminary results.

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MRGFUS THALAMOTOMY MAY SPARE DOPAMINERGIC THERAPY IN EARLY-STAGE TREMOR-DOMINANT PD: A PILOT STUDY

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Objectives: MRgFUS thalamotomy is a safe and effective procedure for drug-resistant tremor in Parkinson's Disease patients [1,2]. The primary objective of this study was to demonstrate that MRgFUS VIM thalamotomy in early-stage tremor-dominant PD patients may prevent an increase in dopaminergic medication 6 months after treatment, compared to a matched control sample of PD patients on standard medical therapy alone.

Materials: We included patients with early-stage PD [3] who underwent MRgFUS VIM thalamotomy (PD-FUS) and patients treated with only standard dopaminergic therapy (PD-ODT) with a 1:2 ratio.

Methods: We collected demographical, clinical data (mainly the motor score by means of MDS-UPDRS-III and the Levodopa-Equivalent Daily

Dose, LEDD) and adverse events at baseline and at 6- and 12-months follow-up.

Results: We included 10 patients in the PD-FUS group and 20 patients in the PD-ODT group. We found a significant increase in total LEDD and LEDD of levodopa plus MAOB-I in the PD-ODT group 6 months after the procedure, while LEDD in PD-FUS remained unchanged. In both groups we observed an improvement in total MDS-UPDRS-III; in the PD-FUS group, this was driven by the dramatic reduction of tremor.

Discussion: In this pilot study we found that after MRgFUS there may be a stabilization of LEDD lasting six to twelve months after surgery. We can confirm the effectiveness of MRgFUS thalamotomy in improving tremor in PD patients [1,2]. Regarding the adverse events, no significant differences were found between PD-FUS and PD-ODT and we can confirm previous data on the safety profile [1].

Conclusions: In early-stage tremor dominant PD patients, MRgFUS thalamotomy may be safe and useful to reduce tremor and avoid the need to increase dopaminergic medications.

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LEVODOPA-RESISTANT AXIAL SYMPTOMS: RESPONSE TO SUPRAMAXIMAL LEVODOPA DOSES

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Objectives: Management of freezing of gait (FoG) and other axial symptoms in Parkinson's disease (PD) is challenging, since their response to dopaminergic therapies is complex. Systematic assessments of their response to progressively increasing levodopa doses are lacking. Our objective was to analyze the resistance to high levodopa doses of FoG, posture, speech, and gait features in PD patients during a daily-ON therapeutic condition.

Materials: We conducted a pre-post interventional study in patients treated with levodopa/carbidopa intestinal gel (LCIG) infusion and with good control of motor symptoms and fluctuations, experiencing disabling FoG in daily-ON condition. Patients were evaluated in three consecutive therapeutic regimens: the usual LCIG infusion rate (T1) and one hour after 1.5x (T2) and 2x (T3) increase of the LCIG infusion rate.

Methods: Primary outcome was the FoG improvement, blinded assessed as the reduction in the count of FoG episodes during a two-minute walk test. Posture and speech improvement by means of standardized test objectively evaluated by blinded rater were secondary endpoints. Gait parameters from inertial motion sensors were collected in a subgroup of patients.

Results: We evaluated sixteen patients with a mean age of 69±9.4 years, treated with LCIG for a mean of 2.2±2.1 years. FoG improved in 83.3% of patients. The number of FoG episodes significantly decreased at each study phase, from a mean of 2.3 at T1 to 1.2 at T3 (p: 0.013). Posture and speech parameters did not show significant changes, while gait and balance analysis in twelve patients showed a significant improvement of stride length (p: 0.049), turn duration (p: 0.001), and turn velocity (p: 0.024) at T2.

Discussion: FoG episodes and gait analysis (in a subgroup of patients) significantly improved after doubling the LCIG infusion rate, while the objective analysis of posture and speech did not show significant changes. Maladaptive plasticity caused by long-term levodopa treatment could be implicated in the difficulty to manage axial symptoms in advanced PD phases. Other possible explanation is the presence of a "Triphasic-ON" FoG, arising in both "ON" and "supra-ON" states, with a narrow therapeutic window between these two states where FoG improves, difficult to achieve with oral therapy.

Conclusions: The increase of levodopa doses can improve 'dopa-resistant' FoG and gait issues in most PD patients with overall optimal control of their symptoms and fluctuations, in the absence of clinically significant dyskinesia worsening. The lack of posture and speech improvements could be due to their different pathophysiology.

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OBJECTIVE OUTCOME MEASURES OF LEVODOPA-CARBIDOPA INTESTINAL GEL EFFICACY ON FREEZING OF GAIT AND OTHER FEATURES OF GAIT: PRELIMINARY RESULTS FROM A 6-MONTHS PROSPECTIVE STUDY

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Objectives: Clinical evidences from the literature suggested that continuous infusion of levodopa-carbidopa intestinal gel (LCIG) may improve Freezing of gait (FoG) and gait difficulties in advanced Parkinson's disease (PD), also in cases refractory to oral dopaminergic therapy. These assessments were primarily conducted by means of expert-delivered rating scales of PD signs and patient judgment of severity of symptoms. The aim of this study is to evaluate the efficacy of LCIG on FoG and spatiotemporal gait parameters in advanced PD patients by means of objective, observer-independent outcome measures.

Materials: This is a 6-month explorative, observational pilot study enrolling patients screened as candidates for LCIG therapy, currently including in the sample 9 patients with several episodes of FoG a day in the month preceding the baseline evaluation. Assessment of FoG and spatiotemporal gait parameters was conducted by means of APDM Mobility Lab™ motion sensors, and with the New Freezing of Gait

Questionnaire (NFoG -Q) for evaluation of patient's subjective impression.

Methods: Assessment by sensors was first performed at baseline, before percutaneous endoscopic gastrojejunostomy implant, in the OFF (after the complete withdrawal of dopaminergic therapy for at least 12 hours) and best-ON oral antiparkinsonian therapy condition and repeated 3 and 6 months after starting the LCIG therapy, during daily-ON condition.

Results: 5 of 9 patients have currently completed the 6-month follow-up, with a significant improvement at the NFOG-Q (from 15,8±4,2 to 10,6±6,1, p=0,013). Results from motion sensors indicate an improvement from baseline best-ON to 6 months daily-ON: a trend is valuable at the Two-minute walking test for gait speed and step duration (increase) and double support (reduction), at the Timed up and go test for duration (reduction), at the 360 degrees Turn Test for Turn angle (increase), and at the Sway test for Sway area (reduction).

Discussion: Our findings confirm previous reports about efficacy of LCIG on FoG and gait impairment in a short-term assessment, improving clinical performance even respect to the best-on phase in oral dopaminergic therapy. Interestingly, patients performed and felt better at six months than at three months assessment: these findings could indicate the need for a longer time to induce synaptic plasticity processes within neuronal networks implicated in the genesis of the FoG.

Conclusions: Preliminary results from motion sensors suggest an improvement of gait features and FoG six months after LCIG start, confirmed by patients' subjective impression.

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COGNITIVE AND AUTONOMIC DYSFUNCTION IN MULTIPLE SYSTEM ATROPHY

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Objective: MSA is a rare pleiotropic lethal neurodegenerative disease, whose clinical hallmark is the combination of progressive autonomic dysfunction and extrapyramidal and cerebellar signs. Dementia is considered a non-supporting feature in the current diagnostic criteria for MSA. Nevertheless, the evidence of cognitive impairment among MSA patients is growing [1]. The link between cardiovascular dysautonomia and cognitive involvement also remains to be clarified, together with the possible differences between the two motor phenotypes. The aim of the present study is to assess cardiovascular function and cognitive profile, evaluated with a thorough neuropsychological battery, in patients suffering from MSA, and subsequently to explore a potential link between dysautonomia and cognitive performances.

Materials and methods: All patients underwent a complete neurologic and neuropsychological evaluation, assessing global cognitive functioning, attention, executive functions, deductive reasoning, verbal fluency, memory, and praxis. Autonomic function was assessed by means of beat-to-beat blood pressure measurement and ECG registration, with subsequent heart rate variability (HRV), at rest and upon active standing.

Results: 9 MSA-P and 11 MSA-C patients were recruited. No difference was observed in terms of age, disease duration, disease severity, and autonomic dysfunction (OH, SH, HRV). All patients had normal MoCA scores. TMT was abnormal in 25 % (part A) and 20% (part B) of patients; Verbal Fluency in 10 %, Digit span in 25 % forward and 10 % backward, Corsi block in 15% forward and 10% backward, Prose Memory in 25 % of patients, Clock Drawing Test in 5 %, FAB in 10%, and PASAT in 15% of patients. MSA-C showed worse performances at Attentional Matrices (p=.045), TMT part B (p=.045) and B-A (p=.035), Clock Drawing Test (p=.029) and FAB (p=.034). No significant correlations were found between neuropsychological tests and autonomic functions.

Discussion: This is, to our knowledge, the first study assessing cognitive and autonomic functions in the same experimental session in MSA. MSA-C patients reached lower scores in tests of executive functions and verbal memory, no statistically significant difference in cardiovascular autonomic parameters was identified between the two groups. Further prospective studies, with more copious cohorts and longitudinal assessments, are needed to understand whether MSA-P and MSA-C may have distinctive patterns of cognitive involvement and elucidate the possible role of concomitant dysautonomia.

Conclusions: In a context of good cognitive functioning, patients with MSA-C performed inferiorly in attentive-executive tests compared to MSA-P patients [1]. However, this does not appear to be related to a different impact of autonomic dysfunction.

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CAREGIVER'S BURDEN IN CARDIOVASCULAR DYSAUTONOMIA ASSOCIATED WITH PARKINSON'S DISEASE

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Objective: Cardiovascular autonomic neuropathy (cAN) is one of the most common disabling and frequently unrecognized features of Parkinson's disease (PD), with an estimated prevalence of at least 30-50%. However, its impact on caregivers' burden has been scarcely investigated. We sought to estimate the impact of cAN on informal caregivers of patients with PD, defined as individuals providing regular care to a friend, partner, or family member with PD, and to evaluate the mutual relationship between caregivers' burden and patient health-related quality of life (HRQoL).

Materials: We enrolled 36 consecutive PD patients and their caregivers. The clinical assessment encompassed the MDS Unified Parkinson's Disease Rating Scale, the Montreal Cognitive Assessment (MoCA), 39-Item Parkinson's Disease Questionnaire (PDQ-39, Single Index), and the Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire (SCOPA-AUT). The cAN assessment included a

standardized battery of autonomic tests, scored by means of the Composite Autonomic System Score (CASS). Caregivers were assessed by means of the Zarit Burden Interview (ZBI).

Methods: Differences in caregivers' burden and strength of association between caregivers' burden, cAN severity, and patients' HRQoL were assessed using ANCOVA, logistic regression, and linear regression analyses. Analyses were adjusted for patients' and caregivers' age, PD duration, PD motor and cognitive disability.

Results: cAN+ patients showed a significantly higher impairment in non-motor and motor experience of daily living (MDS-UPDRS part I and II), lower MoCA scores, and higher PDQ-39 single index scores. Moderate-severe caregivers' burden was reported in 41.7% of PDcAN+ vs. 8.7% of PdcAN- ($p<0.001$). The ZBI score was higher in PdcAN+ vs. PdcAN- (31.48±3.36 vs. 15.23±2.31; $p<0.001$), with 10-fold higher odds ($p= 0.012$) of moderate-severe caregivers' burden in PdcAN+, even after adjusting for potential confounders, such as patient's age, disease duration, cognition, motor disability, and caregiver's age. The ZBI score directly correlated with higher CASS (Beta= 0.466; $p= 0.005$), SCOPA-AUT (Beta= 0.432; $p= 0.012$), and PDQ-39 single index (Beta= 0.627; $p<0.001$) scores.

Discussion: Our study highlights the independent role of cAN in determining a moderate-to-severe caregivers' burden, with a direct correlation between ZBI scores and cAN severity. Importantly, we found a strong association between caregivers' burden and patients' HRQoL.

Conclusion: These results highlight the significant impact of cAN on PD caregivers, with caregivers' distress possibly reflecting on the patient's quality of life, and viceversa. Our findings underline the need for targeted interventions addressing this frequently overlooked and insufficiently treated source of disability in PD.

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PRESURGICAL AXIAL SYMPTOMS AND SUBTHALAMIC DEEP BRAIN STIMULATION OUTCOME IN PARKINSON'S DISEASE

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Objective: Subthalamic Deep Brain Stimulation (STN-DBS) is an established therapy for Parkinson's disease (PD) patients not adequately controlled by medical therapy; however, some patients fail to obtain a significant benefit. We sought to identify clinical and demographic factors predicting bilateral STN-DBS outcomes.

Materials: At the time of surgery, we collected sex, age, disease duration, levodopa equivalent daily dose (LEDD), and cognitive data. The presurgical motor evaluation was performed during a levodopa challenge test.

Methods: We analyzed data of 181 PD patients treated with STN-DBS. The Wilcoxon test was used for comparisons between pre- vs. 1-year post-surgical scores of motor score (UPDRS-III), dyskinesia (UPDRS 4.1), Off time (UPDRS 4.3), and Activities of daily living (ADL - UPDRS II). A multivariate linear regression analysis was used to evaluate the association between main clinical/demographic characteristics and the extent of STN-DBS response.

Results: We observed a significant improvement of motor symptoms ($P<0.001$), dyskinesia ($P<0.001$), and daily Off time ($P<0.001$) 1 year after surgery. ADL did not change significantly. Sex, age, PD duration, levodopa equivalent daily dose, motor response at the levodopa challenge test (LCT), cognitive status, and axial symptoms in Off and On condition explained 15.5% of the motor improvement ($R = 0.394$, $P = 0.011$), with severity of axial symptoms in Off (Beta = 0.103, $P = 0.012$) and On condition (Beta = −0.132, $P = 0.043$) being the strongest predictors of improvement. The same model explained 21.2% of the daily Off time improvement ($R = 0.460$, $P < 0.001$), with the severity of axial symptoms in Off condition and pre-surgical motor response to levodopa (Beta = 1.633, $P = 0.023$) being the strongest predictors of improvement (Beta = 0.538, $P < 0.001$). The dyskinesia improvement was not significantly explained by the model, with disease duration being the only significant predictor of variance (Beta = 0.054, $P = 0.010$).

Discussion: We found that higher severity of axial symptoms in the Off and the lower severity in the On condition are important predictors of DBS outcome. These data strengthen the relevance of the LCT in predicting DBS outcome, with a special consideration to the response of axial symptoms to levodopa.

Conclusion: Our findings highlight the relevant role of axial symptoms as predictors of STN-DBS outcome. A deeper phenotypic characterization of patients is warranted for a fine-grained stratification of candidates and to choose the most appropriate device-aided therapy.

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RISK FACTORS ASSOCIATED TO PARKINSON'S DISEASE: A CASE-CONTROL STUDY

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Objective: With the increased life expectancy worldwide, the number of individuals with Parkinson's disease (PD) is expected to increase by more than 50 % by 2030. Our objective was to investigate lifestyle and exposure to various environmental factors with the aim of highlighting possible new associations with the onset of PD.

Materials: We enrolled 264 PD patients and 277 healthy controls from three clinical centers, between 2016 and 2018, and conducted a questionnaire-based case-control study. We assessed demographic characteristics, place of residence, comorbidities, marital status, occupation, hobbies, sports activity, smoke-alcohol consumption, and diet.

Methods: Controls were matched with cases for age, sex, and province of residence. Statistical analyses were conducted using the t-test for continuous variables and the chi-square test for categorical ones.

Results: There was no significant difference regarding marital status and demographic characteristics between cases and controls. Gynecological conditions and previous appendicectomy were significantly more frequent among controls (p=0.044 and p=0.00001, respectively). Occupational exposure to solvents (p=0.049) and metals and metal fumes (p=0.002), and recreational exposure to solvents (p=0.02), pesticides (0.024) and glues (p=0.038), was higher among cases. Overall, there was a statistically significant difference in sport activity (p=0.027) and in activities performed outdoors (p=0.016), with higher prevalence in the controls group. Controls were active smokers in greater numbers than cases at the time of the questionnaire, with a statistically significant difference (p=0.0009), while no significant differences were found in alcohol consumption. In the dietary regime survey the only difference was in cereal consumption (p=0.0018), which was greater among controls.

Discussion: In agreement with the literature, we have found exposure to environmental pollutants (pesticides, solvents, glues and metals) and cardiovascular diseases to be risk factors, and sports, tobacco use and appendicectomy to be possible protective factors for the development of PD. In addition, our data suggest that other factors, such as gynecological conditions and cereal consumption, can be protective, highlighting a possible role of estrogens and food in modifying the risk of developing PD.
Conclusions: Our findings highlight the possible relevant role of environmental and lifestyle factors in the development of Parkinson's disease. In view of the increasing prevalence of the disease, it is important to carefully consider every possibility of prevention and early diagnosis.
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PHYSIOTHERAPY WITH DUAL TASKS IMPROVES COGNITION AND RESTING-STATE FUNCTIONAL CONNECTIVITY IN PARKINSON'S DISEASE WITH POSTURAL INSTABILITY AND GAIT DISORDERS

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Objectives: To explore whether dual-task with Action Observation Training (AOT) and Motor Imagery (MI) ameliorates cognitive performance and resting-state (RS) brain functional connectivity (FC) in Parkinson's disease (PD) patients with postural instability and gait disorders (PIGD).

Materials: 20 PD-PIGD patients were randomized into 2 groups: i) DUAL-TASK+AOT-MI group, who performed a 6-week training consisting of AOT-MI combined with practicing observed-imagined gait and balance exercises; ii) DUAL-TASK-group, who performed the same exercises combined with landscape-videos observation.

Method: At baseline and after the 6-week training, all patients underwent neurological and motor evaluations, computerized cognitive assessment (through the Cambridge Neuropsychological Test Automated Battery) and RS functional MRI scans. Cognitive and RS-FC changes (and their relationships) over time within and between-groups were assessed.

Results: After training, all PD-PIGD improved in terms of accuracy and reaction times in test assessing executive-attentive (mainly dual-task) skills. At 6-week visit, DUAL-TASK+AOT-MI group had increased RS-FC within the Anterior Salience Network (aSAL), right Executive Control Network and Precuneus, and reduced RS-FC within the anterior Default Mode Network (aDMN). Instead, DUAL-TASK group showed increased RS-FC within the Visuospatial Network. Group x Time interactions showed that, compared to DUAL-TASK group, DUAL-TASK+AOT-MI group showed increased RS-FC within the aSAL, which correlated to reduced response latency, and reduced RS-FC within the aDMN, which correlated to better accuracy in executive-attentive tests.

Discussion: In PD-PIGD patients, both trainings promote cognitive improvement and brain functional reorganization. DUAL-TASK+AOT-MI training is further useful for obtaining a functional reorganization of extra-motor brain networks involved in motor control and executive-attentive abilities with specific effects on dual-task mobility and balance.

Conclusions: The combination of AOT and MI with dual-task training can ameliorate the performance of PD-PIGD patients in those cognitive domains which are the most challenging for these patients.

VIRTUAL REALITY FOR REHABILITATION IN PARKINSON'S DISEASE AND ATYPICAL PARKINSONISMS

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Objectives: To determine the potential long-term effect of Virtual Reality (VR) in improving motor and cognitive impairment in Parkinson's disease (PD) and Atypical Parkinsonisms (AP).

Design: Retrospective cohort study with 2-years follow-up. Setting: Rehabilitation hospital. Participants: Inpatients with extrapyramidal disorders (N=12).
Interventions: Neurorehabilitation treatment with the use of VR treadmill, 60 minutes a day, five days a week, for four weeks every year from 2019 to 2021.

Main outcome measures: UPDRS III score at entry and discharge and MMSE score. Results: 3/12 patients were diagnosed with PD and 9/12 patients were diagnosed with AP. The UPDRS III score was 43.3 ± 5.8 at entry in 2019 vs 35 ± 4.4 at discharge in 2021 in PD (p-value 0.01, SMD 1.63); 45.6 ± 9.0 at entry in 2019 vs 34.4 ± 7.2 at discharge in 2021 in AP (p-value 0.00002, SMD 1.36). The MMSE score was 23.5 ± 2.5 in 2019 vs 23.7 ± 2.4 in 2021 in PD (p-value 0.53, SMD 0.07); 19.7 ± 3.9 in 2019 and 18.9 ± 3.9 in 2021 in AP (p-value 0.02, SMD 0.22).

Conclusions: Current literature has demonstrated the effectiveness of VR in the neurorehabilitation of motor and cognitive disorders in PD patients, but only in the short-term. Analysis of our data showed short-term and long-term benefits to the motor performance for both PD and AP patients. Despite the limited sample size, the promising results obtained encourage a continuation of the research by including other functional outcome measures, especially when considering the lack of studies on the benefits of rehabilitation in Atypical Parkinsonisms.

ALZHEIMER DISEASE BIOMARKERS IN CLINICAL SUBTYPES AND MOTOR PROGRESSION OF PARKINSON'S DISEASE

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Introduction: In this study, we evaluated the ability of a panel of plasma biomarkers to predict disease progression in PD patients.

Materials: We measured plasma p-tau181, p-tau231, Aβ40, Aβ42, GFAP and NfL using Single molecule array (Simoa) assays in healthy controls (HC) and consecutive PD patients who underwent an extensive motor and non-motor assessment at baseline and two to five years of follow-up.

Methods: Differences in biomarkers level between PD and HC were evaluated adjusting for the effect of age and sex. In PD patients, the correlation between plasma biomarkers and motor scores at baseline and at follow-up were evaluated using partial correlation analyses. Linear regression and Cox regression analyses were applied to evaluate the best combination of biomarkers able to predict motor progression and disability milestones adjusting for the effect of age, sex disease duration and baseline severity.

Results: One hundred seventy PD and 106 HC entered the analyses. PD patients exhibited higher p-tau181, p-tau231 and lower Aβ42 compared with HC but similar NfL, GFAP and Aβ40 levels. All biomarkers correlated with age and disease duration, whereas NfL, GFAP and ptau181 additionally correlated with baseline motor severity. At follow-up, NfL emerged as best predictor of motor progression (linear regression analyses).

Discussion: We demonstrated NfL as the best biomarker predictor of motor severity and motor progression of disease in PD, being the only one able to indipendently predict motor progression measured by UPDRS-III. However, our results showed that including other biomarkers could improve the predicting capacity of the model.

Conclusions: The present findings confirm plasma NfL as the best predictor of motor progression in PD in comparison with other plasma biomarkers. Larger on-going studies with longitudinal plasma assessment are needed to evaluate the potential value of other biomarkers for identifying co-pathologies or defying subtypes of disease suitable of different intervention strategies.

ASSOCIATION BETWEEN TOTAL ELECTRICAL ENERGY DELIVERED AND VERBAL FLUENCY SIX MONTHS AFTER SUBTHALAMIC DEEP BRAIN STIMULATION IN PATIENTS WITH PARKINSON'S DISEASE

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Objective: Worsening of verbal fluency after treatment with deep brain stimulation of the subthalamic nucleus (DBS-STN) in Parkinson's disease (PD) patients is one of the most often reported cognitive adverse effect. We investigated the cognitive outcome in PD patients after bilateral DBS-STN, and the possible effect of the amount of total electrical energy delivered (TEED) on neuropsychological alterations.

Material: Twenty-one patients with PD (10 female, mean [±SD] age 59 ± 7.07 years) who underwent bilateral STN-DBS were included in this study.

Methods: Cognitive functions were assessed in all patients using the Montreal Cognitive Assessment (MoCA) [1], phonemic [2] and semantic verbal fluency test [3] before surgery (T0) and 6 months after STN-DBS implantation (T1). At T1, we recorded stimulation parameters, in order to estimate TEED to the STN.

Results: One-way repeated measures ANOVAs revealed a significant main effect of 'Time' on phonemic fluency ($F [2,40] = 10.39$; $p < 0.001$; $\eta 2 = 0.34$) and semantic fluency ($F [2,40] = 11.21$; $p < 0.001$; $\eta 2 = 0.33$). Bonferroni-corrected post-hoc tests showed that phonemic and semantic verbal fluency worsened at T1 (phonemic fluency T0 vs T1: mean ± SD = 42.38 ± 10.85 vs. 36.33 ± 10.80; $p = 0.001$; semantic fluency T0 vs T1: mean ± SD = 48.14 ± 8.36 vs. 40.86 ± 9.41; $p < 0.001$). There was no significant main effect of 'Time' on MoCA test ($F [2,40] = 1.04$; $p = 0.362$). TEED did not differ significantly between the left and right STN at T1 ($t (16) = 0.533$; $p = 0.601$). We found no significant correlations between cognitive performance and TEED left ($p > 0.05$), TEED right ($p > 0.05$), or TEED laterality ($p > 0.05$).

Discussion: Our preliminary observations suggest that STN-DBS can be considered a significant contribution to the treatment of severe PD, although it can induce language changes. Chronic stimulation has been proposed as an underlying mechanism, but we did not find a correlation with TEED.

Conclusions: It is possible that these and other effects underlie the etiology of cognitive sequences in DBS of the STN, and that factors such as patient age, preoperative neuropsychological functioning, surgical trauma, electrode placement within subdivisions of STN, and natural history of PD interact in a complicated manner to influence the outcome. Finally, we highlight the need for more systematic investigations of the large degree of heterogeneity in the prevalence of verbal fluency worsening after DBS, as well as provide suggestion for future research.

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COMPLICATIONS OF CONTINUOUS LEVODOPA-CARBIDOPA INTESTINAL GEL FOR ADVANCED PARKINSON'S DISEASE

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Background: Levodopa-carbidopa intestinal gel (LCIG) is a therapy of the advanced stage of Parkinson's Disease (PD) helpful in diminishing dyskinesia and motor fluctuations, providing a stable level of levodopa in plasma and avoiding interferences with foods in stomach.

Purpose: Complications are common in percutaneous endoscopic gastrostomy with a jejunal extension tube (PEG-J). We report our data on LCIG in patients with advanced PD in the years 2012-2021.

Findings: All complications were retrospectively analyzed. 52 patients with advanced PD had LCIG treatment and followed for 12 months. We found a total of 85 complications. The most common complications were tube occlusion, granulation in stoma and stoma diastases with leaking and skin problems. We didn't find cases of death related to PEG-J complications.

Conclusion: Our data show a reduction of complications in comparison with other reports regarding the safety of LCIG therapy in appropriate PD patients in advanced stages of the disease. This result is related to the improvement of the technique and to a close co-operation between neurological and endoscopic units.

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SUPPLEMENTARY MOTOR AREA FUNCTIONAL CONNECTIVITY IN "DRUG-NAÏVE" PARKINSON'S DISEASE PATIENTS WITH FATIGUE

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Aims: Fatigue is a common and disabling nonmotor manifestation in patients with Parkinson's disease (PD), and the supplementary motor area (SMA) has been implicated in its pathophysiology. SMA is usually divided in its rostro-caudal axis, with the rostral (pre-) SMA playing a major role in motor planning, and the caudal (proper) SMA related to movement execution. In this study we aimed at investigating brain functional connectivity of SMA subregions in early, drug-naïve PD patients.

Materials: Seventeen PD patients affected by fatigue, 18 without fatigue, and 16 matched healthy controls were recruited. All the participants were not depressed and did not suffer from daytime sleepiness.

Methods: Parkinson Fatigue Scale (PFS) was used for fatigue screening (cut-off > 3.3 points) and severity rating. Seed-based resting-state functional MRI was used to compare the functional connectivity from bilateral SMA subregions to the whole brain. Voxel-based morphometry analysis was also employed to test whether functional connectivity results were related to brain structural differences. Linear correlations were run between imaging and behavioural data.

Results: PD-related fatigue was associated with an increased connectivity between the left pre-SMA and the left postcentral gyrus as well as a decreased connectivity between the left SMA proper and the left middle frontal gyrus (ps < 0.01). These patterns of functional connectivity were tightly correlated with PFS scores (Pearson's rs < 0.01). No structural brain changes were observed.

Discussion: The altered connectivity of the pre-SMA might underlie a poor attenuation of sensory signals from the somatosensory systems to higher order motor system, whereas the altered connectivity of the SMA proper might be associated to poor explicit contingency awareness causing an overgeneralization of perceived physical effort load.

Conclusions: In early PD, altered functional connectivity of both SMA subregions might play a crucial role in fatigue pathophysiology. These results offer new insights into the mechanisms responsible for fatigue in PD, suggesting possible targets for neuromodulation strategies oriented to modulate the SMA activity. Further studies involving larger PD populations are needed to support our hypothesis.

DIFFERENCES IN KINEMATIC AND SPATIO-TEMPORAL PARAMETERS ASSESSED BY INSTRUMENTED "TIMED UP AND GO" TEST BETWEEN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS ASSOCIATED WITH PARKINSONISM AND PARKINSON'S DISEASE

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Objectives: To assess differences in quantitative gait parameters and motility during standardized tasks between idiopathic Normal Pressure Hydrocephalus (iNPH-P) and Parkinson disease (PD).

Materials: We selected one group of 21 patients with clinical diagnosis of "possible iNPH" by adapted Relkin criteria and the simultaneous presence of parkinsonism in accordance with the MDS diagnostic definition. We enrolled another group of 21 patients of newly diagnosed "clinically probable" PD based on current MDS diagnostic criteria, who were untreated with dopaminergic medication.

Methods: Both iNPH-P and PD patients performed the instrumented Timed Up-and-Go test (iTUG) at the time of the diagnosis, wearing an inertial sensor. For each of the six phases of the test, several kinematic parameters were recorded: phases duration; average and peak angular speeds during turning; accelerations in antero-posterior, medio-lateral and vertical axes; spatio-temporal parameters of gait during walking.

Results: The mean age was significantly higher for iNPH-P as compared to PD (71.4±10.7 vs 60.6±10; p=0.007). MMSE score was significantly lower in iNPH-P (23.9±4.3 vs 27.9±1.3; p =0.003). There were no significant differences in disease duration (2.7±2.3 vs 2.9±2.1; p =0.788) and UPDRS-ME score (23.8±8.6 vs 28.5±10.3; p =0.154) between the two groups. Concerning iTUG performances, both turning tasks showed significantly longer duration in iNPH-P, while peak and average angular speeds were lower. Vertical variation in acceleration during the sit-to-stand phase was lower in iNPH-P patients while duration of the stand-to-sit phase was significantly longer. iNPH-P showed smaller stride length and a longer gait cycle duration with a more represented swing and single support phase. At multivariate analysis adjusting for age and MMSE as potential confounders, average angular speed on turning-before-sitting was the discriminating parameter between the two groups. Applying ROC curve analysis, an average angular speed cut-off of 49 °/s on turning-before-sitting discriminated iNPH-P from PD with a sensitivity of 67% and a specificity of 91%.

Discussion: When adjusting estimates for possible confounding effects due to age and cognition, average angular speed on turning-before-sitting remained the only significant kinematic parameter differentiating the two groups. This peculiar task is expression of kinematic adaptation on turning preceding postural adjustment before sitting, and it may reflect a specific abnormal postural control in iNPH-P patients.

Conclusion: Patients with iNPH-P showed specific abnormal balance performances with respect to untreated PD, specifically during adaptation manoeuvres and postural changes.

CORTICAL THINNING IN PATIENTS WITH VASCULAR PARKINSONISM: PRELIMINARY FINDINGS FROM CORTICAL THICKNESS EVALUATION

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Background and objective: Vascular parkinsonism (VP) is a heterogeneous disorder clinically characterized by parkinsonian motor symptoms (symmetrical lower-body parkinsonism, postural instability, falls, freezing of gate) and pathologically associated with multiple ischemias in the basal ganglia and white matter. Cognitive impairment may also occur in VP either at the onset or early in the course of the disease, mainly consisting in a subcortical, dysexecutive syndrome. Growing evidence suggests that the basal ganglia, periventricular and subcortical white matter lesions are critical for cognitive impairment development in VP. However, it is possible hypothesize that damage in the subcortical loops finally spread in the cortical structures critical for cognitive integrative functions. To test this hypothesis, in this study we investigated cortical thickness in VP patients compared with Parkinson´s disease (PD) and control subjects (HC).

Methods: MRI scan were acquired from 40 subjects (13VP, 15PD, and 12 age- and sex- matched HC). All enrolled subjects underwent a neurological and neuropsychological examination. DAT-SPECT was also acquired for VP and PD patients. Cortical thickness was carried out by using FreeSurfer. We obtained cortical thickness for 68 regions of interest (ROIs), comparing among the three groups the main global-thickness value provided by FreeSurfer ($p<0.05$ FDR [False Discovery Rate] correction for multiple comparisons).

Results: Compared to PD and HC, the VP group showed a significant reduction in several cortical region mainly belonging to the cingulate cortex (right isthmus of cingulate gyrus [$p = 0.032$]; right anterior cingulate cortex [$p = 0.037$]; right posterior cingulate cortex [$p = 0.045$]); temporal cortex (left and right superior and transverse temporal gyri [$p= 0.036$; $p=0.037$ respectively]), and insula ($p= 0.037$). VP patients had significantly lower scores than PD on several neuropsychological tests evaluating executive functions, memory, anxiety, and depression. No other differences among groups were found.

Conclusion: This is the first study investigating the cortical thickness in VP. This study demonstrates a thinning in cortical regions that play a critical role in cognitively relevant events to guide flexible behavior and emotional information processing, thus suggesting that cognitive dysfunctions might contribute to cognitive impairment in VP.

STRUCTURAL COVARIANCE REDUCTION IN PATIENTS WITH VASCULAR PARKINSONISM: A 3T MRI STUDY

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Background and objective: Vascular parkinsonism (VP) is a parkinsonian syndrome with heterogeneous clinical presentation characterized, on a neuropathological level, by multiple subcortical ischemic lesions in the striatum, globus pallidus, and white matter. These findings are visually appreciable on conventional Magnetic Resonance Imaging (MRI) scans as extensive white matter lesions, multiple cerebral infarctions in basal ganglia, or both. We hypothesized that the status cribrosus of basal ganglia might produce abnormalities in the topographical organization of structural connections between the striatum and widespread areas in the brain. To test this hypothesis, we studied the structural covariance between the striatum and brain regions in patients with VP compared to Parkinson´s disease (PD) and control subjects (HC). Furthermore, we evaluated the relationship between altered brain connectivity and clinical features of our patients.

Methods: We enrolled 40 subjects (13 VP, 15 PD, and 12 HC, matched for demographical variables) that underwent a careful motor and neuropsychological exam and a 3T MRI scan including structural T1-weighted sequence. DAT-SPECT was also acquired for VP and PD patients. Left and right putamen and caudate nuclei were chosen as regions of interest (ROIs) and used as seeds for structural covariance analysis (statistical threshold: $p<0.05$ fwe, whole-brain correction; $p<0.05$ fwe cluster-level correction). Then we performed a modulation analysis to evaluate the relationship between structural covariance and clinical variables.

Results: No differences were observed between VP and PD in the disease duration and severity. DAT-SPECT showed reduced uptake in patients with both PD and VP without significant differences. VP patients had significantly lower scores than PD on several neuropsychological

tests evaluating executive functions, memory, anxiety, and depression. In comparison to PD and controls, VP subjects showed a reduced structural covariance between the bilateral corpus striatum (both putamen and caudate) and several brain regions, including cortical (insula, hippocampi, anterior cingulate cortex, gyrus rectus, fronto-orbital cortex) and subcortical (thalami) areas. Moreover, this structural covariance reduction was significantly modulated by cognitive performances in VP.

Conclusion: This study demonstrates for the first time a reduction in structural covariance between the striatum and several brain areas in VP patients that were firmly in relationship with deficits in several neuropsychological tests evaluating executive functions, memory, anxiety and depression. This compelling clinical-imaging evidence point out the hypothesis that the structural vulnerability of basal ganglia in VP patients may produce a progressive structural disconnection that may have a critical role in the development of cognitive impairment in VP.

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SENSITIVITY AND SPECIFICITY OF CLINICAL AND KINEMATIC MEASURES OF BRADYKINESIA IN PATIENTS WITH PARKINSON'S DISEASE AND ESSENTIAL TREMOR AND IN ELDERLY HEALTHY SUBJECTS

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Objectives: Bradykinesia is the cardinal symptom of Parkinson's disease (PD) [1], and it can be also observed in essential tremor (ET), where it configures the diagnosis of ET-plus, and to some extent in elderly healthy people [2-3]. In some cases, bradykinesia detection by clinical examination can be challenging, and the use of objective techniques for movement analysis may be necessary. Here we aim to assess the sensitivity and specificity of clinical and kinematic measures of bradykinesia in patients and healthy subjects.

Materials: Simultaneous video and kinematic recordings of finger tapping were performed in 44 PD, 69 ET, and 77 healthy controls (HCs). Methods: Videos were blindly evaluated by 7 neurologists using standardized clinical scales. Kinematic recordings were blindly analyzed. We calculated the inter-raters' agreement by the Fleiss' K. Clinical and kinematic data were compared in the three groups. Clinical evaluation scores-stratified density plots served to evaluate the overlapping in the distribution of kinematic data. Receiver operating characteristic (ROC) curves were used to identify kinematic cut-offs to distinguish subjects with and without bradykinesia.

Results: We found a fair agreement among raters (Fleiss K=0.32). As expected, we found the highest clinical bradykinesia scores in PD, and higher scores in ET than in HCs (all ps<0.001). At the kinematic analysis, the groups differed in terms of movement velocity, with the lowest values being detected in PD (all ps<0.001). Density plots demonstrated an overlapping between kinematic data curves. ROC curves showed that kinematic distinguished subjects with and without bradykinesia (AUC = 0.845, CI 95%: 0.727 - 0.963). The cut-off of 729.864 degrees/sec had a sensitivity of 0.842 (95%CI 0.604, 0.966) and specificity of 0.865 (95%CI 0.805, 0.913).

Discussion: We demonstrated a gap between the clinical and kinematic assessment of bradykinesia and proposed objective cut-offs distinguishing subjects with and without bradykinesia.

Conclusions: Our results are relevant for bradykinesia detection and more accurate classification of patients.

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NEUROPHYSIOLOGICAL ASSESSMENT OF JUVENILE PARKINSONISM DUE TO PRIMARY MONOAMINE NEUROTRANSMITTER DISORDERS

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Aims: No studies have investigated voluntary movement abnormalities and their neurophysiological correlates in patients with parkinsonism due to inherited primary monoamine neurotransmitter (NT) disorders.

Materials: Nine NT disorders patients and 16 healthy controls (HCs) were enrolled. Objective measurements of repetitive finger tapping were obtained using a motion analysis system. Data of primary motor cortex (M1) neurophysiology where obtained with transcranial magnetic stimulation (TMS).

Methods: M1 excitability was assessed by recording the input/output (I/O) curve of motor-evoked potentials (MEPs) and using a conditioning test paradigm for short-interval intracortical inhibition (SICI) assessment. M1 plasticity-like mechanisms were indexed according to MEPs amplitude changes after the paired associative stimulation protocol. Patient values were considered abnormal if they were greater than two standard deviations from the average HCs value.

Results: Patients with aromatic amino acid decarboxylase, tyrosine hydroxylase, and 6-pyruvoyl-tetrahydropterin synthase defects showed markedly reduced velocity (5/5 patients), reduced movement amplitude, and irregular rhythm (4/5 patients). Conversely, only 1 out of 3 patients with autosomal-dominant GTPCH deficiency showed abnormal movement parameters. Interestingly, none of the patients had a progressive reduction in movement amplitude or velocity during the tapping sequence (no sequence effect). Reduced SICI was the most prominent neurophysiological abnormality in patients (5/9 patients). Finally, the I/O curve slope correlated with movement velocity and rhythm in patients.

Discussion: We provided an objective assessment of finger tapping abnormalities in monoamine NT disorders, also demonstrating M1 excitability changes possibly related to alterations in motor execution.

Conclusions: Our results may contribute to a better understanding of the pathophysiology of juvenile parkinsonism due to dopamine deficiency.

MACHINE LEARNING ANALYSIS OF VOICE IN STUTTERING

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Objective: Stuttering is a childhood-onset neurodevelopmental disorder affecting speech fluency. Given the lack of standardized acoustic analysis, stuttering is currently evaluated by means of perceptual examination with dedicated clinical scales. Advanced voice analysis techniques based on machine learning have already been applied to discriminate voice characteristics in movement disorders [1,2]. We aimed to detect objectively stuttering-related voice abnormalities through these automatic machine learning techniques. Also, we investigated the relevance of speech-tasks as well as technological apparatus (i.e., smartphone) for the objective assessment of stuttering.

Materials: Fifty-three people with stuttering (24 females and 29 males; mean age±SD 16.7±7.6 years, range 7-30) and a group of 71 age- and sex-matched controls (29 females and 44 males; mean age±SD 16.2±6.5 years, range 7-30) were recruited. Common smartphones available on the market were used for voice recording sessions. SVM algorithm was employed for the machine learning analysis.

Method: Voice evaluation consisted in 3 self-administrated tasks recorded with a common smartphone. The first speech-task consisted of the sustained emission of the vowel /e/ for 5 s whereas the second and third tasks were based on the reading of standardized sentences of the connected-speech. Afterwards, voice samples were analysed using machine learning algorithms in order to compare controls and people with stuttering, during the emission of speech tasks.

Results: Machine learning algorithm objectively discriminated with high accuracy between controls and people with stuttering, as shown by the receiver operating characteristic (ROC) curves calculated during the sustained emission of the vowel /e/ (accuracy: 87.7; AUC: 0.934), sentence 1 (Acc.: 83.6; AUC: 0.906) and finally, sentence 2 (Acc.: 81.1; AUC: 0.881).

Discussion: Machine learning analysis of voice features in stuttering achieved high accuracy and reliability in discriminating controls from people with stuttering through for all speech-tasks included in the experimental paradigm. Compared to previous studies [3], our machine learning algorithm provided higher values of accuracy in discriminating stuttering-related voice abnormalities, in a large and homogeneous cohort of participants. In addition, these results proved common smartphones reliable and maneuverable instruments in objective voice analysis.

Conclusions: Machine learning analysis of human voice through smartphone represents a reliable tool for the objective and automatic detection of stuttering-related changes of voice features in patients with stuttering. Future studies would disclose whether machine learning analysis here proposed would help clinicians in the objective diagnosis of developmental disorders of speech, including stuttering.

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OCT AND OCT ANGIOGRAPHY CORRELATIONS WITH MOTOR AND NON MOTOR SYMPTOMS IN PARKINSON'S DISEASE

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Objectives: We aimed to investigate the structural changes in retinal and choroidal vascular networks and to evaluate any relationship with clinical features in patients affected with Parkinson's Disease (PD).

Materials: A total of 50 eyes from 25 PD patients and 50 eyes from 25 healthy controls was included in this prospective study.

Methods: The ganglion cell complex (GCC), retinal nerve fiber layer (RNFL) and subfoveal choroidal thickness (SFCT) was measured by Spectral Domain-Optical Coherence Tomography (SD-OCT). The vessel density (VD) of retinal, choriocapillary vascular networks in macular area and the foveal avascular zone (FAZ) area were evaluated by OCT Angiography (OCTA). All patients underwent clinical evaluation using Unified PD Rating Scale (UPDRS-III) and Hoehn and Yahr scale (HY). Non-motor symptoms (NMS) were assessed with Non-Motor Symptoms Scale (NMSS), SCOPA-AUT Questionnaire, Epworth Sleepiness Scale (ESS) and Apathy Evaluation Scale (AES).

Results: The GCC and RNFL were significantly thinner in patients respect to controls (p= 0.014; p=0.011). At OCTA exams, PD patients showed statistically lower values in VD of superficial capillary plexus (SCP), radial peripapillary capillary (RPC) plexus (p=0.002; p<0.001), whereas FAZ area turned to be significantly increased (p=0.004). We found a negative relationship between the age at onset and VD of SCP (rho=-0.574, p=0.003) and DCP (rho=-0.429, p=0.037). UPDRS-III score was negatively correlated with DCP vessel density (rho=-0.413, p=0.045). We observed a negative relationship between HY and RNLF thickness (rho=-0.539, p=0.007), and FAZ (rho=-0.609, p=0.002). A positive relationship was found between GCC and ESS, NMSS and SCOPA-AUT scores.

Discussion: We found retinal layer thinning and abnormal retinal vascularization in PD patients in comparison to controls. An inverse relationship between the age at onset and decreased VD of SCP and DCP was observed, suggesting that PD with earlier onset may present with higher impairment of microvascular distribution. RNFL thinning and FAZ impairment may be potential biomarkers of disease severity and progression.

Conclusions: The retinal structural and vascular impairment may be potential biomarkers of disease severity and progression in PD. Furthermore, retinal degenerative impairment may be considered a non-motor manifestation of the disease.

IMMUNE-MEDIATED MOVEMENT DISORDERS: A SINGLE CENTER EXPERIENCE WITH LONG TERM FOLLOW-UP

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Background: In the last years a growing attention is pointed to immune-mediated movement disorders. The spectrum of these syndromes includes an extensive and clinically heterogeneous group of conditions. We describe the clinical and laboratory findings as well as the clinical outcome in a group of antibody mediated movement disorders diagnosed in a tertiary center.

Methods: We included patients diagnosed with immune-mediated between 2015 and 2020. For all included patients' demographical features, target antigens antibodies, clinical features (movement disorder), tumor detection and clinical outcome after immunotherapy were reported.

Results: We included in the study 13 patients. Mean age at symptoms onset was 57.2 years (S.D: 20.1), mean of follow up: 2.3 years (SD: 2.0); F/M: 7/6; Clinical onset was: stiff person syndrome in 5 pt (38.5%), parkinsonism in 3 (23.1%), ataxia in 3 (23.1%), other clinical syndromes in 2 patients. Associated antibodies were directed against GAD65 in 7 patients (53.8%), Amphiphysin in 2 (15.4%), NMDA-R in 2 patients (15.4%) and other in 2 patients (CV2 ang glycine receptor). Antibodies were detected in serum in 11 patients (84.6 %) and in CSF in 7 patients (53.8%). All included patients received a first line immunotherapy first-line therapies including corticosteroids (46.2%), intravenous immunoglobulins (61.5%) and plasma exchange (15.4). 46.2% of patients received also immunosuppressant therapy. In 8/15 patients a clinical improvement after treatment was reported.

Conclusion: The expansion of identified autoantibodies associated to movement disorders makes the field increasingly important for the movement disorder specialist and for the general neurologist. In particular, a correct diagnostic approach and classification to these pathologies is important for the therapeutic implications. Further investigations are needed for characterization improvement and treatment algorithm development.

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IRON DEPOSITION WITHIN THALAMIC SUBREGIONS IS RELATED TO COGNITIVE DYSFUNCTIONS IN EARLY DRUG-NAÏVE PARKINSON'S DISEASE PATIENTS WITH MILD COGNITIVE IMPAIRMENT

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Objectives: Iron deposition using Quantitative Susceptibility Mapping (QSM) has been reported in several cortical and subcortical areas within the dopaminergic pathways in patients with Parkinson's disease (PD), and a relationship with cognitive decline has been proposed. Mild cognitive impairment (MCI) is a common nonmotor symptom in PD and it is considered a risk factor for future development of dementia. In this study, we aimed at o exploring the QSM signature underling MCI in early drug-naïve PD patients, focusing on several subcortical areas, and particularly on the thalamic subregions.

Materials: 3T MRI images of 59 drug-naïve PD patients (20 PD-MCI and 39 PD-noMCI), were analyzed and compared. Methods. MDS Task Force Level II diagnostic criteria were applied to determine the presence of MCI. QSM values were extracted from several subcortical deep gray matter nuclei and 16 thalamic subregions. A Partial correlation analyses were run between MRI metrics and clinical data. Finally, a ROC curve was performed to test the ability of QSM values in distinguishing PD-MCI from PD-noMCI.

Results: Compared PD-noMCI, PD-MCI patients showed higher susceptibility values in right subthalamic nucleus, in bilateral inferior pulvinar and in bilateral ventral posterolateral nuclei of thalamus. Moreover, higher susceptibility values in the thalamus correlated with worse motor/cognitive severity and quality of life in patients. The ROC curve analysis showed that QSM values extracted from left inferior pulvinar and right ventral posterolateral nuclei of thalamus could significantly and accurately identify the presence of MCI in drug-naïve PD.

Discussion: The subthalamic nucleus is involved in motor output, the inferior pulvinar in visual and attentive functions, and the ventral posterolateral nucleus of the thalamus is crucial for sensorimotor integration. Higher QSM values in these areas may determine altered motor outflow, cognitive dysfunctions and altered sensorial perception/integration in PD-MCI patients relative to PD-noMCI. This is consistent with previous studies showing that the involvement of these areas was related to motor, cognitive and sensitive abnormalities in PDas well as in other neurodegenerative disorders.

Conclusions: This study provides evidences of higher iron deposition within lateral and posterior regions of thalamic nuclei in drug-naïve PD patients with MCI patients compared to those without. We hypothesize that these findings may reflect the presence of more diffuse neuropathological changes occurring at the disease onset, potentially leading to altered cognitive processing and sensorial perception/integration in PD patients.

PRIMARY FAMILIAL BRAIN CALCIFICATION DUE TO A NOVEL MUTATION IN SLC20A2 GENE: A CASE REPORT

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Introduction: Primary familial brain calcification (PFBC) is a rare neurodegenerative disorder characterized by extensive intracranial calcium deposition. Patients mostly present with parkinsonism and cognitive impairment. Pathogenic variants in six genes (SLC20A2, PDGFB, PDGFRB, XPR1, MYORG and JAM2) have been associated with PFBC, but genotype-phenotype correlations have not been established. We report the case of a PFBC patient with a novel heterozygous mutation in SLC20A2 presenting with postural tremor.

Case report: A 69-year-old man was followed in our clinic for bilateral arms tremor beginning 10 years earlier. His past medical history was significant for vocal cord cancer. He had a significant family history (tremor and epilepsy in two siblings, tremor and psychiatric disorder in his mother). His first neurological consult at age 62 found bilateral axisymmetric postural and kinetic hands tremor. In the suspect of essential tremor, different pharmacological therapies (propranolol, primidone, valproic acid) were started unsuccessfully. Low dose levo-dopa therapy (levodopa/benserazide 100mg/25mg bid) was prescribed with minor improvement therefore he underwent brain CT and MRI that revealed bilateral calcifications in the cerebellum, thalami and basal ganglia. DAT-scan showed mildly diminished right striatal binding. Routine serum biochemical parameters of bone and mineral metabolism were unremarkable. Follow-up neurological evaluations documented persistent mild hands tremor with dystonic component on the left side, anticholinergic therapy was added (trihexyphenidyl 4mg daily). At 68 y.o. patient begin to complain craving for sweet food, insomnia and nocturnal hyperactivity. Cognitive evaluation revealed attentive deficits and behavioural disinhibition (MMSE 29/30). Episodic tongue protrusion during stress was described. Right hand rest tremor appeared without bradykinesia or rigidity. Genetic test identified the c.410G>A, p.(Trp137Ter) heterozygous variant of SLC20A2 gene. This is a novel mutation, yet not

described on GnomAD database (https://gnomad.broadinstitute.org/), that gives rise to a stop codon and is considered as pathogenic by many prediction programs. The patient's sons refused to be tested.

Conclusions: We describe a novel c.410G>A variant of SLC20A2 gene in a patient with isolated bilateral hands tremor for almost 10 years before the onset of behavioral alterations and other motor symptoms. For patients classified as having essential tremor-plus phenotype, PFBC must be considered in the differential diagnosis, especially this novel SLC20A2 variant.

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ADAPTIVE DBS STABILIZES LEVODOPA-INDUCED CHANGES IN SUBTHALAMIC BETA ACTIVITY IN PARKINSON'S DISEASE

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Objective: To study the effect of adaptive deep brain stimulation (aDBS) on the changes induced by levodopa administration on subthalamic beta oscillatory activity.

Background: Thanks to the advances in DBS technology, with the introduction of implantable pulse generators able to record neuronal activity in the target area while stimulation is ON, aDBS is getting closer to clinical practice. aDBS implementation uses a specific oscillation of local field potentials (LFPs) in the beta range (10-35 Hz) as biomarker of clinical state for Parkinson's disease (PD) [1–3]. LFP-based aDBS showed to be effective in treating PD motor symptoms [1,3], and to be superior to conventional DBS in controlling dyskinesias when electrical stimulation is combined to levodopa administration (MedON/StimON condition) [2]. It can be therefore hypothesized that aDBS stabilizes patient's condition following levodopa dynamic and controlling fluctuations.

Methods: We analyzed LFP beta dynamics in 10 PD patients, bilaterally implanted with DBS electrodes and treated with aDBS, following a protocol described in (1) in a two-days experiment: in one day, they received only levodopa medication, and in the other day they received aDBS while following their normal levodopa schedule. Beta oscillation recording and aDBS administration were done using AlphaDBS_Vext (Newronika spa), a CE marked device, and were conducted for 8 hours per each day. To evaluate stability, we modelled the recorded beta oscillations using the Auto Regressive Moving Average (ARMA) model and extracted both temporal characteristics (signal entropy) and model-related characteristics (conditional variance) that represent stability over time. We analyzed these characteristics in four conditions (Day 1: MedOFF/StimOFF and Med ON/StimOFF; Day 2: MedOFF/StimON and MedON/StimON), and evaluated the differences between the MedOFF and the MedON states in the two days (Day1: no DBS, Day2: aDBS)

Results: We found that the levodopa-induced change of beta entropy in Day2 was significantly lower than 0 (Wilcoxon rank sum test $p = 0.007$) whereas in Day1, being more dispersed, they were attributable to a population with zero median (Wilcoxon rank sum test $p = 0.105$). Similarly, the distribution of MedOFF-MedON differences in conditional variance values is narrower on Day2 than on Day1, thus being significantly lower than 0 (Wilcoxon rank sum test $p = 0.009$) but not in Day1 (Wilcoxon rank sum test $p = 0.193$). Both entropy and conditional variance correlated with UPDRSIII scores.

Discussion: Our results suggest that aDBS stabilizes beta oscillations in presence of levodopa, thus supporting their use as biomarker.

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DEVELOPMENT AND VALIDATION OF AUTOMATED MR PARKINSONISM INDEX 2.0 TO DISTINGUISH PSP-P FROM PD

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Background: The clinical differential diagnosis between PSP-P and PD may be challenging. Several MR imaging biomarkers have proven to be useful in differentiating PSP-Richardson's syndrome (PSP-RS) from PD but failed to accurately distinguish PSP-P from PD patients, probably due to the lower degree of brain atrophy in this milder PSP subtype.

Objective: The current study aimed to develop an automated MR Parkinsonism Index 2.0 (MRPI 2.0) algorithm to distinguish progressive

supranuclear palsy-parkinsonism (PSP-P) from Parkinson's disease (PD), and to validate its diagnostic performance in two large independent cohorts.

Methods: We enrolled 676 participants: a training cohort (n=346; 43 PSP-P, 194 PD, 109 controls) from our center, and an independent testing cohort (n=330; 62 PSP-P, 171 PD, 97 controls) from an international research group. We developed a new in-house algorithm for MRPI 2.0 calculation and assessed its performance in distinguishing PSP-P from PD and controls in both cohorts using receiver operating characteristic curves.

Results: The automated MRPI 2.0 showed excellent performance in differentiating PSP-P from PD patients and controls both in the training cohort (AUC=0.93, 95% confidence intervals [0.89-0.98]; AUC=0.97 [0.93-1.00], respectively) and in the international testing cohort (PSP-P vs PD, AUC=0.92 [0.87-0.97]; PSP-P vs controls, AUC=0.94 [0.90-0.98]), suggesting the generalizability of the results. The automated MRPI 2.0 also accurately distinguished between PSP-P and PD in the early stage of the diseases (AUC=0.91 [0.84-0.97]). A strong correlation ($r=0.91$, $p<0.001$) was found between automated and manual MRPI 2.0 values.

Discussion: Our study provides an automated, validated and generalizable MR biomarker to distinguish PSP-P from PD. The use of the automated MRPI 2.0 algorithm rather than manual measurements could be important to standardize measures in PSP-P patients across centers, with a positive impact on multicenter studies and clinical trials involving patients from different geographic regions.

VIDEO-OCULOGRAPHIC BIOMARKERS FOR EVALUATING VERTICAL OCULAR DYSFUNCTION IN PROGRESSIVE SUPRANUCLEAR PALSY

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Background: Progressive supranuclear palsy (PSP) patients show reduced amplitude and velocity of vertical saccades, but saccadic abnormalities have also been reported in Parkinson's disease (PD). We investigated amplitude and velocity of vertical saccades in PSP and PD, to establish the best video-oculographic (VOG) parameters for PSP diagnosis.

Methods: Fifty-one PSP patients, 113 PD patients and 40 controls were enrolled. The diagnosis was performed on a clinico-radiological basis (MR Parkinsonism index [MRPI] and MRPI 2.0). We used VOG to assess the diagnostic performances of saccadic amplitude, peak velocity, and their product (AxV) in upward or downward direction and in vertical gaze (upward and downward averaged) in distinguishing PSP from PD patients. The vestibulo-ocular reflex, necessary to establish the supranuclear nature of ocular dysfunction, was evaluated clinically.

Results: PSP patients showed significantly reduced amplitude and peak velocity of ocular saccades in upward and downward directions compared to PD and healthy subjects. In PD patients, upward gaze amplitude was lower than in controls. In vertical gaze, the peak velocity showed 99.1% specificity and 54.7% sensitivity for PSP classification. The AxV product showed high specificity (94.7%) and sensitivity (84.3%) and yielded higher accuracy (91.5%) than velocity and amplitude used alone in distinguishing PSP from PD.

Conclusion: Our study demonstrates that the peak velocity of vertical saccades was a very low sensitive parameter and cannot be used alone for PSP diagnosis. A new index combining amplitude and peak velocity in vertical gaze seems the most suitable video-oculographic biomarker for differentiating PSP from PD and controls.

STN-DBS DOES NOT INCREASE THE RISK OF SIALORRHEA IN PATIENTS WITH ADVANCED PARKINSON'S DISEASE

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The objective of this study was to evaluate the effect of STN-DBS on the development of sialorrhea in PD patients, assessing its incidence rate and risk factors in the long-term follow-up. Sialorrhea development was retrospectively evaluated at each follow-up visit after baseline in two groups of STN-DBS and medically managed PD patients. A total of 132 patients [88 with DBS and 44 on medical treatment] were included. The demographic and clinical variables were similarly distributed between the two groups at baseline. The prevalence of sialorrhea at baseline did not differ significantly between the two groups: 19.3% among DBS patients and 11.4% among controls ($p = 0.2$). Throughout the follow-up period [mean 7.9 (±6.2) years for the DBS group and 4.6 (±2.9) years for the control group], 31 patients developed new onset sialorrhea, 24 DBS patients and 7 controls. The incidence rate of sialorrhea did not differ between the STN-DBS and the control groups: 49.2 [95% confidence interval (CI) 31.5–73.2] and 43.7 (95% CI 17.5–90.2) per 1,000 person-years of observation respectively ($p = 0.8$). In the final Cox regression model, male sex [hazard ratio (HR) 1.6, 95% CI 1.1–2.3, $p = 0.006$], Hoehn and Yahr (HY) stage (HR 2.6, 95% CI 1.3–5.3, $p = 0.006$), and dysphagia (HR 3.5, 95% CI 1.6–7.8, $p = 0.002$) were independent risk factors for sialorrhea. Interestingly, STN-DBS did not significantly increase the risk of developing sialorrhea (HR 1.4, 95% CI 0.7–2.8, $p = 0.3$). Comparing DBS patients with and without new onset sialorrhea, no difference was found for stimulation parameters. In this retrospective case-control study the main finding is that the incidence rate of sialorrhea did not significantly differ between the groups of patients with and without DBS in the long-term follow up. By fulfilling the eligibility criteria for DBS, patients in both groups had an advanced disease but no severe axial symptoms or cognitive impairment, both strongly associated with sialorrhea, minimizing the risk of selection biases. In our cohort, the risk factors for sialorrhea were male sex, HY stage, and dysphagia, which were all previously described as risk factors for sialorrhea in general PD population. Moreover, no stimulation parameter was specifically associated to sialorrhea development. The present study shows that STN-DBS does not increase the risk of developing sialorrhea, supporting the hypothesis that sialorrhea is a consequence of the underlying neurodegenerative disease, regardless of DBS.

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CANNABINOIDS FOR PAINFUL DYSTONIA IN CORTICOBASAL SYNDROME: A REPORT OF THREE PATIENTS

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Introduction: The clinical phenotype of corticobasal syndrome (CBS) includes limb dystonia, which can be associated with severe pain frequently difficult to treat despite numerous therapeutic attempts. Cannabinoids are increasingly used to treat pain and some reports suggest a potential benefit in dystonia. We aimed to assess the efficacy of cannabinoids in painful dystonia of CBS patients.

Material and methods: Three patients with CBS complained painful limb dystonia. All three patients were treated with different pain medication, without achieving satisfactory pain relief. Therefore, we added cannabis-based oily solutions to the therapy, collecting Numeric Rating Scale (NRS) values for pain before and after three months from the start. Results: Case 1 presented main involvement of the right arm. Her therapy included botulinum toxin injections, amitriptyline, clonazepam and baclofen. She started Bedrolite® oil (THC 1%, CBD 9%, 20 drops/die) therapy, and the NRS value changed from 8 to 3. Case 2 presented main involvement of the left arm. Her therapy included botulinum toxin injections, amitriptyline, clonazepam, baclofen and oxycodone. She started Bediol® oil (THC 6.5%, CBD 8%, 25 drops/die) therapy, and the NRS value decreased from 10 to 1. Case 3 presented main involvement of the right leg. His therapy included botulinum toxin injections, clonazepam, pregabalin, baclofen and oxycodone. He started Bedrolite® oil (60 drops/die) therapy, and the NRS value decreased from 9 to 2. The therapy was well tolerated in all patients.

Conclusions: Cannabinoids should be considered as a useful add-on therapy for painful dystonia in CBS patients.

DYSAUTONOMIA AND CLINICAL OUTCOMES IN PARKINSON'S DISEASE: A 5-YEAR PROSPECTIVE STUDY EVALUATING THE INDIVIDUAL IMPACT OF AUTONOMIC DOMAINS

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Objectives: Autonomic failure is a well-known negative prognostic factor for Parkinson's disease (PD) (i.e., 3-to-7-fold higher risk of developing dementia and higher risk of mortality at 10 years) [1,2]. Nonetheless, the impact of cardiovascular, gastrointestinal, urogenital, thermoregulatory, and pupillomotor autonomic dysfunctions on PD clinical outcome still remains unclear. Primary aim of the study was to determine the five-year risk of developing dementia, falls, postural instability, dysarthria, and dysphagia in PD patients with and without autonomic impairment at baseline, and assess possible associations between abnormalities in each autonomic domain and these remarkable clinical outcomes. Additional aim was to determine the impact of abnormalities in each autonomic domain on activities of daily living (ADLs, measured by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale-MDS-UPDRS-part I and II) and health-related quality of life (HRQoL, measured using the PD Quality of Life Questionnaire-PDQ-8 single index).

Materials and Methods: We enrolled 65 consecutive PD patients in a five-year cohort study involving standardized evaluations of autonomic symptoms (Scale for Outcomes in Parkinson's Disease-Autonomic-SCOPA-AUT, considering both total and subdomain scores), orthostatic hypotension (OH), supine hypertension (SH), and motor and non-motor features, including cognitive functions. Associations were tested using both univariate and multivariate analyses, adjusting for age, disease duration, and baseline level of motor impairment.

Results: At 5-year follow-up, cardiovascular dysautonomia was found associated with a seven-fold higher risk of developing dementia (95%CI:1.154-50.436; p=0.035), a five-fold higher risk of falls (95%CI:1.099-18.949; p=0.039), and a more severe impairment in ADLs (p=0.042) and HRQoL (p=0.031). Neurogenic OH was found associated with a five-fold higher risk of developing dementia (95%CI:1.289-26.943; p=0.029), and a seven-fold higher risk of falls (95% CI:1.212-41.921; p=0.030). Stronger associations were observed when considering individuals with hemodynamically relevant OH (i.e., orthostatic mean arterial pressure ≤75 mmHg). For the dementia risk only, the concomitant presence of SH further increased the risk of dementia (OR:8.265; 95%CI: 2.026-32.103; p=0.012). Neurogenic OH was also associated with a higher impairment in ADLs (p= 0.046) and lower HRQoL (p=0.042). No relevant associations were found between the other autonomic domains and these outcomes.

Discussion and Conclusions: In PD, cardiovascular dysautonomia, but no dysfunctions in other autonomic domains, is significantly associated with worse clinical outcomes at five-years. This indicates a relevant pathophysiological and negative prognostic impact of cardiovascular dysautonomia on PD progression and cognitive decline [3]. An early identification and treatment of dysautonomia in PD is advisable to try to reduce the risk of motor and cognitive disabilities.

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SEX DIFFERENCES IN LEVODOPA PHARMACOKINETICS IN LEVODOPA-NAÏVE PATIENTS WITH PARKINSON'S DISEASE

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Introduction: Levodopa (LD) is the most effective drug in the treatment of Parkinson's disease (PD) [1]. Women seem more prone to develop LD prolonged use related complications, such as motor/non motor fluctuations (MNMF) and dyskinesias (DYS) [2]. Nonetheless, there is a paucity of prospective studies examining gender-related predictors of MNMF and DYS. Among several factors, which concur with a very complex scenario, changes in LD pharmacokinetics influence the drug effectiveness.
Objective: To assess gender-related differences in LD pharmacokinetics in PD patients at their first ever intake of LD.

Methods: This multicentric study enrolled LD-naïve PD patients who received a single dose of LD/benserazide (100/25 mg) formulation. To measure plasma LD concentrations and pharmacokinetic parameters (AUC, Cmax, Tmax, t1/2), fasting blood samples were collected before drug intake and then at 8 time points until 260 minutes. LD concentrations were measured by ultra-high performance liquid chromatography coupled with mass spectrometry. Multiple linear regression analyses were performed to identify the predictors of the parameters.

Results: 35 patients (16 women and 19 men) were consecutively enrolled. AUC and Cmax were significantly higher in women than men ($p=0.0006$ and $p=0.0014$, respectively). No statistically significant difference was found regarding Tmax and t1/2. Multiple linear regression analyses revealed that female sex ($p<0.0001$) and BMI ($p=0.014$) significantly predicted AUC. Only female sex significantly predicted Cmax ($p=0.001$). Moreover, only BMI significantly predicted t1/2 ($p=0.017$). Stratifying by gender, BMI was confirmed to significantly predict t1/2 in women ($p=0.027$), but not in men.

Conclusions: This study provides novel insights on gender differences in LD pharmacokinetics, possibly contributing to the later development of motor complications and dyskinesia in PD.
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A BAYESIAN APPROACH TO ESSENTIAL TREMOR PLUS: A PRELIMINARY ANALYSIS OF THE TITAN COHORT

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Objective: The entity of Essential Tremor-Plus (ET-plus) was proposed for those patients with ET and additional rest tremor or other neurological signs of uncertain significance. Whether these patients belong to the ET spectrum or not is unknown. To apply a Bayesian approach to patients with ET-plus recruited in The ITAlian Tremor Network (TITAN), to estimate their probability of not having ET.

Materials: The TITAN project is a multi-center prospective study to assess the phenomenology and natural history of tremor syndromes, diagnosed according to the new Movement Disorders Society tremor classification. Patients are assessed by means of the TETRAS and SARA scales and demographic and clinical historical features gathered by a structured questionnaire.

Methods: For the current study, the sensitivity/specificity of each soft sign, and consequently their positive and negative likelihood ratios, were calculated based on published literature or from unpublished data of one of the authors (RE). Given that these values have been calculated in the literature either against a particular syndrome (dystonia, parkinsonism, etc) or against elderly healthy subjects, the cumulative effects of the soft signs here reported indicate the estimated probability of not having ET.

Results: We extracted from the TITAN database data of 274 patients with ET-plus (117 female, 157 male; mean age 69.8 ± 11). Age at onset was 54.5 ± 18.1 years. The majority of patients (240/274; 87.5%) had a single soft sign. The post-test probability of not having ET for these patients was as follows: 0.85 (questionable bradykinesia), 0.64 (rest tremor), 0.46 (questionable dystonia), 0.19 (soft gait impairment), and 0.09 (questionable cognitive issues). The remaining 34 patients (12.5%) had multiple soft signs: post-test probabilities of not having ET were lower than 0.5 in 55.8% of cases, especially for patients with soft gait impairment and/or questionable cognitive issues.

Discussion: The effects of multiple soft signs are not addictive. Furthermore, given that the post-test probability of not having ET was less than 0.5 for some single soft signs (e.g. uncertain gait impairment and / or questionable cognitive problems) as well as for their combination, it could be conceivable that these signs are part of the ET spectrum.

Conclusion: The post-test probability of not having ET for a patient with ET-plus depends on each soft sign and their combination. Future studies should calculate sensitivity/specificity values of each soft sign against a particular syndrome: by applying a Bayesian approach this would enhance the interpretation ET-plus.

STRUCTURAL CONNECTIVITY CHANGES IN ESSENTIAL TREMOR WITH REM SLEEP BEHAVIOUR DISORDER

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Objective: REM sleep behavior disorder (RBD) is an important risk factor for the dementia development and for the deterioration of autonomic functions in patients with Parkinson's Disease. RBD has also been reported in patients with Essential Tremor (ET). However, little is until know on the significance of RBD in ET patients. This study aimed to investigate brain covariance structural differences in ET patients with and without RBD.

Methods: Magnetic resonance imaging data were acquired from 46 participants (36 ET and 1O ET with a PSG-confirmed diagnosis of RBD, ET-RBD). All patients completed a battery of neuropsychological assessment of memory, executive function, attention, language and visuospatial function. T1-weighted scans were obtained for all participants and volumes of grey matter tissue were estimated across 152 regions of the AAL3 template using the Cat12 toolbox. An adjacency matrix for each group was calculated using Pearson correlation between the average volume of each couple of brain regions. Group-specific matrices were thresholded using a fixed density of 0.4 and nodal measures such as strength and clustering coefficient were calculated. Differences between the two groups were computed using a set of10000 random networks.

Results: Compared to ET patients, significantly reduced strength in the left Precuneus (p=0.01 fdr corrected) was present in ET-RBD. Moreover, ET-RBD patients had a reduced clustering coefficient in the bilateral anterior and middle cingulate cortex, bilateral precuneus, right insula and right orbitofrontal cortex (p<0.05 fdr corrected). ET-RBD patients also showed lower scores on several neuropsychological tests.

Discussion and Conclusions: This study improves the knowledge in ET, since our preliminary findings demonstrate that a reduced ability to integrate and segregate information in several regions could be involved in the pathophysiology of RBD symptoms and cognitive impairment in ET.

A-SYNUCLEIN SEEDING ACTIVITY IN GASTROINTESTINAL BIOPSIES VIA RT-QUIC ASSAY IN PARKINSON'S DISEASE PATIENTS

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In Parkinson's Disease (PD), several evidence indicates the involvement of the gut-brain axis as one of the primary physio-pathological mechanisms underlying α-Syn aggregation and following propagation to CNS. Furthermore, gastrointestinal (GI) dysfunctions represent one of the main non-motor symptoms in PD, often preceding the development of proper motor symptoms. We aimed to investigate α-Syn seeding activity in stomach-duodenum biopsies of PD patients by real-time quaking-induced-conversion (RT-QuIC) assay. The αSyn RT-QuIC assay follows the seeded aggregation of monomeric αSyn into amyloid fibrils upon seeding by traces of αSyn aggregates present in biospecimens (2). Patients with advanced and early PD were included in the study. A mean of 2 (2mm3) wall biopsies were sampled from each patient, homogenized, and analyzed by RT-QuIC assay. Control biopsies were included from age-and-sex-matched patients undergoing routine diagnostic endoscopy. In PD patients α-Syn seeding activity was also assayed in skin biopsies from cervical region (C5-C6). We found a relevant α-Syn seeding activity in most GI biopsies of PD patients (also in early PD patients), with a higher response in the stomach biopsies than duodenum and no activity was detected in the biopsies of controls. Analysis of α-Syn seeding activity in skin confirmed the results in GI biopsies and confirmed its best performance in the assay showing a shorter lag phase. The enteric nervous system could be one of the earliest implicated structures in the processes of αSyn aggregation and an unmet clinical need is a reliable early diagnostic biomarker for PD. We suggest that the combination of endoscopic biopsy of the gastric and duodenal mucosa to the high sensitivity of the RT-QuIC assay in the detection of α-Syn seeding activity could be a helpful new biomarker to evaluate the early stages of PD.

HEMICHOREA SYNDROME SECONDARY TO DIABETIC STRIATOPATHY WITH CONTRALATERAL DRUG-INDUCED PARKINSONISM: A DIFFERENT THRESHOLD FOR DRUG INDUCED MOVEMENT DISORDERS?

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Background and objectives: Hemichorea syndrome secondary to non-ketotic hyperglycemia also called "Diabetic striatopathy" (DS) is characterized by the presence of choreic unilateral or bilateral involuntary movements and striatal hyperintensity on T1-weighted magnetic resonance imaging (MRI) [1]. Here we report two patients with acute DS who developed early contralateral parkinsonism after dopamine depletion treatment.

Results: An 81-year-old male patient with type-II diabetes mellitus in poor glycemic compensation switched from insulin to oral antidiabetic therapy. After 20 days he complained of the insidious appearance of choreic movements involving left limbs. The second patient was a 71-year-old diabetic woman who was admitted to our department for the acute onset of choreic involuntary movements involving proximally left upper limb. In this case no therapeutic switch had been made. On admission their Glycated Hemoglobin value was 76 and 105 mmol/mol (standard value 20-42), respectively. Brain MRI showed an area of altered signal in the right putaminal region in the T1-weighted sequences in both patients [2]. DaT-scan was performed in the second patient, revealing a slight but non-significant reduction of the radiotracer uptake in the right putamen. Treatment with Haloperidol was started up to 2-3 mg/day in both patients, with a good response within a few weeks. After 2 months they both complained of clumsiness with right upper limb movements and a tendency to crawl the homolateral foot on the ground. Neurological examination detected marked right-sided bradykinesia with moderate rigidity, therefore haloperidol therapy was gradually reduced and then withdrawn, with rapid improvement of the hypokinetic disorder.

Conclusions: DS rarely happens during a therapeutic switch as in our first patient, in fact there are no literature's reports. Iatrogenic parkinsonism (IP) relative risk is usually related to the duration of treatment with neuroleptic drugs [3]. In view of the good response to withdrawal therapy and the absence of resting tremor or non-motor symptoms, the diagnosis of IP has never been questioned. So generally, no dopamine transporter imaging is required in these cases although some patients with a subclinical pathology might be more vulnerable to antipsychotics for developing parkinsonism than healthy population [3]. We could therefore hypothesize a different dopamine-depletors susceptibility of basal ganglia: a structural damage of the striatal pathway could result in a higher threshold, making the neuroleptic drug efficacious against the hyperkinetic disorder. At the same time, a lower threshold in the healthy basal ganglia side could cause the early appearance of parkinsonism as in our patients.

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FUNCTIONAL MRI AND GAIT ANALYSIS CHARACTERISTICS IN PATIENTS WITH IDIOPATHIC REM SLEEP BEHAVIOR DISORDER

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Objectives: Clinical, gait analysis, and MRI features might predict the conversion from idiopathic REM sleep behavioral disorder (iRBD) to clinically manifested alpha-synucleinopathies. The aims of this study were to assess gait analysis, neurological, neuropsychological and resting-state functional MRI (RS-fMRI) functional connectivity (FC) characteristics in iRBD patients and to study the correlations between clinical features and RS-fMRI alterations.

Materials: Ten patients with a polysomnography-confirmed iRBD underwent clinical, cognitive, and RS-fMRI evaluations. Ten age/sex-matched healthy controls underwent neuropsychological evaluation and RS-fMRI.

Methods: Gait analysis was performed using a stereophotogrammetric system to assess asymmetry of spatio-temporal gait parameters during a four-meter walking test with and without a cognitive dual-task.

Results: IRBD patients showed mild asymmetry of spatio-temporal gait parameters, particularly during dual-task gait. IRBD patients showed an increased FC in the right executive control, sensorimotor and dorsal default mode networks compared to healthy controls. Basal ganglia and cerebellar networks showed reduced FC. Correlation analyses showed that an increased asymmetry in the lower limb swing time during gait correlated with an increased FC in the right executive control network, whereas an increased asymmetry of lower limb stride length during dual-task gait correlated with an increased FC in the sensorimotor network.

Discussion: This study suggested that RS-fMRI and gait analysis characteristics could be promising biomarkers for early alpha-synucleinopathy detection and prediction.

Conclusions: The collection of longitudinal data in a larger sample will allow the assessment of conversion from iRBD to parkinsonian syndromes and to test a multifactorial prediction model combining fMRI, gait analysis, clinical and neuropsychological data.

Funding: Italian Ministry of Health [grant number # RF-2018-12366746]

DIVERGENT SEX-SPECIFIC FUNCTIONAL STRIATAL CONNECTIVITY IN DRUG-NAÏVE PATIENTS WITH PARKINSON'S DISEASE

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Aims: Compelling evidence suggests that a sex-specific pattern and functioning within the nigrostriatal and striatocortical pathway may underlie the clinical divergence observed in male and female patients with Parkinson's disease (PD) over the disease course. We aim to investigate the potential effect of sex on the regional striatal functional connectivity (FC) in a cohort of drug-naïve PD patients applying a seed-based approach to resting-state functional MRI data.

Materials:147 drug-naive PD patients (82 male and 65 female) were consecutively enrolled. Motor, non-motor and neuropsychological assessments as well as rs-fMRI were performed at baseline. 38 age- and sex-matched controls were also enrolled in the study.

Methods: Using connectivity-based parcellation, we subdivided the striatum into three functional subregions (namely, from dorsal/caudal to anterior/ventral: sensorimotor, limbic and executive). Seed-based resting-state functional MRI was used to compare the FC from each striatal subregions to the whole brain between male and female patients as well as between patients and controls.

Results: Both male and female PD patients showed decreased FC between the sensorimotor striatal subregion and the substantia nigra compared to controls. However, the sensorimotor striatal subregion showed decreased FC with the superior frontal gyrus in female PD patients compared to male PD and controls whereas decreased FC with the cingulate gyrus was found in male PD patients compared to female PD and controls. The limbic striatal subregion showed increased FC with the insula in male PD patients compared to controls whereas increased FC with the hippocampus was found in female PD patients compared to controls. The executive striatal subregion showed increased connectivity with the insula as well as decreased connectivity with the superior frontal gyrus in female PD patients compared to controls.

Discussion: As striatal degeneration follows a disease-specific temporo-spatial gradient, we used a functional striatal atlas to compare FC from the striatum to the whole brain in male and female PD patients. Male PD patients showed more pronounced functional rearrangements within the frontostriatal limbic network whereas female PD patients were more likely to present early disconnection between the striatum and frontal cortical areas involved in motor programming and execution. This pattern may potentially lead to the characteristic vulnerability upon the development of different clinical milestones between genders over time.

Conclusions: Our findings revealed the presence of a disease-related, sex-specific divergent functional striatal connectivity in PD patients even in the early stages. This may potentially be used to predict different sex-related PD progression routes.

PROKINETICIN-2 EXPRESSION IS INCREASED IN OLFACTORY NEURONS OF PATIENTS WITH PARKINSON'S DISEASE AND DIRECTLY CORRELATES WITH A-SYNUCLEIN OLIGOMERS ACCUMULATION

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Objectives: To shape the activity of Prokineticin-2 (PK2) pathway and evaluate the correlations with synucleinopathy in olfactory neurons (ONs) of patients with Parkinson's disease (PD) at different disease stages.

Materials and Methods: ONs were collected through non-invasive mucosa brushing from n=38 PD patients (n=26 de novo, newly-diagnosed and untreated) and n=21 sex/age matched healthy controls. Patients were assessed by H&Y scale, MDS-UPDRS pars III, non-motor symptoms and cognition scores, LEDD calculation. Real Time-PCR was used to measure expression levels of PK2 and other PK2 pathway-related factors (PK2 receptors type 1 and 2, PK2-long peptide) in ONs; immunofluorescence was also performed to quantify PK2 and α-synuclein species (total and oligomeric).

Results: ONs expression of PK2 was significantly increased in PD compared to controls; levels were higher in de novo patients than those more

advanced. In de novo group, PK2 expression directly correlated with MDS-UPDRS pars III. The oligomeric α-synuclein specie, but not the total one, was higher in PD patients than controls. Oligomeric α-synuclein and PK2 were directly associated in PD group.

Discussion: Novel neuroprotection targets are urgently needed in PD field. PK2 is a chemokine-like peptide, which showed, in PD animal models, promising neuroprotective effects especially at early stages of neurodegeneration. However, dynamics of PK2 pathway in PD patients remain unexplored. PK2 is preferentially expressed into the olfactory system, which, in turn, is one of the earliest sites of neuropathology in PD. ONs can be easy withdrawn, representing an ideal human-derive tissue for molecular analysis in vivo. By this study we demonstrated, for the first time, that PK2 pathway is activated in ONs of PD patients, mostly at early disease stages and proportionally to motor impairment. We also found that PK2 expression rose in parallel with oligomeric α-synuclein accumulation, which suggests a defensive effect of pathway activation.

Conclusions: We support PK2 pathway as a candidate target for neuroprotection in PD. ONs well reflect molecular events underlying PD, representing a valuable source for model development or biomarkers discovery.

COMPARISON OF THE CLASSIFICATION PERFORMANCES BETWEEN DIFFERENT SUPERVISED MACHINE LEARNING ALGORITHMS IN THE DETECTION OF IMU-BASED GAIT DEFICIT IN PARKINSON'S DISEASE: A NEED FOR AN APPROPRIATE PROCEDURE

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Objectives: Several studies applied machine-learning (ML) for the detection, quantification, and classification of gait abnormalities in people with Parkinson disease (pwPD). One of the most critical challenges with supervised ML algorithms is the risk of overfitting. Therefore, knowing which algorithm is the most efficient and which is the least efficient is critical. The major goal of this research was to identify the supervised machine learning method that shows the best accuracy, precision, recall, and generalizability with the preselected dataset of IMU-derived gait characteristics.

Materials: We collected data samples from 81 pwPD (25 F, 56 M, aged 72.1 ± 6.7 years) in 1-3 Hoehn and Yahr and from a group of 80 speed-matched healthy subjects (HS).

Method: The spatio-temporal and trunk-derived stability indexes gait data were collected using an inertial sensor (BTS GWALK, Milan, Italy). Python (Python 3.7.11 Software) was used to manage the machine learning algorithms, and statistical analyses were performed using the IBM SPSS ver. 27). We first performed features selection through Shapiro–Wilk test, Pearson correlation and sequential backward selection approach to both identify the most significant and clinical meaningful gait parameters that significantly distinguished pwPD from HS, and to reduce the dimensionality of the initial feature subset while preserving classifier performance. Then, we split the final set into two subgroups training set (80% of data) and test set (20% of data) and applied five different ML approaches: Decision trees (DT), Random Forests (RF) K-Nearest Neighbors (KNN), Support Vector Machine (SVM), artificial neural networks (ANNs). We calculated accuracy, precision, recall, and F1 score, generalization error to assess the performance of the classifiers.

Results: After features selection procedure, a significant main effect of the ML algorithms was found for all the performance measures. SVM outperformed DT, KNN, and ANN in all the classification performance measures and showed comparable precision values when compared with RF.

Discussion: SVM had the best ability to accurately classify pwPD and HS, followed by RF and DT, which had equal classification abilities. These findings support the use of SVM in gait prediction while also showing the potential use of tree-based approaches like RF and DT. However, because of the black-box nature of SVM, clinicians are unaware of the decisional processes besides the final classification.

Conclusions: We argue that RF and DT might make clinicians engage in the decision-making process and be utilized in patient decision-making since they are simple to explain and interpret.

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VALIDATION OF NEW DIAGNOSTIC CRITERIA FOR FATIGUE IN PATIENTS WITH PARKINSON'S DISEASE

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Background: Although disabling fatigue is common in Parkinson's disease (PD), available consensus-based diagnostic criteria have not yet been empirically validated. The aim of the study was to evaluate the clinimetric properties of the criteria.

Methods: A sample of outpatients with PD was evaluated for demographic, clinical, behavioural, and cognitive features. Fatigue was diagnosed according to the new diagnostic criteria and was rated by means of the Parkinson Fatigue Scale (PFS) and Fatigue Severity Scale (FSS). Acceptability, concurrent and discriminant validity, and inter-rater reliability were evaluated with binary logistic regression analyses and Cohen's kappa (κ).

Results: Out of 241 included patients, 17 (7.1%) met the diagnostic criteria for PD-related fatigue. Eight out of nine symptoms described in section A of the diagnostic criteria occurred in >50% of patients with fatigue. Acceptability (missing data=0.8%) of the criteria was good, as well as their concurrent validity with the PFS (Odds Ratio=3.65) and FSS (Odds Ratio=3.63). The discriminant validity of fatigue criteria with other PD-related behavioural and cognitive features was good (Odds Ratio<1.68). The inter-rater reliability was excellent (κ=0.92).

Conclusions: This is the first study to test the clinimetric properties of case definition diagnostic criteria for PD-related fatigue. Our results suggest that current diagnostic criteria may be useful in both clinical practice and research. Future longitudinal studies should examine their long-term

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ELEVATION OF SUBSTANCE P IN PERIPHERAL BLOOD IN PARKINSON'S DISEASE PATIENTS AND ITS CORRELATION WITH MOTOR DISTURBANCES

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Objective: To assess Substance P (SP) blood levels in patients diagnosticated with Parkinson's disease (PD) and healthy subjects, testing possible correlations with the main clinical parameters of the disease to establish a potential value for SP as disease biomarker.

Materials and Methods: SP serum levels were measured in 22 PD patients and 12 age-/sex-matched healthy controls (CTRLs) using a competitive commercial ELISA kit. Clinical assessment was made using Unified Parkinson's Disease Rating Scale Part III (UPDRS III), Non-Motor Symptom Scale, Mini-mental State Examination, levodopa equivalent daily dose calculation. Clinical parameters for PD patients were obtained in ON state. Biochemical data were compared between the two groups and correlated with clinical parameters.

Results: Serum SP was significantly higher in PD patients than in CTRLs [$t(32) = 4.3$; $P = 0.0001$]. Receiver operating characteristic analysis provided an area under the curve of 0.89 ($P = 0.0001$). PD patients were differentiated from CTRLs by a cutoff value of 85.6 pg/mL with a sensitivity of 82% and a specificity of 83.3%. A direct association between serum SP and UPDRS III was found using linear regression ($B = 0.84$; $P = 0.01$), even when dopaminergic therapy was considered as covariate ($B = 0.96$; $P = 0.025$).

Discussion: SP is a neurotransmitter, neuromodulator, and neurotrophic factor in central nervous system. This neuropeptide belongs to the family of tachykinins and its concentration is particularly high in nervous structures critically involved in Parkinson's disease (PD) pathogenesis, including enteric nervous system, vagus nerve, autonomic centers, neocortex and limbic areas, and especially substantia nigra [1,2]. Levels of SP might thus track neurodegeneration in these systems. Since pathological changes occurring either at central or peripheral level reflect in blood, SP could be measured in serum. An elevation of SP in peripheral blood can be observed in patients with cerebrovascular accidents or traumatic brain injury; overall, SP typically increases in the CNS during neuroinflammatory processes [3]. Therefore, the higher circulating levels of SP found here in PD patients might depend on neuroinflammation occurring in PD-related neurodegeneration.

Conclusion: This preliminary study, although limited by sample size, showed that SP serum level was higher in PD patients than CTRLs, and increased proportionally to the severity of motor disturbances. Even if further studies are needed to confirm and extend these preliminary findings, this work suggests serum SP either as potential biomarker or candidate therapeutic target in PD.

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CLINICAL CORRELATES OF ESSENTIAL TREMOR: RESULTS FROM THE TITAN STUDY

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Objective: To outline the clinical features of "pure" essential tremor, according to the new classification of tremor.

Materials: The ITAlian tremor Network (TITAN) is a multicenter prospective study to assess the phenomenology and natural history of different tremor syndromes, diagnosed according to the new tremor classification. Patients are evaluated using the TETRAS and SARA scales, whereas demographic and clinical historical features are gathered using a structured questionnaire.

Methods: We extracted data of ET patients from the TITAN database. Statistical analyses were performed on the whole group as well as stratifying patients by age at onset and presence of family history (FH).

Results: Out of 679 patients recruited as of 01/31/2022, 209 (122M/87F) had with ET. The mean age at onset was of 47.23 ± 22.56 years and the mean disease duration of 20.39 ± 20.17 years. It was observed a bimodal distribution in terms of age at onset, with 39 years representing the age with lower incidence between two peaks. According to this, patients were stratified in two groups: those with onset ≤ 39 years and with onset > 39 years. Tremor severity was higher in the young onset than in the older onset, but this did not affect functioning, likely because postural tremor was more severe than kinetic tremor. A significantly higher percentage of patients with unilateral onset site was found in the older onset group than in the younger (20.24% vs 2.41%, $p<0.001$). No differences were observed in terms of tremor asymmetry at examination and cranial involvement. FH for any movement disorder was present in 102 (63%) patients, of whom 77 (47.53%) reported FH for tremor. In patients with positive FH the age at onset was lower than those without ($p<0.05$), especially for those patients with FH for tremor ($p=0.03$). No other differences were observed between these two groups.

Discussion: Applying the new diagnostic criteria for ET, it is confirmed that it has a bimodal distribution in terms of age at onset., with patients with a young age at onset being more likely to have a genetic background. Age at onset is the only feature predicting tremor severity, possibly due to a longer disease duration in our cohort. However, this did not impact on functioning suggesting a relatively benign course.

Conclusions: ET represents a largely mono-symptomatic disorder with a relatively bening course and a strong genetic susceptibility. The genetic causes of ET are to be elucitaded.

FUNCTIONAL REORGANIZATION OF THE MOTOR CONNECTOME AFTER MRGFUS VIM THALAMOTOMY: A RESTING STATE FMRI STUDY ON 30 PATIENTS

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Essential Tremor is thought to be correlated with a self-sustained cerebellar-thalamo-cortical dysfunctional loop centered on the Vim. Promising results have been recently published on thalamotomy of the Vim using Magnetic Resonance-guided high-intensity Focused Ultrasound (MRgFUS). There are few studies describing functional connectivity correlates of Vim ablation in ET, with most data after stereotactic radiosurgical thalamotomy. Here we used resting state functional connectivity MRI (rs-FC fMRI) to longitudinally (baseline, 3, 6 months) explore dynamics of functional interactions between different nodes of the cerebellar-thalamo-cortical "tremor-network" following MRgFUS Vim ablation in a cohort of patients with ET. We were interested in finding out potential treatment induced changes as well as correlations with clinical outcome at 6 months, patient sample's features (age, disease duration, thalamic volume), MRgFUS operative parameters. 30 patients were assessed clinically by the Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS), the iADL for the quality of life, and by 3T rs-FC fMRI before and after MRgFUS treatment with longitudinal evaluation (0, 3 months, 6 months). All potential covariate of interest were fed into a regression model to assess their impact on potential FC changes. Then, ROI-to-ROI FC differences across three-time points were tested using parameters with an influence on FC as covariates of no interest. All results were FDR corrected at cluster-level. At 6 months we found decreased FC between untreated side (unTS) Lob V of Cerebellum and treated (TS) Lingual Gyrus. Thalamic volume, n° of sonications, mean time, Power peak of each sonication correlated with FC changes after MRgFUS. In particular: the more the atrophy of thalamus, the less the re-connection after MRgFUS between unTS Substantia Nigra reticulata and TS Lob VIIb/VIIIa of Cerebellum; bigger lesions corresponded to greater dis-connection between unTS Internal Pallidum and TS VIM; more sonications per treatment corresponded to greater re-connection between TS Substantia Nigra compacta and reticulata with unTS Lob VIIb/VIIIa of Cerebellum; the longer the time of each sonication, the greater the re-connection between TS and unTS Dentate Nucleus with the Ventral Tegmental Area; the higher the Power of each sonication, the greater the re-connection between TS and unTS Dentate Nucleus with the TS Supplementary Motor Area. MRgFUS is a minimally invasive neurosurgery procedure fully executed in the MRI setting, allowing real-time monitoring of ablative effects on patients. We found that rs-FC between tremor-related cortical, subcortical and cerebellar brain areas was effectively modulated by MRgFUS treatment at 6 months after treatment.

GENDER DIFFERENCES IN PATIENTS UNDERGOING ADVANCED THERAPIES IN PARKINSON'S DISEASE

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Objectives: Parkinson's disease affects more frequently men than women with an overall prevalence gender-ratio of 1.48:1. In advanced PD, motor complications, such as dyskinesia and motor fluctuations are more common in women than in men. A few data are available on the different request of men and women for advanced therapies including Deep brain stimulation (DBS), MRgFUS thalamotomy therapy, Levodopa-carbidopa intestinal gel (LCIG) and Apomorphine infusion. Our aim was to assess whether a gender difference exists in the request for advanced therapies.

Materials and methods: All patients consecutively referring to the Parkinson-Advanced Therapies Center of L'Aquila between March 2018 and December 2021 were screened for the inclusion in the study. Demographical and clinical variables as well as the different request for advanced therapies in men and women were investigated. Descriptive statistics was used to compare groups.

Results: Two hundred one patients (mean age 69.9, mean disease duration 12.67) respectively undergoing MRgFUS (n=78), LCIG (n=36) and DBS (n=12) were included. A higher proportion of men was recognized for all the treatments investigated (MRgFUS, 68 men and 10 women; LCIG, 24 men and 11 women; DBS 9 men and 4 women). Out of patients undergoing MRgFUS (n=78), women showed a similar age profile as compared to men (68.0±9.7 vs 68.3±9.7) but a higher disease duration (14.9±4.9 vs 8.8±4.7) and UPDRS III score (36.3 vs 29.8). Out of patients undergoing LCIG (n=36), women were older than men (81.6±7.8 vs 72.3±7.8), had similar disease duration (10.2±5.2 vs 10.5±5.2) and UPDRS III scores (35.5 vs 37.6). Out of patients undergoing DBS (n=12), women were young than men (61.2±9.18 vs 66.4±8.53), had a shorter disease duration (10.0±4.79 vs 13.0±4.91) and a lower UPDRS III score (21.5 vs 22.4).

Conclusions: Previous studies showed disparities in the request for DBS between men and women as women are less likely to undergo DBS. No data are available about gender differences in the request for other advanced therapies. Our study moves a step forward in showing the general tendency of women to use traditional rather than advanced therapies, likely as a consequences of various psychological, social and environmental factors.

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SCREENING OF SNCA P.A53T MUTATION IN THE SELE RIVER VALLEY: THE CONTURSI KINDRED 2.0

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Objectives: Parkinson disease (PD) is a common progressive neurodegenerative condition with unknow etiology. The majority of cases of PD are sporadic, however, also rare familial forms exist. The first identified mutation was a missense mutation resulting in an alanine to threonine substitution at position 53 (A53T) in the alpha-synuclein gene (SNCA) in the Contursi Kindred, a large family originating from Contursi, in the Salerno province [1]. The aim of the present study is to describe the prevalence of SNCA p.A53T mutation in individuals with Parkinsonism in the Sele River Valley and the clinical differences between patients with and without this mutation. We also fully characterized all pedigrees of the Contursi Kindred.

Methods and Materials: We tracked the prevalence of individuals with parkinsonism in the Sele river Valley through the electronic database of the National Health System. Neurological examination and blood sampling were proposed to all the individuals in such lists and their relatives as well as to affected and unaffected subjects belonging to families known to harbor the p.A53T mutation. Genetic testing for SCNA missense mutation (A53T) was performed using real-time polymerase chain reaction (PCR).

Results: The Sele Valley includes 12 villages for a total of 29.070 inhabitants (14.571 <45 years; 7.917 45-64 y; 6.309 >64 y). Exploration of the

National Health System Electronic Database disclosed 154 subjects affected by Parkinsonism (0,52% total prevalence; 0,01% <45 y; 0,11% 45-64 y; 2,23% >64 y). A total of 166 subjects were visited and 134 subjects performed genetic analysis. We found 23 subject belonged to three main pedigrees, whom 17 p.A53T+ (12 affected and 5 unaffected) and 8 p.A532T-. Thirty are healthy of the remaining 109 subjects. Subjects affected with p.A53T mutation showing autosomal dominant inheritance pattern and presented heterogeneous manifestations with a significative difference for the presence of myoclonus (p=0.03), pyramidal signs (p=0.03), dystonia (p=0.02), behavioral disorders (p=0.01), apraxia (p=0.04) and with bradykinesia, rigidity (p=0.05) and ocular motor disturbance tendent to significatively, compared to subjects without mutation.

Discussion: As expected, the prevalence of PD increases with age. The three main pedigrees have an autosomal dominant pattern of inheritance pattern and intrafamilial clinical heterogeneity.

Conclusions: All subjects with parkinsonism and positive family history from the Sele river Valley should be investigated for SNCA p.A53T.

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DIFFERENT PATTERNS OF ACUTE SACCADIC RESPONSES TO LEVODOPA CHALLENGE TEST IN DE NOVO PARKINSON'S DISEASE: POSSIBILE PROGNOSTIC IMPLICATIONS

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Objectives: To explore possible different patterns of acute saccadic responses to Levodopa Challenge Test (LCT) in a de novo drug-naïve Parkinson's Disease (PD) population and potentially related differences in clinical progression.

Materials and methods: Patients fulfilling MDS criteria for PD were enrolled. Eye movements were recorded by Eyelink 1000 Plus. Visually-guided saccades were assessed at baseline and after 2 hours from the administration of Levodopa/Carbidopa 250/25 mg. Saccadic velocities, latencies and accuracy were assessed. Nonhierarchical cluster analysis using k-means method was performed based on peak-of-dose parameters. Main sequence and saccadic latencies distribution analysis were performed. Patients were clinically followed-up at 2 years.

Results: Thirty-two de novo PD patients were enrolled. Two clusters were identified among PD patients: Cluster A (21 patients) and B (11 patients). No significant differences in demographical characteristics and clinical assessment both at baseline and peak-of-dose were found between clusters. Improved saccadic velocities and accuracy as well as increased latencies were found at peak-of-dose in cluster A. An opposite trend was demonstrated in cluster B. Different main sequence patterns were found between clusters. An increased cumulative frequency of short-latency saccades was found at peak-of-dose in Cluster B. After a 2 years follow-up, Cluster B patients referred more autonomic symptoms and Levodopa (LD) side effects compared to Cluster A patients.

Discussion: Saccadic eye movements abnormalities were described in PD. To date, few studies with conflicting results assessed LD effects on a drug-naïve population through a standardized LCT. Here we identified two distinct saccadic patterns after LD administration, suggesting that previous inconsistent findings could be at least in part related to an intrinsically heterogeneous saccadic LD response in PD. Moreover, patients with worse oculomotor response at peak-of-dose on LCT prospectively developed more autonomic symptoms and intolerance to dopaminergic treatment, as expression of poorer outcome. Taken together, these findings highlight the possible prognostic role of saccadic LD response to LCT in de novo PD.

Conclusions: Different patterns of saccadic LD responses were demonstrated among de novo PD. Patients with worse oculomotor response to LD prospectively developed a poorer clinical outcome, suggesting a possible prognostic role of saccadic assessment on LCT. Further studies are needed.

DIAGNOSTIC AND PROGNOSTIC VALUE OF EXTERNAL ANAL SPHINCTER EMG PATTERNS IN MULTIPLE SYSTEM ATROPHY

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Objectives: To explore the diagnostic and prognostic value of a novel classification of EMG patterns of the external anal sphincter (EAS), and their correlations with clinical features and cardiovascular autonomic function in patients with multiple system atrophy (MSA).

Materials and methods: We retrospectively collected clinical data and EAS EMG findings in 72 patients with MSA and 21 with Parkinson's disease (PD). Sixty-one and 56 MSA patients also underwent cardiovascular reflex tests and 24-hour blood pressure monitoring, respectively. Motor impairment in subjects with MSA was assessed by means of the motor section of the Unified Multiple System Atrophy Rating Scale (UMSARS II). We ascertained the survival times of 49 MSA patients who died during follow-up.

Results: Based on the evaluation of spontaneous activity, motor unit action potential (MUAP) duration and recruitment, we identified four EAS EMG patterns ranging from normal findings (pattern I) to mild, moderate or severe neurogenic damage (patterns II, III and IV, respectively). Pattern I was frequently observed in PD patients, while it was associated with prolonged survival when identified in a few MSA patients. Conversely, patterns II, III and IV were predominant in MSA. Subjects with MSA and EAS EMG abnormalities often showed fecal incontinence and urogenital symptoms, which were frequently present at disease onset when MUAP recruitment was impaired. Abnormal EAS EMG patterns correlated with MSA diagnosis ($p<0.001$), with a sensitivity of 88.9%, specificity of 85.7%, and odds ratio of 48.0 (95% confidence interval: 11.5–199.8). Pattern IV was associated with the highest likelihood of MSA diagnosis ($p<0.001$), and with the worst prognosis in the MSA cohort (vs. pattern I, $p<0.001$; vs. pattern II, $p=0.001$; vs. pattern III, $p=0.007$). EAS EMG patterns were not related to motor impairment or cardiovascular autonomic function in MSA.

Discussion: The increasing severity of EAS EMG patterns paralleled diagnostic accuracy and survival in MSA. EAS EMG patterns correlated with symptom type at disease onset and with prevalence of urogenital symptoms and fecal incontinence.

Conclusions: In suspected MSA, EAS EMG investigation can be a valuable diagnostic and prognostic tool, which should be recommended especially when the clinical picture is unclear. A normal EAS EMG pattern in MSA patients could identify a small subset of subjects characterized by less neurodegeneration and prolonged survival. Longitudinal EMG assessments are warranted to verify whether EAS EMG patterns change over time, while neuroimaging and neuropathological studies could clarify the pathophysiological correlates of EAS EMG patterns in MSA.

OPICAPONE FOR THE TREATMENT OF PARKINSON'S DISEASE: THE EXPERIENCE OF THE PARKINSON'S DISEASE AND MOVEMENT DISORDERS CENTER OF IRCCS MONDINO FOUNDATION

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Background: Catechol-O-methyl transferase inhibitors (COMT-I) are currently used as first-line add-on therapy to levodopa for the treatment of end-of-dose motor fluctuations in Parkinson's disease (PD) patients, as they increase levodopa bioavailability. Opicapone is a new long-acting, peripherally selective, third-generation once-daily catechol-O-methyl transferase inhibitor. In June 2016, Opicapone received the approval for marketing authorization from the European Commission as adjunctive therapy to levodopa/ DOPA decarboxylase inhibitors in patients with PD and end-of-dose motor fluctuations.

Objective: To confirm the safety and efficacy of the opicapone treatment for PD based on experience made at the Parkinson's Disease and Movement Disorders Center of the IRCCS Mondino Foundation.

Methods: PD patients with motor fluctuations were included. Clinical assessment included H&Y stage, UPDRS III, LD equivalent dose (LEDD), daily time spent in OFF and in ON, and Clinical Global Impression-Improvement (CGI-I).

Result: One hundred eighty-five PD patients have received opicapone 50 mg once-daily, starting from October 2018 at our Center. 60 patients out of 185 (32%) were not included in the analyses due to lack of efficacy in 18 patients and poor tolerability in 17 patients; 25 patients missed the follow-up. Finally 125 PD patients have continued treatment and had reach follow up a 12 months. The patients who persisted with opicapone a 12 moths (68 males and 57 females; mean age 68,1 ±9,7; mean disease duration: 9,9 ± 4,2 years; baseline UPDRS-III 25,6±14,2) were categorized at baseline as "entacapone switchers" (56%) or "opicapone as first treatment" (43%). After 12 months of treatment with opicapone 50 mg, the majority of patients (71.3%) showed beneficial effects with improvement at CGI-I, decrease in daily OFF time (mean at baseline 4.6 hours, mean at follow-up 3 hours), reduction in L-dopa equivalent daily dosage (LEDD) (from a mean at baseline of 908,2 mg to a mean of 806,8 mg at follow up). Notably, in 5 PD patients on Levodopa-Carbidopa intestinal gel (LCIG) infusion therapy, the introduction of Opicapone led to reduction of LCIG daily by 20% without a worsening of motor symptom.

Conclusion: Opicapone is a useful drug for management of motor fluctuations in PD. The use of opicapone as an add-on therapy to LCIG infusion in advanced PD patients could reduce the LCIG infusion daily dose and potentially the costs associated with this advanced therapy.

HEMICHOREA-HEMIBALLISMUS AS AN UNUSUAL PRESENTATION OF DIABETES MELLITUS – A CASE REPORT

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Aims: To describe the clinical and neuroradiological findings in a patient with hyperglycemia-induced hemichorea-hemiballismus syndrome (HHHS).

Materials and Methods: A patient with recent history of uncontrolled diabetes and acute onset of hemichorea underwent neurological examination, routine blood and urine analysis, head computerized tomography (CT) scan, and brain magnetic resonance imaging (MRI).

Results: A 78-year-old woman was admitted to our hospital complaining of 6 days of choreic movements affecting her left upper and lower extremity (videorecording). Her cognitive status was normal. She had been diagnosed with type 2 diabetes two weeks before, but despite therapy she reported poor control of blood glucose values. Blood tests showed blood glucose level of 357 mg/dL and serum osmolality of 301 mOsm/kg. Her venous pH was 7.39, and bicarbonate 29 mmol/L. Urine analysis tested negative for ketonuria. Glycosylated hemoglobin (HbA1c) was 138 mmol/mol. Brain MRI revealed a high intensity signal on T1-weighted images in both lentiform nuclei, more evident on the right side, with slight signal hypointensity of the same areas on T2/FLAIR sequences. Abnormal limb movements persisted even after normalization of the blood glucose levels. Symptomatic treatment attempt with haloperidol was started. At a visit by teleconsultation about 2 months after hospital discharge, movements were only noticeable in her left distal upper limb.

Discussion: HHHS is now a well-recognized clinical entity. Although the exact mechanisms underlying HHHS are not well understood, the classic hypothesis refers to petechial hemorrhages as the main reason for the so-called "diabetic striatopathy" [1]; more recently, a selective impairment of basal ganglia network has been related to the activation of anaerobic pathway in Krebs cycle that results in a reduction of GABAergic tone, thus enhancing thalamo-cortical transmission [2,3]. HHHS can be an early manifestation during hyperosmolar hyperglycemic state, and rarely the first presentation of diabetes. Brain imaging often show typical findings and is crucial in differentiating HHHS from vascular chorea. Restoration of normal blood glucose values plus symptomatic therapy often rescue symptoms, but some may take up to months.

Conclusions: Nonketotic hyperglycemia is an unusual, potentially easily-treatable cause of chorea-ballismus. Since it can represent a life-threatening condition, early recognition is crucial in order to start a prompt management and prevent further complications. HHHS should always be suspected in new-onset chorea/hemichorea, especially in elderly patients and even in those with no history of diabetes. The prognosis is excellent in most of the cases.

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MACHINE LEARNING CAN PREDICT MILD COGNITIVE IMPAIRMENT IN PARKINSON DISEASE

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Background and Aim: Several mechanisms are likely to contribute to cognitive decline in PD [1]. Clinical markers of cognitive decline encompass some mental non-motor symptoms like visual hallucinations, apathy, anxiety and depression. In addition, also freezing of gait (FOG) and specific gait alterations have been associated with cognitive dysfunction in PD [2]. Finally, although some findings suggest that low cerebrospinal fluid levels of amyloid-β42 may predict cognitive decline and dementia in PD, to date PET imaging of amyloid-β (Aβ) plaques in vivo failed to demonstrate consistently the association between Aβ plaques deposition and mild cognitive impairment (MCI) in PD [3] (PD-MCI). The aim of the present study was using machine leaning approaches to find significant markers associated with PD-MCI.

Materials and Methods: Patients were assessed through an extensive clinical and neuropsychological examination. Clinical evaluation included the

assessment of visual hallucinations, apathy, sleep disorders, anxiety, depression and FOG by means of the MDS-UPDRS I and II. Based on neuropsychological examination patients were classified in patients without and with MCI (MCI-, MCI+). Patients' gait was assessed while performing a dual task, namely a working memory task. A subgroup of PD patients also underwent amyloid PET imaging. MCI- and MCI+ subjects were compared on demographic data, clinical variables, gait analysis features and amyloid PET variables. Then, a machine learning analysis was performed twice: a first model was implemented with age, clinical variables (hallucinations/psychosis, depressed mood, anxiety, apathy, sleep problems, FOG) and gait features, while a second model was implemented with PET features combined with the top-5 features of the former model.

Results: Seventy-five PD patients were enrolled (33 MCI+ and 42 MCI-). MCI+ vs MCI- resulted older and showed worse gait pattern, characterized by increased measures of dynamic instability and reduced step and cycle length; conversely, the two groups did not significantly differ on amyloid PET tracer retention. As regards the machine learning analyses, evaluation metrics were satisfactory for the first model overcoming 80% for accuracy and specificity, whereas they were disappointing for the second model.

Discussion and Conclusions: The present study demonstrates that a data mining approach using specific clinical and quantitative gait variables exhibits high accuracy, specificity and sensitivity in predicting the presence of PD-MCI, whereas amyloid PET tracer retention does not appear to increase prediction of MCI in PD. In addition, our results prompt that machine learning on gait parameters might represent a reliable surrogate biomarker of PD-MCI.

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AXIAL IMPAIRMENT AND FALLS IN PARKINSON'S DISEASE: 15 YEARS OF SUBTHALAMIC DEEP BRAIN STIMULATION

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Background and Objectives: In people with Parkinson's disease (PD), the sustained clinical benefits from subthalamic nucleus-deep brain stimulation (STN-DBS) are frequently undermined by the occurrence of axial impairment and falls that are refractory to available therapies. So far, a definite consensus concerning the effects of STN-DBS on axial impairment and falls in PD people with STN-DBS is still absent. Moreover, risk factors predicting the occurrence of these disorders after STN-DBS surgery in PD are largely unknown. This study aims to examine the short- and long-term evolution of axial impairment and falls and investigate risk factors for their occurrence in PD people with STN-DBS.

Materials and Methods: We retrospectively analysed PD people with STN-DBS operated between 1993 and 2010 and followed longitudinally. Axial scores and falling frequency were collected and compared at baseline, 1, 10 and 15 years after surgery. Preoperative demographic and clinical data, including disease duration and severity, phenotype, motor and cognitive scales, medications, and vascular changes in neuroimaging were examined as possible risk factors through Kaplan-Meier and Cox regression analyses.

Results: Of 417 screened individuals, 302 people were included at baseline and 1-year evaluation, whereas 102 and 57 were available at 10- and 15-year follow-ups, respectively. Axial scores were similar at baseline (1.94±1.80) and 1 year (1.97±2.14) ($p=0.746$), but higher at 10 (6.11±4.24) and 15 years (7.39 ±4.73) ($p<0.001$). The prevalence rate of frequent fallers progressively increased from baseline (5.3%) to 15 years (37.3%) ($p<0.05$). Preoperative axial scores, frontal dysfunction and age at disease onset were risk factors for axial impairment progression after surgery. Similarly, axial scores, akinetic/rigid phenotype, age at disease onset and disease duration at surgery predicted frequent falls.

Discussion and Conclusions: Axial function in PD is unchanged in the short-term after STN-DBS surgery but progressively worsens in the long-term period. This would reflect the natural history of the disease as observed in non-operated patients. The progressive impairment of axial functions may reflect neurodegenerative processes in non-dopaminergic pathways which are unaffected by STN-DBS. Conversely, the progressive increase of falls since the first year after surgery would partially depend on the raised activity levels associated with STN-DBS-induced motor improvement. Risk factors for axial impairment progression and falls after STN-DBS surgery imply specific motor, cognitive and demographic features. The observed risk factors suggest the contribution of specific disease-related variables, as well as their relationship with ageing, to the pathophysiology of axial impairment and falls in PD people with STN-DBS.

PARKINSON'S DISEASE AND DEEP BRAIN STIMULATION: DOES IMAGE-GUIDED PROGRAMMING HELP TO OPTIMIZE DIRECTIONAL STIMULATION?

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Introduction: Deep brain stimulation (DBS) is a well-established surgical procedure for treatment of motor complications in advanced Parkinson's Disease (PD). The recent development of directional leads offers highly individualized, yet time-consuming and often very complex programming. The GUIDE™ XT is a commercially available software for visualization of DBS leads within the patient -specific anatomy from fusions of preoperative magnetic resonance imaging (MRI) and postoperative computed tomography (CT) scans, helping clinicians to visualize the stimulated field in order to optimize and personalize DBS parameters for each patient.

Objective: Compare changes in motor symptoms of Parkinson's Disease (PD), dopaminergic therapy and total electrical energy delivered (TEDD) achieved by DBS programming using GUIDE XT ™ versus standard-of-care clinical programming

Methods: We evaluated a cohort of 56 PD patients who underwent DBS surgery with directional leads (44 STN and 12 GPi, 38 Male and 18 Female, mean age 62 years) from 2017 to 2022. Of these, 27 were re-evaluated in OFF medication after clinical (T1) and imaging-guided programming (T2). Time span between T1 and T2 was six months. Clinical status was evaluated through the Unified Parkinson's Disease Rating Scale (UPDRS) part III and IV. We compared the two groups using the Wilcoxon matched-pairs signed rank test. A p-value of less than 0.05 was considered significant.

Results: Imaging-guided programming produced a significant clinical improvement as measured with the UPDRS scale; mean UPDRS part III scores

decreased significantly between T1 and T2 (T1= 17,3±10,6; T2 15,6 ± 10,7 p=0,008). Similarly, we observed a meaningful effect on motor fluctuations measured with UPDRS part IV (T1=3,26 ±3,53; T2 =1,92± 2,2; p=0,003). There was no relevant difference of levodopa equivalent daily dose (LEDD) between T1 and T2.

Discussion and Conclusion: Imaging-based DBS programming using GUIDE XT™ resulted in non-inferior motor symptom control compared to the standard-of-care procedure that is time-intensive clinical evaluation mostly of effects of directional current shaping. Prospective randomized trials are needed to better understand if DBS imaging-guided is more suitable than clinical programming alone.

MOBILE HEALTH TECHNOLOGY IDENTIFIES GAIT IMPAIRMENT IN NEWLY DIAGNOSED PARKINSON'S DISEASE

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Objective: Evaluate patterns of gait in supervised conditions in newly diagnosed Parkinson's disease with and without clinically relevant gait alterations.

Materials: The prospective study included consecutive early PD patients, subdivided into PDs with (PD-G) and without (PD-nG) clinically evident gait alterations, respectively, and age-matched controls. Each subject underwent gait analyses in supervised normal and dual-task conditions using mobile health technology. A complex clinical assessment including motor and non-motor scales was performed too.

Methods: The study evaluated gait parameters differentiating HC from both PD-G and PD-nG using ANCOVA adjusting for the effect of age, sex and height. Pairwise multiple comparisons with Bonferroni correction were used to identify which means differ.

Results: Seventy-one early PD patients, including 37 Normal Gait PDs and 34 Impaired Gait PDs, and Forty-four age-matched controls entered the study. The two early PD subgroup were similar in clinical and gait characteristics except for the mean value of MDS-UPDRS-III. PD-G and PD-nG patients showed shortened mean step lengths in comparison to HCs both in single gait and dual task tests. Step time under supervised conditions had a longer duration in both simple gaits and while performing checking boxes in PD-G, while step time duration in PD-nG was longer only in dual task tests in comparison to controls. Double Limb support showed longer duration only in dual task tests in both PD-G and PD-nG in comparison to HCs.

Discussion: Mobile health technology enables the detection of subtle gait changes in all parkinsonian patients, independently from clinical evaluation. Specifically, Step length differentiates PD-G and PD-nG patients from controls in all settings. On the contrary time parameters identify PD only if gait alterations are clinically evident or during dual task tests.

Conclusion: Mobile health technologies are able to identify altered gait parameters even in early PDs without clinically relevant gait alterations. Larger ongoing longitudinal studies are needed in order to evaluate gait alterations within the prodromal phases of the disease and the impact of dopaminergic medication on gait performance over-time.

EPILEPSY

NEUROPHYSIOLOGICAL EFFECTS OF VAGAL NERVE STIMULATION IN EPILEPSY: A SOMATOSENSORY EVOKED POTENTIAL AND QUANTITATIVE EEG STUDY

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Objective: VNS is a viable choice in non-surgical cases of drug-resistant epilepsy (DRE), however its specific mechanisms of action remain still unclear. People with epilepsy (PwE) report benefits from VNS beyond the mere seizure frequency. Reduction of seizure severity and post-ictal symptoms can result in a global improvement of alertness, cognition and quality of life. To test the hypothesis that these effects sources in a restoration of physiological cortico-subcortical and cortical activity, we designed a somatosensory evoked potentials (SEPs) and quantitative EEG (qEEG) study.

Methods: Eight PwE undergoing VNS therapy (four women, 49±11 years-old), were enrolled. A 35-minute high-density EEG and SEPs from right hand were recorded both before VNS therapy (T0) and 6 months later (T1). We matched T0 with two paired conditions: T1 ON and T1 OFF (VNS active and inactive mode, respectively). N20 and N24/P24 amplitude and latency for SEPs and Individual Alpha Frequency (IAF) and PSD (Power Spectrum Density) in classical frequency bands for qEEG were calculated. Seizure frequency, McHugh and global clinical impression (GCI) scales were recorded at each timepoint.

Results: One patient reported a seizure frequency reduction >50%, 4 (50%) PwE a reduction in seizure's severity at McHugh scale and 6 (75%) improved at GCI scale after VNS therapy. N20 amplitude increased from T0 to T1 (p=0.004 and p=0.038, respectively for OFF and ON condition). P24/N24 amplitude was higher in T1 OFF respect to T1 ON (p=0.048). EEG analysis revealed a decrease in delta and an increase in alpha power after VNS therapy (p=0.04, T0 vs T1 OFF).

Discussion and Conclusions: We demonstrated that VNS therapy induces SEPs and EEG changes, which are consistent with a physiological cortico-subcortical and cortical activity improvement. Present neurophysiological data reveal the possible pathways subtending the improvement of ictal severity and its consequences mediated by VNS.

ELECTROCORTICOGRAPHY FOR TAILORED-SURGERY IN DRUG-RESISTANT EPILEPSY WITH TEMPORAL ENCEPHALOCELE

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Rational and objectives: Temporal lobe encephaloceles are increasingly recognized as a potential cause of medically refractory epilepsy and surgical treatment has proven effective. Here we describe two patients with drug-resistant temporal lobe epilepsy with temporal encephalocele who underwent a tailored temporal lobectomy.

Methods: Patients underwent serial intraoperative electrocorticography (ECoG) recordings with strip electrodes placed on the temporal pole cortex before resection, on the surgical neocortical margin of the resection and, lastly, on the mesial temporal structures. Both bipolar and referential electrode montages were reviewed to identify epileptiform activity and help guide surgical planning. Density (number of sharp waves and spikes over 10 sec-periods) of epileptiform abnormalities was calculated for each patient.

Results: Patient 1, a right-handed 38-year-old male, presented with drug-resistant temporal lobe seizures that had started 6 months before. Left temporal

spikes and one seizure arising from the left temporal channels were recorded at the video-EEG long-term monitoring (VLTM). A 3T brain MRI showed an encephalocele of the left temporal pole. The intraoperative ECoG showed sporadic spikes on the neocortical temporal surface (spike density 1.27) before surgical resection, while no epileptic activity was recorded on the amygdala and hippocampus. Therefore, the mesial structures were spared. The patient is seizure-free at a 9-month follow-up. Patient 2, a left-handed male of 20 years old at the time of surgery, presented with temporal seizures since the age of 19. A 3T brain MRI revealed a left mesial temporal pole encephalocele (5x5x4 mm). The VLTM was characterized by frequent left temporal slow activity and spikes. Three seizures were recorded with a left temporal lobe onset. The intraoperative ECoG revealed recurring repetitive spikes and polyspikes, sometimes with a subcontinuous trend, and rapid activity in short bursts on the neocortical temporal surface (spike density 6.77) before surgical resection, and persistent epileptic activity on the posterior temporal resection margin, so the surgical procedure was extended until the sylvian vein. No epileptic activity was seen on the hippocampus thus it was spared. Pathology showed a high level of gliosis. The patient is seizure-free at a 5-month follow-up.

Discussion and conclusion: Resection of the encephalocele and associated cortex is often sufficient to provide seizure control. However, it is difficult to determine the extent of adjacent temporal lobe that should be resected. These two cases demonstrate the usefulness of ECoG for a tailored surgical resection according to the irritative zone.

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NEUROPHYSIOLOGICAL EFFECTS OF VAGAL NERVE STIMULATION IN EPILEPSY: A SOMATOSENSORY EVOKED POTENTIAL AND QUANTITATIVE EEG STUDY

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Objectives: VNS is a viable choice in non-surgical cases of drug-resistant epilepsy (DRE) however its specific mechanisms of action remain still unclear. People with epilepsy (PwE) report benefits from VNS beyond the mere seizure frequency. Reduction of seizure severity and post-ictal symptoms can result in a global improvement of alertness, cognition and quality of life. To test the hypothesis that these effects source in a restoration of physiological cortico-subcortical and cortical activity, we designed a somatosensory evoked potentials (SEPs) and quantitative EEG (qEEG) study.

Materials and methods: Eight PwE undergoing VNS therapy (four women, 49±11 years-old), were enrolled. A 35-minute high-density EEG and SEPs from right hand were recorded both before VNS therapy (T0) and 6 months later (T1). We matched T0 with two paired conditions: T1 ON and T1 OFF (VNS active and inactive mode, respectively). N20 and N24/P24 amplitude and latency for SEPs and Individual Alpha Frequency (IAF) and PSD (Power Spectrum Density) in classical frequency bands for qEEG were calculated. Seizure frequency, McHugh and global clinical impression (GCI) scales were recorded at each timepoint.

Results: One patient reported a seizure frequency reduction >50%, 4 (50%) PwE a reduction in seizure's severity at McHugh scale and 6 (75%) improved at GCI scale after VNS therapy. N20 amplitude increased from T0 to T1 (p=0.004 and p=0.038, respectively for OFF and ON condition). P24/N24 amplitude was higher in T1 OFF respect to T1 ON (p=0.048). EEG analysis revealed a decrease in delta and an increase in alpha power after VNS therapy (p=0.04, T0 vs T1 OFF).

Conclusions: We demonstrated that VNS therapy induces SEPs and EEG changes, which are consistent with a physiological cortico-subcortical and cortical activity improvement. Present neurophysiological data reveal the possible pathways subtending the improvement of ictal severity and its consequences mediated by VNS.

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LATE SEIZURES ASSOCIATED WITH CEREBRAL VENOUS THROMBOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Aim of the study: There are many unsolved issues regarding seizures in the context of cerebral venous thrombosis (CVT). We aimed to address existing data regarding the prevalence and risk factors for post-cerebral venous thrombosis late seizures (LS). The identification of predictors of CVT-LS can be useful for prognosis and management.

Materials: Medical-scientific platforms such as Medline (Pubmed interface), Google Scholar and Scopus were used to select papers on predictors of seizures in CVT. Data concerning seizure prevalence, study design, duration of follow-up (minimum 1 year, on average 2 years), included population (children, adults or both), data on the selected variables (acute symptomatic seizures, acute status epilepticus, antiepileptic drug prophylaxis, coma, focal neurological signs, presence of hemorrhagic lesions, sex, age, involvement of specific venous sinuses or cortical veins) were extracted.

Methods: We estimated odds ratios (ORs) for all the variables of interest. ORs were pooled and synthesized in a meta-analysis with random effect modeling due to heterogeneous setting and design across studies. Risk of bias was assessed with Ottawa-Newcastle Scale.

Results: Four studies were included, reporting data on 1309 patients with CVT, of whom 142 were diagnosed with CVT-LS, corresponding to a prevalence of 11%. The recurrence risk after the first CVT-LS was 70% in the largest included study. The most relevant predictors of CVT-LS were acute symptomatic seizures (OR 5.66, 95% confidence interval, CI 3.83-8.35), stupor/coma (OR 6.81, 95% CI 1.18-39.20), focal neurologic signs (OR 6.81, 95% CI 1.18-39.2), hemorrhagic component (OR 3.52, 95% CI 2.45-5.06), and superior sagittal sinus involvement (OR 1.52, 95% CI 1.04 -2.21).

Discussion and Conclusion: We identified several risk factors for CVT-LS, that should be considered in clinical practice. Based on the high recurrence risk of CVT-LS, this condition may be considered as symptomatic epilepsy, according to ILAE criteria. Further high-quality studies are warranted to develop a predictive model for CVT-LS.

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CLINICAL INTERACTIONS IN PATIENTS WITH ATRIAL FIBRILLATION TREATED WITH NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS (NOACS) AND ANTI-SEIZURES MEDICATIONS (ASMS): THE INTERNOAS STUDY

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Background: Both non-vitamin K antagonist (NOACs) and some anti-seizures medications (ASMs) are substrates of the CYP3A4 and their metabolism is dependent on P-gp protein. Data on potential interactions between NOACs and ASMs are limited and current guidelines do not support the use of or recommend great caution in patients concurrently treated with NOACs and ASMs [1,2]. The aim of this study is to evaluate potential clinical interactions between ASMs and NOACs.

Materials and Methods: This retrospective study involves five centres in Italy and included three cohorts: patients with non-valvular atrial fibrillation (AF) and epilepsy concurrently treated with NOACs and ASMs (ASM+NOAC cohort); patients with non-valvular AF treated with NOACs (NOAC cohort); patients with epilepsy treated with ASMs (ASM cohort). Baseline and clinical data were collected. A propensity score matching was estimated using a logistic regression model adjusted for CHA2DS2-VASc. The primary outcome was the composite of ischemic stroke, transient ischemic attack (TIA) and major bleeding.

Results: Overall, we included 189 patients in the ASM+NOAC Cohort, 298 in the NOAC Cohort and 50 patients in the ASM Cohort. The mean follow-up was 3 years. ASM+NOAC patients had more often a history of previous stroke and of previous major bleeding compared to the other cohorts. After propensity score matching, the mean CHA2DS2-VASc score was 4.5±1.8 in the ASM+NOAC Cohort and 4.3±1.5 in the NOAC Cohort. The cumulative incidence of thromboembolic events and major bleeding at 365 days was 5.7% (95% CI 2.2-9.0) in ASM+NOAC patients and 1.2% (95% CI 0-2.8) in NOAC patients [Hazard ratio (HR) 6.7, 95% CI = 2.3-20.0]. Specifically, at 365 days the cumulative incidence of ischemic stroke or TIA was 5.2% in ASM+NOAC patients and 1.7% in NOAC patients (HR 4.8, 95% CI 1.1-25.0). One-year incidence of major bleeding was 0.5% in ASM+NOAC patients and 1.2% in NOAC patients (HR 0.6, 95% CI 0.1-6.3). After matching patients from ASM+NOAC and ASM Cohorts, the mean CHA2DS2-VASc score was 2.5±0.4 in ASM+NOAC patients and 2.5±0.4 in ASM patients. The cumulative incidence of the primary outcome at 365 days was 3.1% in ASM+NOAC patients and 0% in ASM patients. Neither ischemic stroke or TIA nor major bleeding occurred in ASM patients during the study period.

Conclusion: AF patients concurrently treated with NOACs and ASMs seemed to have an increased risk of the composite of thromboembolic events and major bleeding compared to patients treated with NOAC only. This risk was mainly driven by an increased incidence of thromboembolic events.

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PATIENT SELF-COLLECTED VERSUS NURSE-COLLECTED FINGERPRICK VOLUMETRIC ABSORPTIVE MICROSAMPLING FOR ANTISEIZURE MEDICATION THERAPEUTIC MONITORING

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Aim: Therapeutic drug monitoring (TDM) of antiseizure medication (ASMs) is a valuable tool for individualizing drug treatment based on ASMs plasma concentration from venous blood. Volumetric absorptive microsampling (VAMS - Mitra®-Neoteryx) is increasingly proposed as a clinically practical alternative to invasive venipuncture. VAMS requires a smaller blood volume and a less invasive sampling procedure by fingerprick allowing for sample self-collection. The study's aim was to establish the feasibility of patient self-collected VAMS for ASMs TDM1: ASMs concentrations from patient VAMS self-collected versus nurse-collected VAMS were compared [1]. ASMs plasma concentrations were used as reference-standard to compare blood concentrations found in VAMS.

Material: Morning venous blood samples were collected in lithium heparin-coated vacutainers. Capillary blood was collected using VAMS

devices. ASMs included were carbamazepine (CBZ), ethosuximide (ETS), lacosamide (LCM), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (MHD), phenytoin (PHT), phenobarbital (PB), perampanel (PMP), rufinamide (RFN), topiramate (TPM), valproic acid (VPA) and zonisamide (ZNS).

Methods: Epileptic patients on chronic steady-state ASMs were enrolled for this prospective single-center study. Venous and VAMS capillary blood were collected by nurses [1]. Afterward, patients performed VAMS collection by themselves. ASMs blood and plasma concentration analyses were performed by ultra-high liquid chromatography-mass spectrometry [2,3]. ASMs blood concentrations from nurse-collected VAMS were compared to plasma concentrations by linear regression analysis. A cross-validation study was performed comparing ASMs concentrations obtained by nurse-collected versus patient self-collected VAMS samples according to European Medicine Agency Guidelines.

Results: 301 patients (173 females, mean age: 44.33±16.10 years) were enrolled providing a total of 456 ASMs concentration measurements (CBZ 11,7%; ETS 0,4%; LCS 5,9%; LTG 25,6%; LEV 13,1%; MHD 6,4%; PHT 2,8%; PB 3,4%; PMP 5,3%; RFN 1,1%; TPM 4,2%; VPA 13,6%; ZNS 6,6%). Linear correlation analyses between ASMs plasma and blood nurse-collected VAMS concentrations showed heterogeneous results depending on the analyte (R2 ranging from 0.4 to 0.9; $p<0.001$). Cross-validation analysis between nurse-collected vs patient self-collected VAMS showed a bias within ±20% for more than 78% of intrasubject ASMs determinations.

Discussion: ASMs blood concentrations from self-collected VAMS were comparable with those from nurse-collected, demonstrating that patients' self-sampling can be feasible after minimal training. VAMS offers benefits in terms of minimizing blood volume collection and can be a useful support for at-home TDM.

Conclusions: To our knowledge, this is the first study considering the real-world application of patient self-collected VAMS for ASMs TDM. The results give a promising basis for future at-home VAMS applications.

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THE CONTINUUM BETWEEN RETT SYNDROME AND DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES: TWO CASES WITH DE NOVO MUTATIONS IN KLHL20 AND MEF2C

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Objectives: Rett syndrome (RTT) is a neurodevelopmental disease, whose diagnosis is based on Neul's criteria [1]. Mutations in MECP2 cause 95-97% of typical RTT1. FOXG1 and CDKL5 are known genes related to atypical forms, which may present with epilepsy onset in the first year of life2. We report the epilepsy outcome of two individuals with atypical RTT due to de novo mutations in genes not usually associated with this condition.

Materials: We selected patients according to Neul's criteria. Data on epilepsy, EEGs, brain MRIs were collected in our epilepsy center.

Methods: Patients previously performed array-CGH and Sanger sequencing of MECP2, FOXG1 and CDKL5, which shiwed normal results. Trio-based exome sequencing (ES) was performed.

Results: Patient 1 is a 23-years-old girl. At the age of 6 months, delayed psychomotor development and secondary microcephaly were noticed. She walked at 7 years old, never acquired language nor hand purposeful skills. Hand stereotypies appeared at 2 years of age. Epilepsy presented with focal neonatal convulsions at 15 days of life. The EEGs showed multifocal epileptiform discharges, exacerbated during sleep. Seizures had worsened since the menarche period, when she further underwent motor regression with loss of walking. She has experienced several episodes of status epilepticus. Brain MRI showed a low insertion of tentorium. ES revealed the de novo mutation c.1777G>T(p.Gly593Trp) in KLHL20. Patient 2 is a 31-years-old girl. At the age of 6 months, delayed psychomotor development appeared. She acquired purposeful hand skills at 17 months. Stereotypies presented at 2 years old. She has never acquired spoken language, walked few steps at 8 years old. When seizures exacerbated since puberty, she lost walking and hand skills. Epilepsy onset was at 10 months with Non-Convulsive Status Epilepticus during febrile infection. She also presented with focal seizures with loss of awareness. Since puberty, atonic and myoclonic-atonic seizures have appeared. EEGs have shown polyspikes during sleep and focal epileptiform discharges. Brain MRI showed delayed myelination and corpus callosum hypoplasia. ES revealed the de novo mutation c.58A>C(p.Thr20Pro) in MEF2C. Both patients present with distinct facial dysmorphisms and supportive Neul's criteria.

Discussion: Atypical RTT is a clinical diagnosis which may overlap with Developmental and Epileptic Encephalopathies. Next-generation-sequencing has broadened the genetic spectrum associated with this phenotype [2]. Despite MEF2C-phenotype has already been described [3], KLHL20 was unknown to date.

Conclusion: We broadened the genetic spectrum associated with RTT and described the phenotype related to an unknown gene: KLHL20.

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CLINICAL CHARACTERISTICS OF PATIENTS ACHIEVING SEIZURE FREEDOM IN A PHASE 2 TRIAL EVALUATING ADJUNCTIVE CENOBAMATE

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Purpose: Cenobamate is an antiseizure medication (ASM) approved in Europe as adjunctive therapy for adults with inadequately controlled focal seizures. This post-hoc analysis examined baseline clinical characteristics of patients

who became seizure free with cenobamate treatment during the open label extension (OLE) of Study C017.

Materials and methods: A double-blind, randomized, placebo-controlled, dose-response study evaluated cenobamate treatment in adults with focal seizures despite therapy with 1-3 concomitant ASMs through ≥1 year of follow up. Post-hoc analysis of patients who achieved seizure freedom (zero seizures for ≥1 year) examined duration of epilepsy, concomitant ASMs, number of previously failed ASMs, and seizure type reported in these patients.

Results: As of June 2020, 23.2% (65/280) of participants achieved seizure freedom for ≥1 year from the first day of the OLE study. Seizure free patients had a median duration of epilepsy of 24.2 years compared with a median duration of 24.4 years for patients who did not achieve seizure freedom. Analysis of concomitant ASM grouped by mechanism of action found that 25.5% of those taking concomitant GABAA modulators and 23.5% of those taking GABAA modulators with benzodiazepines or sodium channel blockers were seizure free for ≥1 year. Among patients who experienced secondarily generalized tonic-clonic seizures, focal onset unaware seizures, or focal onset aware seizures at baseline, 27.6%, 22.3%, and 17.5% achieved seizure freedom for ≥1 year, respectively.

Discussion and conclusions: Nearly a quarter of patients treated with cenobamate experienced total seizure freedom for at least 1 year in the long-term follow-up. This proportion was generally consistent across diverse types of patient characteristics at baseline. Supported by: Study C017 (NCT01866111) was sponsored by SK Life Science, Inc. (Paramus, NJ, USA); analyses were supported by Angelini S.p.a. (Rome, Italy).

DECREASE IN DAILY DEFINED DOSE OF ANTISEIZURE MEDICATIONS IN PHASE 3 TRIAL OF ADJUNCTIVE CENOBAMATE FOR FOCAL SEIZURES

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Purpose: An ongoing phase 3 safety study (C021), evaluated adjunctive cenobamate, an antiseizure medication (ASM) approved in Europe for adults with inadequately controlled focal seizures. This post-hoc analysis evaluated changes in concomitant ASM drug load and incidence of adverse events.

Materials and methods: Patient ASM drug load was quantified using World Health Organization defined daily dose (DDD) at baseline and during post-baseline periods up to 30 months. Patients were grouped into 3 categories based on baseline DDD (0-<1, 1-<3, ≥3). Changes in DDD over time and incidence of treatment emergent adverse events (TEAEs) were reported for DDD categories

Results: As of the June 2020 data cutoff (median treatment duration=33.4 months), 1340 patients were included in the post hoc analysis. Overall, the mean (SD) DDD at baseline was 2.86 (1.63) units, with 137 (10%) patients with DDD 0-<1, 607 (45%) with DDD 1-<3, and 596 (44%) with DDD ≥3. At month 30, the overall mean DDD reduction from baseline was 0.61 (1.01) units; in patients with baseline DDD ≥3, the mean DDD reduction was 1.14 (1.28) units. Patients with lower DDD at baseline had a lower incidence of TEAEs (0-<1: 99/137, 72%; 1-<3: 506/607, 83%; ≥3: 542/596, 91%) and serious TEAEs (0-<1: 3/137, 2%; 1-<3: 49/607, 8%; ≥3: 75/596, 13%) within a year of starting cenobamate. This pattern was observed among patients who experienced a TEAE (0-<1: 107/158, 68%; 1-<3: 413/582, 71%; ≥3: 234/314, 75%) or serious TEAE (0-<1: 8/158, 5%; 1-<3: 72/582, 12%; ≥3: 46/314, 15%) after a year of starting cenobamate.

Discussion and Conclusions: A reduction in concomitant ASMs DDD in patients with focal epilepsy initiating adjunctive cenobamate was observed, with more than 1 unit reduction in patients with DDD ≥3 at baseline. Patients with lower DDD at baseline had fewer TEAEs and serious TEAEs. Supported by: Analyses supported by Angelini S.p.a.

ANTI N-METHYL-D-ASPARTATE RECEPTOR (NMDAR) ENCEPHALITIS DURING PREGNANCY: A CASE REPORT AND A NARRATIVE REVIEW OF THE LITERATURE

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Introduction: The anti N-methyl-D-aspartate receptor (NMDAr) antibodies encephalitis is the most frequent autoimmune encephalitis (AE) occurring in young women. Few cases of anti-NMDAR encephalitis during pregnancy have been described. In treating this condition, the clinician must consider the teratogenic and toxic effects of treatments on the fetus and balance them with benefits for the mother. This study aims to describe a case of an antiNMDAR AE in a young woman during the first trimester of pregnancy and reassume the available data in the literature about the therapeutic management of AE during pregnancy.

Methods: A 29-year-old woman at the 7th gestational week came to our observation for the sudden onset of continuous, ongoing, focal motor seizures involving the right side of the face. In the previous seven days, the patient had presented several episodes of emotional liability with sudden changes in her mood and behavior. The patient underwent a video-EEG recording, which showed continuous high-amplitude rhythmic 5 Hz slow waves and sporadic diphasic sharp-waves over the left fronto-centro-temporal derivations. MRI scans showed hyperintense alterations over the left temporo-fronto-parietal cortex in FLAIR T2-weighted sequences. A lumbar puncture showed mild lymphocytic pleocytosis with increased protein and high levels of anti-NMDAR antibodies. A diagnosis of anti-NMDA AE was made in line with the Grauss criteria. The patient was treated with anti-seizure medication and immunotherapy (steroids and plasmapheresis) with a progressive improvement of the clinical picture. The fetal ultrasound (FU) showed standard biparietal and cerebellar indices, normal abdomen dimension, and heart kinetic.

Discussion: Treatment of anti-NMDAR AE during pregnancy is challenging. In treating this condition, a combined ASM and immunomodulant therapy is usually needed. According to literature, both plasmapheresis and corticosteroid treatment show a better safety profile than Rituximab. In patients with bilateral tonic-clonic seizure, sodium channel blockers seem to be more effective in seizure control.

Conclusion: Even though no randomized trials or large-cohort observational studies are available, our report and the literature evidence support immunomodulatory treatment with systemic steroids and PLEX and ASM treatment with sodium channel blockers as the best approach in anti-NMDAR AE management during pregnancy.

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RAPID VERSUS SLOW WITHDRAWAL OF ANTIEPILEPTIC MONOTHERAPY IN TWO-YEAR SEIZURE-FREE ADULTS PATIENTS WITH EPILEPSY (RASLOW) STUDY: A PRAGMATIC MULTICENTRE, PROSPECTIVE, RANDOMIZED, CONTROLLED STUDY

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Objectives: To establish whether a slow or a rapid withdrawal of antiepileptic monotherapy influence relapse rate in seizure-free adults with epilepsy and calculate compliance and differences in the severity of relapses, based on the occurrence of status epilepticus, seizure-related injuries and death.
Materials: This is a prospective, multi-centre, randomized, open-label, non-inferiority trial in people aged 16+ years who were seizure-free for more than 2 years.

Methods: Patients were randomized to slow withdrawal (160 days) or rapid withdrawal (60 days). Enrolled patients were followed for 12 months after randomization. The primary outcome was the probability of a first seizure relapse within the 12-months follow-up. The secondary outcomes included the cumulative probability of relapse at 3, 6, 9 and 12 months. A non-inferiority analysis was performed with non-inferiority margin of -0.15 for the difference between the probability of seizure recurrence in slow versus rapid withdrawal.

Results: The sample comprised 48 patients, 25 randomized to slow withdrawal and 23 to rapid withdrawal. Median follow-up was 11.9 months. In the Intention-to-Treat population, 3 patients in the slow-withdrawal group and 1 in the rapid withdrawal group experienced seizure relapses. The corresponding probabilities of seizure recurrence were 0.12 for slow withdrawal and 0.04 for rapid withdrawal, giving a difference of 0.08 (95% CI -0.12; 0.27), which is entirely above the non-inferiority margin. No patients developed status epilepticus, seizure-related injuries, or died. Risks were similar in the Per-Protocol population.

Discussion: This study confirms that seizure relapse is not associated with the duration of the tapering period. Patients with long periods of remission have a fairly low relapse rate regardless of the duration of tapering.
Conclusions: Seizure-relapse rate after drug discontinuation is lower than in other reports, without complications and unrelated to the duration of tapering.
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CLINICAL AND INSTRUMENTAL CHARACTERIZATION OF PATIENTS WITH LATE-ONSET EPILEPSY

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Objective: Epilepsy is the third most frequent neurological condition in the elderly, following stroke and dementia. With the progressive aging of the general population, the number of patients with Late-Onset Epilepsy (LOE) is steadily growing. The most common causes of LOE are structural, mainly secondary to cerebrovascular or infectious disease, brain tumors, trauma, and metabolic or toxic conditions. In order to identify the possible causes of the disease, with an important impact in terms of treatment and prognosis, LOE patients should always undergo a comprehensive phenotypic characterization.
Methods: In this work, we collected a detailed review of the main clinical and instrumental techniques for the adequate characterization of patients with LOE in clinical practice.

Results: The characterization of LOE includes first level evaluations: thorough medical history, blood chemistry analyzes (to exclude electrolyte or endocrine alterations), cardiovascular evaluation (to exclude events of non-epileptic nature), neuroradiological investigations (CT and MRI of the brain), and EEG. In the event that these investigations are negative, patients should always be subjected to second level investigations, to be selected on a case-by-case basis: CSF analysis (to exclude infectious, neurodegenerative or autoimmune causes), evaluation of the neuropsychological profile and brain CT / PET (to rule out a neurodegenerative cause).

Conclusions: Despite careful characterization of the phenotype, the causes of LOE remain unknown in a considerable portion of patients, thus defined as late-onset epilepsy of unknown origin (LOEU). In this work, we provide a detailed review of the main clinical and instrumental techniques for the adequate characterization of LOE patients in the clinical practice. This work aims to provide an easy and effective tool that supports routine activity of the clinicians facing LOE.
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THE ROLE OF MOLECULAR BIOMARKERS OF BRAIN TUMORS IN SYMPTOMATIC TUMOR-RELATED EPILEPSY. A PRELIMINARY STUDY ON 149 CASES

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Objective/Background: Patients with brain tumor related epilepsy (BTRE) suffer from two complicated pathologies simultaneously: central nervous system tumors and epilepsy. The pathogenesis of BTRE is not fully understood. The integration of molecular data and histology changed the diagnostic

approach and prognostic characterization for patients with brain tumors. The aim of this study is to explore the associations between molecular/histological data and epilepsy features, in a group of patients suffering from brain tumors.

Methods and Materials: We retrospectively evaluated a cohort of 149 consecutive glioma patients (males 94, females 55, mean age: 56 ± 14.25), with 90 (61.2%) of them suffering from BTRE. The association between tumor data (tumor location, histopathological subtype, synaptophysin, GFAP, ATRX, p53 and IDH status, ki67 index, MGMT gene promoter methylation and 1p/19q status) and epilepsy (seizures' type and clinical characteristics) features is examined by Pearson's chi-squared test. Survival data are analyzed by applying Kaplan-Meier curves and Cox proportional hazards models on progression free survival (PFS) and overall survival (OS).

Results: Negative synaptophysin is significantly associated with the presence of epilepsy (p=0.02). Also, there is a significant association between the absence of ATRX (p=0.012) and p53 (p=0.022) mutations and the epilepsy onset at tumor diagnosis. Survival analysis showed that glioblastoma, the absence of ATRX mutation and IDH1 mutation (IDH1 wild type status), the increased proliferation index Ki67 and the absence of 1p/19q codeletion are negative prognostic factors.

Discussion/Conclusions: Our results suggest that some tumor markers, like synaptophysin, ATRX and p53 may be implicated in epileptogenesis. More studies will be needed in the future to confirm the role of molecular markers in BTRE.

LATE-ONSET TEMPORAL LOBE EPILEPSY OF UNKNOWN ETIOLOGY: NEUROPSYCHOLOGICAL PROFILE, CEREBROSPINAL FLUID BIOMARKERS, AND CONNECTIVITY EEG CHARACTERISTICS

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Background: Temporal lobe epilepsy (TLE) is one of the most frequent types of focal epilepsy in older adults. In this context, two main groups can be identified: patients who have a long history of TLE (long-lasting TLE, LLTLE), and those who develop epilepsy de novo in later life (late-onset epilepsy TLE, LOTLE). Despite the bulk of the literature focused on dementia as a startling cause of epilepsy in the elderly as well as on cognitive performance in young-onset epilepsy, little is known on cognition among people with LOTLE. This study aims to investigate the neuropsychological profile, the cerebrospinal fluid (CSF) neurodegenerative biomarkers, and the resting-state EEG connectivity characteristics in LOTLE patients.

Methods: Twenty-five patients with LOTLE and 25 sex-, age- and seizure frequency-matched patients with LLTE were enrolled. Patients underwent extensive neuropsychological evaluation, CSF neurodegenerative biomarkers assessment (Aβ42, phospho-tau, and total tau classified through A/T/(N) system), and 64-channels resting-state EEG. EEG signals were sectioned into 2-s epochs. Coherence, as measured by weighted phase-lag-index (PLI), weighted PLI (wPLI), and imaginary part of the Coherence, was employed for the functional connectivity (FC) analysis. Connectivity matrices for each epoch for each FC function were built and then averaged across epochs to get subject-level connectivity matrices.

Results: Compared to the LLTLE-group, LOTLE patients showed more impaired working memory, language, and attentive functions. CSF neurodegenerative biomarkers were normal in all patients except for three subjects (1.A+, 2.A+, 3.T+). In the LOTLE-group, FC analysis showed increased whole-brain connectivity in the alpha-band, with significantly higher connectivity in the frontoparietal regions (wPLI p=0.05; wPLID p=0.04; imCoh p=0.03).

Conclusion: Patients with LOTLE present a distinctive neuropsychological and FC profile. Our results highlight a possible neurodegenerative process underlying LOTLE onset. Future longitudinal studies will be necessary to characterize the underlying pathophysiological basis of the cognitive deficits and to assess the progression extent.

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GENETIC DIAGNOSTIC WORK-UP IN AN ADULT POPULATION WITH EPILEPSY AND NEURODEVELOPMENTAL DISORDERS: DIAGNOSTIC YIELD AND CLINICAL MANAGEMENT

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Objectives: The advent of next-generation sequencing techniques in clinical practice has led to significant progress in the discovery of genes responsible for epilepsy within complex and rare neurological presentations. Studies exploring the genetic diagnostic process epilepsy and neurodevelopmental disorders in the adult population are limited [1]. Establishing an etiologic diagnosis is important to start targeting possible individualized treatments for daily clinical management. The aim of the study is to evaluate the diagnostic yield of a specific genetic testing pathway for adult patients with epilepsy and neurodevelopmental disorders and to demonstrate that a molecular diagnosis may guide clinical management decisions, treatments, and surveillance.

Materials: We enrolled twenty-six adults (afferent to the IRCCS Mondino Epilepsy Center in Pavia) with a diagnosis of epilepsy related to encephalopathies (with and without congenital anomalies and intellectual disability, MCA/ID), epileptic encephalopathies (EE), epileptic and developmental encephalopathies (DEE), and familial and/or drug-resistant focal epilepsies (EFF).

Methods: Patients were subjected to genetic diagnostic testing through two steps: step 1, all patients (except those with EFF) performed an CGH-array and, if male, molecular analysis of FMR1 gene; step 2, for negative cases, in EE, DEE and MCA/ID, exome sequencing (WES). Patients with EFF directly performed WES.

Results: 4 of 26 patients (15.4%) were positive on CGH-array: del15q11.2 (2 cases), del16p11.2, del12q24.33 and dup10p15.3p13; after the first step, 17 patients performed WES, with detection of 10 rare causative variants in the genes KIF5C, GNB1, UBE2A, ATP7A, XK, PPP2R5D, STXBP1, DYNC1H1, SLC2A1, IQSEC2. Two cases had dual diagnosis (del15q11.2 and pathogenic variant of UBE2A gene, del12q24.33 and dup10p15.3p13). An incidental finding was reported (SCN5A).

Discussion: We found that diagnostic yield of applied genetic analysis was 5% for CGH-array and 52.6% for WES. In addition, the results showed that all DEE and EFF patients were found to carry pathogenic mutations. Two extremely rare genetic mutations were found, expanding the landscape of the relevant literature (KIF5C and ATP7A gene mutation in female patient). In one patient, the genetic diagnosis made it possible to target an etiopathogenetic

modification for treatment (SLC2A1), and in three cases to set up targeted surveillance of potentially fatal comorbidities (XK, SCN5A, del16p11.2).

Conclusions: This data supports the usefulness of genetic investigations in adults with complex epilepsy to reach an etiologic diagnosis and set up specific treatments and surveillance.

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HEART RATE VARIABILITY MODIFICATIONS IN ADULT PATIENTS WITH EARLY VERSUS LATE-ONSET TEMPORAL LOBE EPILEPSY: A COMPARATIVE OBSERVATIONAL STUDY

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Introduction: Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy. TLE is associated with cardio-autonomic dysfunctions and increased cardiovascular (CV) risk in patients over the fifth decade of age. In these subjects, TLE can be classified as early-onset (EOTLE; i.e., patients who had developed epilepsy in their youth) and late-onset (LOTLE; i.e., patients who developed epilepsy in adulthood). The heart rate variability (HRV) analysis is useful for assessing cardio-autonomic function and identifying patients with increased CV risk. This study compared changes in HRV occurring in patients (older than 50) with EOTLE or LOTLE.

Methods: We enrolled twenty-seven adults with LOTLE (LOTLE group) and 23 EOTLE (EOTLE group). The two groups were matched for age, sex, and seizure frequency. Each patient underwent a 20-minute EEG + EKG recording in a resting state before and during 3-minutes hyperpnea (HP). HRV analysis was performed both in time and frequency domains. Linear Mixed Models (LMM) were used to analyze HRV parameters according to time (baseline and HP) and groups (LOTLE and EOTLE groups).

Results: Compared to LOTLE group, the EOTLE group showed significantly decreased LnRMSSD (p-value=0.05), LnHF ms2 (p-value=0.05), HF n.u. (p-value=0.008) and HF% (p-value=0.01). In addition, EOTLE patients exhibited increased LF n.u. (p-value=0.008) and LF/HF ratio (p-value=0.007). During HP, the LOTLE group exhibited a multiplicative effect for the interaction between group and time with increased LF n.u. (p=0.003) and LF% (p=0.05) values.

Conclusions: EOTLE is associated with reduced vagal tone compared to LOTLE. Patients with EOTLE may have a higher risk of developing cardiac dysfunctions or cardiac arrhythmia than LOTLE patients.

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LAMOTRIGINE USE IN WOMEN WITH EPILEPSY DURING PREGNANCY: A "HANDLE WITH CARE" THERAPEUTIC OPTION

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Background: Pregnancy in women with epilepsy (WWE) represents a challenge for clinicians who have to balance maternal and fetal risks associated with seizures on one hand and structural and cognitive/behavioral teratogenicity of anti-seizure medications (ASMs) on the other. Monotherapy at the lowest effective dose is generally recommended during pregnancy in WWE. This can be very difficult with lamotrigine (LTG), whose plasmatic levels could drastically reduce during conception due to increased renal clearance and pregnancy-related enhanced hepatic glucuronidation. Therefore, an increase of LTG dose may be required, considering that structural malformations are dose-dependent.

Materials and methods: Two anecdotal cases of WWE assuming LTG monotherapy during pregnancy are described, focusing on three main aspects: seizure control, LTG monitoring levels and LTG dose adjustments. The first patient is a 42-year-old woman with unknown epilepsy taking LTG 150mg/day with 7-year seizure control. LTG preconceptional plasmatic levels=4.0 ug/ml (n.r. 3-14). She was seizure-free during gestation, but LTG dose was progressively increased up to 250mg/day due to 60% reduction of its plasmatic concentration. 20 days after birth, LTG plasmatic level was 7.5 ug/ml and LTG posology was slightly reduced to 225mg/day. Case two is a 31-year-old woman with juvenile myoclonic epilepsy taking LTG 350mg/day (plasmatic levels=7.0 ug/ml) without seizure control (weekly myoclonic jerks). She started a twin pregnancy (2F), reporting a 70% decrease in LTG plasmatic levels. Because of this important plasmatic decrease and recurring seizures, LTG dose was progressively increased up to 500mg/day (plasmatic levels=3.1 ug/ml). Due to the persistence of low LTG plasmatic levels and myoclonic jerks, clobazam 10mg/day was added. In both cases progressive increases of LTG dose were necessary due to seizure recurrence and/or dramatic reduction of LTG plasmatic levels.

Discussion and conclusion. Based on these cases and the previous literature, drug monitoring levels during pregnancy in WWE is highly recommended and dose adjustments are strongly encouraged when a decline by >35% from pre-conception plasmatic concentration is registered. An optimal pre-pregnancy drug concentration should be identified and maintained during conception to avoid seizure recurrence and potential maternal and fetal consequences. Not only clinical features, as seizure recurrence, but also a strict drug plasmatic monitoring should guide clinicians in therapeutic decisions. Because the pharmacokinetics of LTG will return to the pre-pregnancy situation, gradual dose adjustments of LTG could be also necessary after birth with the aim of avoiding an overdose and possible maternal and fetal adverse effects after pregnancy.

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FRACTAL-BASED ANALYSIS OF QUANTITATIVE-EEG IN FOCAL EPILEPSY

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Objective: Quantitative Encephalography (qEEG) represents synthetically the features of EEG signal and thus is a promising tool in the assessment of neurophysiological changes induced by anti-seizure medications (ASMs). In this study, we characterized qEEG chronic modifications brought by the first ASM (fASM) in a population of 20 drug-naïve patients with drug-responder Temporal Lobe Epilepsy (TLE).

Methods: We analyzed standard-19 channel-EEG from 20 patients with drug-responder TLE both before (T0) and after (T1, from 3 to 5 months) the introduction of the fASM. We investigated the spectral properties in the classical frequency bands, such as δ (1–3 Hz), τ (4–7 Hz), α (8–13 Hz), β (14–30 Hz) and γ (31–45 Hz) bands and the individual alpha frequency (IAF). Moreover, we estimated the fractal dimension (FD) values and then compared these features between T0 and T1.

Results: In drug-responder TLE, the fASM induces a decrease in Theta power ($p = 0.039$) and an increase in the FD ($p=0.004$) and IAF ($p = 0.020$). Bayesian analysis was used to compare the Bayes Factors (BF) across the three indexes used (Theta (BF=1.131), IAF (BF=4.414), and FD (BF=10.660)), based on the magnitude of the BF, we have found that FD was 9.4 times more sensitive than theta band and 2.4 times respect to IAF.

Discussion: In drug-responder TLE, the fASM induces EEG modifications that can be measured and subtend an increase in the complexity of functional patterns of the patient's brain after drug administration.

Conclusions: qEEG may help to understand the effect of ASMs in the central nervous system and could offer new prognostic biomarkers for patients with epilepsy.

LOGOPAEDIC CHARACTERIZATION OF POSTICTAL APHASIA IN PATIENTS WITH DRUG-RESISTANT FOCAL EPILEPSY

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Objective: Postictal aphasia (PA) is a transient aphasic disorder occurring after a seizure, usually representing a lateralized sign for speech-dominant hemisphere and a localizing sign for temporal origin of the discharge [1]; its prevalence reported in literature in around 34% of all epileptic patients [2]. We aim to assess the prevalence of PA in patients with drug-resistant focal epilepsy undergoing long-term monitoring (EMU), to perform logopaedic analysis of the PA in order to characterize aphasic features and compare the anatomo-electro-clinical data of patients with PA respect to patients without PA.

Materials and methods: A multidisciplinary team reviewed 811 seizure clips from 77 patients who underwent prolonged monitoring at EMU of Istituto delle Scienze Neurologiche di Bologna, selecting focal seizures that were adequately tested for speech in postictal period. The ineffectively tested seizures, clips with audio/video problems and seizures with excessive postictal confusion were excluded. Patients presenting PA were then selected and the logopaedic transcription of the communicative interaction was performed in order to characterize the language disorder. Finally, the main clinical variables of PA patients were compared with the adequately tested cases without PA.

Results: Forty-six over 77 patients were adequately tested for language; 20 of them presented features consistent with PA. Of these 8 patients showed a deficit in both comprehension and production with more difficulty on the lexical side, 9 predominantly in production and 3 predominantly in comprehension. The 25% of patients experienced also ictal aphasia. Comparing the two groups, no significant differences emerged on the lateralization of the epileptogenic zone, whereas the patients with PA had more often temporal origin of the seizures (50% vs 31%, $p<0,001$), lateralized EEG pattern with contralateral diffusion (80% vs 38%, $p<0.03$) and postictal EEG pattern with diffuse or focal slowing (90% vs 39%, $p<0.001$).

Discussion and Conclusion: The present study reported a prevalence of PA in 25% of patients hospitalized in EMU; however, the prevalence rises to 40% when only adequately tested subjects are considered; these data suggest that PA recognition is challenging, and the real prevalence maybe underestimated. We confirm that the disorder prevails in seizures with a temporal origin, while left lateralization were not significantly prevalent in our group. The present study indicates that ictal evolution of the discharge may have a leading role, creating PA in case of bilateral secondary involvement of both hemisphere and post-ictal focal or diffuse slowing.

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ADVANCED NEUROIMAGING ALTERATIONS IN PATIENTS WITH EPILEPSY WITH AUDITORY FEATURES

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Objectives: Epilepsy with auditory features (EAF) is a rare epileptic syndrome with variable age of onset, characterized by simple auditory seizures or receptive aphasia, favorable prognosis and negative qualitative brain MRI1-3. The aim of our work is analyze a cohort of sporadic and familiar EAF patients in order to evaluate brain structural alterations with advanced neuroimaging techniques.

Materials and Methods: Thirty-one EAF patients (mean age 39.53±14.61) and 30 age- and sex-matched healthy controls (HC) were consecutively enrolled and performed 3T brain MRI. T1 3D-volumetric slices were processed through the following approaches: cortical thickness (CT) analysis, surface areas (SA) and subcortical volumes (SV).

Results. CT analysis in EAF patients revealed significant different thickness compared to HC in the following areas: left entorinal cortex ($p<0.01$), left anterior and posterior cingulate areas ($p<0.01$), right parahippocampal cortex ($p<0.01$) and right temporal pole ($p<0.01$). SA analysis showed significant differences in the following regions: left and right frontal poles ($p<0.01$). SV analysis also showed a significant increase in bilateral pallida volumes in EAF patients compared to HC ($p<0.01$).

Discussion. Our study shows the presence of subtle structural abnormalities in EAF patients, specially involving front-temporo-limbic networks and subcortical regions.

Conclusion. Our study suggests that the disruption of cortical-subcortical networks could be a pathophysiological marker of EAF syndrome.

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EPILEPSY MANAGEMENT, TELENEUROLOGY AND THE WHO INTERSECTORAL GLOBAL ACTION PLAN IN SUB-SAHARAN AFRICA: A PIVOTAL EXPERIENCE

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Purpose: The World Health Organization (WHO) Intersectoral Global Action Plan (IGAP) on Epilepsy and other Neurological Disorders aims to improve access to care for one billion people in the next 10 years particularly in developing countries. In Sub-Saharan Africa (SSA), 2/3 of people with epilepsy (PWE) has no access to treatment, there is only one neurologist every two million people, more than 90% of PWE are managed by Health Care Providers (HCPs), at primary care level, whose education in neurology is insufficient. In addition, more than 26 million people are HIV positive, a known risk factor for epilepsy. Due to the ongoing HIV pandemic in SSA, care of HIV and other chronic disorders as epilepsy need to be combined at HIV/primary care centres. We report the preliminary results of an epilepsy program at HIV /primary care centers in SSA, based on education and training to HCPs, coupled with telemedicine and tele-EEG, with the aim to improve access to care to PWE.

Methods: This epilepsy program in SSA is conducted as a partnership between the Italian Society of Neurology, the C. Besta Neurologic Institute, the Mariani Foundation, the Disease Relief through Excellent and Advanced Means (DREAM) program and the Global Health Telemedicine (GHT). DREAM operates in SSA since 2002, it is active in 10 SSA countries, where it offers education, prevention and care for HIV and other communicable and non communicable disorders. The GHT platform offers free telemedicine services to HCP in SSA who receive advices from remote volunteer European specialists and neurologists. The present study focuses on Malawi and Central African Republic (CAR). Here DREAM assists 18770 patients; 15203 (81%) are HIV+.

Results: From February 2021 to March 2022, a number of activities in Malawi and RCA have been done: 9 (7 in Malawi, 2 in CAR) in-person training courses to 90 local HCPs, remote sessions have also been offered. Two video-electroencephalograms were installed; 762 PWE are now regularly followed up at DREAM in Malawi and RCA. In 2021 teleneurology consultations were 802, >90% were for PWE, more than 350 EEG have been done and EEG-recordings transmitted through the GHT platform allowing local HCP to receive advices from to the European specialists.

Conclusions: Education and training to local SSA HCPs coupled with teleneurology can be a valid tool to achieve the IGAP goals at HIV/primary care centres in SSA.

CORRELATES OF PSYCHOLOGICAL DISTRESS IN EPILEPTIC PATIENTS DURING THE COVID-19 OUTBREAK

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Background and Aims: Following the severe consequences of the coronavirus disease 2019 (COVID-19) outbreak, on March 9th, 2020 the Italian Government implemented extraordinary measures to limit viral transmission, including restrictive quarantine measures. Psychological distress represents the seizure precipitating factor most often reported by patients with epilepsy [1]. To date, no studies have analyzed the role played by the different dimensions of psychological distress quarantine-induced in patients with epilepsy.

Methods: We included a total of 40 patients, 18 suffered from generalized, and 22 from focal epilepsy. The patients previously seen in the outpatient clinic during the pre-lockdown period between January and February 2020 were reevaluated after the lockdown period. Psychological distress was evaluated by using the three subscales of Impact of Event Scale-Revised (IES-R). Finally, we employed logistic regression analyses to explore the demographic and clinical features associated to high scores on IES-R.

Results: Patients with higher scores on IES-R Intrusion and IES-R Avoidance subscales demonstrated an increased number of epileptic attacks compared to prelockdown period. Multivariate logistic regression analyses showed that a specific subgroup of patients (i.e., older, female with more anxious symptoms) are at higher risk of increased seizure frequency.

Conclusions: Our study confirmed that the frequency of epileptic seizures increased during lockdown when compared to pre-lockdown period [2]. The early identification of patients more vulnerable to worsening is crucial to limit the risk of requiring hospital or clinical treatment during the COVID-19 outbreak.

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GLUT1-DEFICIENCY SYNDROME WITH EXTREME PHENOTYPIC VARIABILITY IN A FIVE-GENERATION FAMILY CARRYING A NOVEL SLC2A1 MUTATION

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Aims: GLUT1 deficiency syndrome (GLUT1ds) is a heterogeneous metabolic disorder due to reduced expression of GLUT1, a glucose transporter of central nervous system. Developmental delay, intellectual disability, movement disorders, ataxia, infantile-onset seizures, acquired microcephaly are the main clinical features. Most of cases of GLUT1ds are caused by de novo mutation of SLC2A1 gene; about 10% of patients carry an autosomal dominant inherited mutation [1,2]. Here, we report a five-generation Italian family with extremely heterogenous phenotypes consistent with milder GLUT1ds that was associated with a novel heterozygous missense mutation of SLC2A1.

Materials: We present clinical and genetic features of a five-generation Italian family.

Methods: All subjects underwent a detailed clinical and laboratory investigation. Genetic analysis included array comparative genomic hybridization. Massive parallel sequencing was performed on MiSeq Illumina platform. Variant filtering and interpretations were performed on Sophia DDM™ platform according to American College of Medical Genetics and Genomics criteria [3].

Results: The family included 14 affected members that presented with mild heterogeneous phenotypes, including isolated mild cognitive impairment (3/14), behavioral disturbances (5/14), epileptic seizures (9/14) and gait disabilities (1/14). Notably, brain MR depicted hippocampal sclerosis in the 8-year-old proband who also had drug-responsive absence seizures associated with attention-deficit-hyperactivity disorder. His 52-year-old father, who had self-limited occipital epilepsies of childhood, developed a mild spastic paraparesis related to a reversible dorsal myelitis. The CSF analysis revealed a glucose ratio below 0.45. Molecular study revealed a novel heterozygous variant (c.446C>T) in exon IV of SLC2A1 that co-segregated with the illness. This variant causes an amino acids substitution (p.Pro149Leu) at the fourth transmembrane segment (TM4) of GLUT1, an important domain located at the catalytic core of the protein. Many prediction programs predicted that this variation had deleterious effect.

Discussion: Our study emphasizes the extreme phenotypic variability in familial GLUT1ds, ranging from milder classic phenotypes to more subtle neurological disorder including paraparesis. Most important, we identified a novel pathogenic variant (c.446C>T) of SLC2A1 gene, located in exon IV, which represents a mutational hotspot [2]. Indeed, nearly a third of patients with GLUT1ds harbored mutations in exon IV. This new variant (c.446C>T) leads to an aminoacidic substitution (p.Pro149Leu) at fourth transmembrane segment of GLUT1, located at the catalytic core of GLUT1.

Conclusion: Our study provides new insight into spectrum and pathophysiology of GLUT1ds. The extreme heterogeneous phenotypes of family members carrying the same mutation indicates that secondary genes and other modifying factors may modulate the expression level of GLUT1.

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SHORT-TERM OUTCOMES AND PREDICTORS OF ACUTE POSTOPERATIVE SEIZURES IN PATIENTS UNDERGOING SUPRATENTORIAL CRANIOTOMY

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Objectives: Acute postoperative seizures (APOS) are relatively common comorbidity in patients undergoing craniotomy [1]. Despite their clinical relevance, the frequency and risk factors of APOS are not well established. Moreover no formal recommendations for the prophylactic use of AEDs in patients undergoing craniotomy were formulated [2,3]. This study investigates the epidemiology and risk factors of APOS and assess the prophylactic use of anticonvulsant therapy in patients undergoing supratentorial craniotomy for non-traumatic pathology.

Methods: A retrospective, single center study of 780 consecutive patients. Patients who undergone supratentorial craniotomy for non-traumatic pathology with adequate medical documentation were included, while patients with a history of epilepsy unrelated to the intracranial conditions for which they underwent brain surgery were excluded. Based on the indication for craniotomy, three main patient groups were identified: chronic subdural hematoma (cSDH), meningiomas and gliomas. According to the center's policy cSDH patients were started on AEDs if they developed seizures or in doubtful cases, while glioma and meningioma patients started a preoperative prophylaxis in most of cases. Common variables for the entire court and specific variables for each group were analyzed.

Results: A total of 125 patients (16%) developed APOS. APOS occurred more often in cSDH patients than in meningioma and glioma patients (34.4% vs 8.2% and 10.3%; $p < 0.0001$). In the cSDH group membranectomy (OR 6.55), infections (OR 4.81) and recurrence of cSDH (OR 3.95) after surgery were predictors of APOS, while the use preoperative prophylaxis was a protective factor (OR 0.26). The predictors of APOS in meningioma patients were non-skull-base location (OR 12.58), peritumoral edema (OR 9.35), meningioma recurrence (OR 3.68) and postoperative hyponatremia (OR 9.28). In glioma group gross total resection was associated with lower risk of developing APOS (OR 0.314) and patients that received intraoperative prophylaxis in addition to preoperative prophylaxis had lower incidence of APOS (p 0.014). In all groups the duration of hospitalization in patients with APOS was significantly longer than that of patients without seizures after surgery. The mean postoperative mRS was significantly higher in patients with APOS.

Discussion and Conclusion: APOS in all groups were associated with worse clinical outcome at discharge and longer hospitalization. Perioperative AED prophylaxis is not meaningless in patients undergoing craniotomy. In cSDH patients the administration of preoperative prophylaxis is useful, especially in those who have risk factors. In a subset of glioma patients AED preoperative prophylaxis is necessary but insufficient and should be more aggressive administering intraoperative prophylaxis. Identifying risk factors is important to tailor the postoperative care of patients on an individual basis.

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ELECTRIC SOURCE IMAGING IN PRE-SURGICAL EVALUATION OF EPILEPSY: AN INTER-ANALYSER AGREEMENT STUDY

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Aims: To explore electric source imaging (ESI) inter-analyser agreement in epilepsy presurgical evaluation.

Materials: Twenty-five patients (median age 32 yo, range 12-63 yo, 13 females, 17 temporal-lobe, 8 extratemporal-lobe epilepsy) were consecutively enrolled. All patients underwent MRI and low-density (LD, 40 channels, long-term-monitoring) and high-density (HD, 256 channels, one-two hours recording) EEG. Six experts performed ESI independently, blinded to clinical data.

Method: Individual head models were derived from 3D-T1-weighted isotropic MRI scans segmentation and co-registered with digitalized electrode's positions. ESI was performed on inter-ictal and ictal epileptiform discharges (EDs) with a standardized pipeline. As for inter-ictal ESI, five-ten EDs were visually identified and averaged in a template. The template was used for subsequent automated detections. As for ictal ESI, EDs were visually selected. EDs with same temporal and spatial topography were grouped and averaged in common patterns. Patterns were analysed with equivalent current dipole (ECD) and distributed source model (DSM) methods at the onset of the EDs and at the peak of the ascending slope. Aforementioned analyses were performed with BESA-MRI and BESA-Research (BESA, Gräfelfing, Germany). Inter-analyser reliability was calculated by applying Gwet-AC1 [1].

Results: Overall, analysers obtained a substantial agreement (AC1: 0.65, CI: 0.59-0.71). This remained substantial when evaluating overall ECD (AC1: 0.65, CI: 0.56-0.74) and DSM (AC1: 0.65, CI: 0.57-0.74). Substantial agreement was achieved for overall inter-ictal HD-EEG (AC1: 0.66, CI: 0.53-0.80) and LD-EEG (AC1: 0.71, CI: 0.60-0.82), HD-EEG's ECD (AC1: 0.66, CI: 0.46-0.86) and LD-EEG's ECD (AC1: 0.67, CI: 0.49-0.89), and HD-EEG's DSM (HD-AC1: 0.66, CI: 0.47-0.86) and LD-EEG's DSM (AC1: 0.75, CI: 0.60-0.90). Ictal ESI had an overall moderate agreement (AC1: 0.58, IC: 0.50-0.68), with a moderate agreement for DSM (AC1: 0.54, CI: 0.42-0.67) and a substantial agreement for ECD (AC1: 0.62, CI: 0.48-0.77).

Discussion: ESI has proven to provide important and non-redundant information in presurgical evaluation for epilepsy [2]. However, its inter-analyser reproducibility remained unknown. Here, ESI was performed following a standardized pipeline and analysers obtained a substantial agreement in all ESI modalities except DSM ictal ESI. Seizure onset selection and the lower signal-to-noise ratio of ictal patterns could have influenced the analysis. Nevertheless, ECD ictal ESI inter-analyser agreement remained substantial, suggesting the lower signal-to-noise ratio to be the main cause of DSM ictal ESI lower agreement.

Conclusion: Despite inevitable subjective decisions of the individual analyser, using a standardized pipeline results in a substantial agreement in ESI source localization and therefore should be integrated into clinical practice.

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PERI-ICTAL NEUROIMAGING OF STATUS EPILEPTICUS: PRELIMINARY RESULTS OF A PROSPECTIVE STUDY

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Objectives: Peri-ictal MRI abnormalities (PMAs) following status epilepticus (SE) show variable prevalence (12%-100%) in the literature [1,2,3]. These alterations are frequently transitory, but the timing of appearance and disappearance is poorly investigated. We aimed to further characterize the type and timing of the MRI findings associated with SE.

Materials: We enrolled consecutive patients with SE, cluster of seizures, or a single seizure.

Methods: The primary outcome was the presence of cortical high DWI signal at MRI during or immediately after an epileptic event. Subjects with MRI abnormalities underwent further studies until normalization.

Results: 78 patients were recruited, mean age was 61,5 years. Twenty-three (29,4%) had SE, 21 (26,9%) had cluster of seizures and 33 (42,3%) had a single seizure. First MRI was positive in 15 cases (65,2%) from the SE group, 10 (47,6%) for the cluster group and 18 (54,5%) for the single seizure group.

Discussion: There was no statistical difference among the three groups for the primary outcome (p value= 0.49). Nineteen patients completed the follow-up MRI. In seven cases the follow-up was terminated for identification of a specific etiology of the lesion (vascular, neoplastic). In seven patients the alterations were no longer present (confirming as PMAs). Five patients had persistent anomalies and follow-up is still ongoing.

Conclusions: Our findings emphasize that PMAs are not specific to SE, given the non-significant differences in prevalence between the three groups investigated. These preliminary data warrant further investigation.

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INTRAOPERATIVE ELECTROCORTICOGRAPHY IN EPILEPSY SURGERY: DATA FROM THE EPILEPSY CENTER OF MODENA

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Objectives: The intraoperative electrocorticography (ECoG) is used in epilepsy surgery to identify the presence of epileptiform activity related to the epileptogenic lesion. Moreover, it may be of utility in defining the epileptogenic zone (EZ) to allow a more precise surgical resection. We present the following data regarding the intraoperative electrocorticographic (ECoG) recordings collected from 2019 to 2021 at the Epilepsy Center of Modena.

Materials: From 2019 to 2021, all patients addressed to epilepsy surgery underwent serial intraoperative ECoG recordings with 1 x 4 strip with platinum-iridium electrodes placed over and along the lesional cortex before resection and along the surgical neocortical margin of the resection. The distance from electrode to electrode is 10 mm and contact diameter is 4 mm.

Method: Both bipolar and referential electrode montages were reviewed by clinical neurophysiologists to identify epileptiform abnormalities. ECoG patterns were subdivided according to Palmini et al. classification: (A) sporadic spikes; (B) continuous rhythmic spiking; (C) repetitive bursts; (D) electrographic seizures.

Results: In total, 46 patients underwent a surgical procedure as epilepsy treatment. In 26 patients (19 males and 7 females; mean age 38.2±13.6) we could obtain at least one ECoG recording, for a total of 41 recordings. In 15/26 (57.7%) patients, both pre-resection and post-resection ECoG recordings were available. One patient had only a post-resection ECoG recording. Among the 25 pre-resection recordings, the following patterns were found: A (12/25), A+B (2/25), A+C (1/25), A+C+D (1/25), B (3/25), B+D (2/25), C (1/25), absence of epileptiform abnormalities (3/25). In 3/25 patients with tumoral lesions (2) and focal cortical dysplasia (FCD) (1/25), intraoperative electrographic seizures were recorded (D pattern). In relation to the histopathological diagnosis, abnormal ECoG patterns were found in 8/10 patients with FCD (type Ia, IIb, IIIa), in 4/6 patients with a tumoral lesion, 3/3 with hippocampal sclerosis, in 2/2 with gliosis and in 3/4 with a cavernoma.

Discussion: These findings demonstrated that there is a good concordance between the histopathological data and the ECoG patterns.

Conclusions: These preliminary data showed that the intraoperative ECoG could be a valuable operative instrument to identify epileptiform abnormalities during the surgical procedure with the potential to help in guiding the surgical resection extent.

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INCIDENCE OF EPILEPSY IN PATIENTS WITH DEMENTIA IN UMBRIA: POPULATION STUDY BASED ON ADMINISTRATIVE REGIONAL HEALTH DATA

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Introduction: Dementia is the second most common neurological disorder in older people. The risk factors and the epidemiology of epilepsy in patients with dementia are still unclear. This project aims to estimate the incidence of dementia, the incidence of epilepsy in patients with dementia and the real-world treatment of these patients in Umbria.

Materials and methods: In this retrospective study, population consists of all patients with a hospitalization due to dementia in Umbria between 2013 and 2017. Patients with dementia were identified in the administrative databases using ICD-9-CM codes. Epilepsy in patients with dementia was identified with the prescription of at least one EEG and one or more anti-seizure medications (ASMs) according to Franchi and colleagues. A matched case-control analysis has been carried out with 5 subjects without dementia matching the gender and age of 1 subject with dementia. Cox proportional hazards models were performed.

Results: During the study period, 7314 incident cases of dementia were identified (65% females/ 35% males; 57% of patients with >80 years old). Following these patients until 2018, 148 (2.02%), people presented epilepsy. The cumulative incidence rate of seizures during the first year after dementia diagnosis was 1.45% and 1.96% after three years. Diabetes, hypertension and heart failure were not associated with epilepsy onset in patients with dementia. Comparing patients with dementia (7314) with age- and sex-matched case controls (35280), multivariable Cox regression showed that onset of epilepsy was associated with dementia (HR=4.58, 95%CI=3.67-5.72), male gender (HR=1.35, 95%CI=1.07-1.69) and young age dementia onset (HR=1.03, 95%CI=0.96-0.98). Levetiracetam and valproic acid were the more commonly prescribed ASMs (LEV 32.4% vs VPA 31.8%) for the management of epilepsy in patients with dementia.

Conclusion: This is the first study of incidence of epilepsy in patients with dementia using administrative healthcare data in Italy. The data collected showed that risk factors for epilepsy onset were dementia, male gender and young age dementia onset.

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DETERMINANTS OF MEDICATION ADHERENCE IN PEOPLE WITH EPILEPSY: A MULTICENTRIC, CROSS-SECTIONAL SURVEY

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Objectives: Non-adherence to treatment in people with epilepsy (PwE) is cause of increased mortality, hospitalization and reduced quality of life and represents a challenge for clinicians. We realized an extensive survey to define clinical, demographic and neuropsychological factors that could influence medication adherence in PwE evaluated throughout the Morisky Medication Adherence Scale (MMAS-8).

Materials and Methods: We performed a multicentric and cross-sectional study where a population of 200 PwE answered online questionnaires containing the following clinical scales: MMAS-8, Quality of Life in Epilepsy Inventory (QoLIE), Beck Depression Inventory (BDI-II), Generalized Anxiety Disorder (GAD) and Resilience. We used ANOVA test and Spearman's correlation to evaluate the relationship between medication adherence and demographic, clinical (seizure frequency, number of Anti-Seizure Medications) and neuropsychological characteristics. We trained separate machine learning models (logistic regression, random forest, support vector machine) to classify patients with medium-high adherence (MMAS≥6) and poor adherence (MMAS<6) and identify the principal variables that influence medication adherence.

Results: We found that women were more adherent to therapy than men (p-value = 0.03577). MMAS-8 showed direct correlation with Resilience (p-value=0.001), age (p-value=0.001), inverse correlation with BDI (p-value=0.001) and GAD (p-value=0.001). We also evidenced that the most influential variables in our model were subitems of QoLIE-31 and individual characteristics as age, resilience, GAD, years of school, disease duration.

Discussion and Conclusion: Our study confirms that gender and age are main determinants of medication adherence in PwE. Furthermore, we provided initial evidence that machine learning on multidimensional self-report questionnaires could help to develop decisional support system in outpatient epilepsy clinics.

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A RETROSPECTIVE, MULTICENTER, OBSERVATIONAL REAL LIFE STUDY TO INVESTIGATE DOSE-RELATED THERAPEUTIC RESPONSE OF PERAMPANEL WHEN USED AS THE ONLY ADD-ON TREATMENT OF PEOPLE WITH EPILEPSY

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Objectives: Perampanel (PER) is indicated as adjunctive antiseizure medication (ASM) in adolescents and adults with epilepsy. Data from clinical trials show good efficacy and tolerability, while fewer information are available on the routine clinical use of PER, especially when used as only add-on treatment.

Materials: This is an observational, retrospective, multicenter study on people aged >12 years with focal or generalized epilepsy, consecutively recruited from 52 Italian epilepsy centers. All patients received PER as the only add-on treatment to a previous ASM according to standard clinical practice.

Methods: Retention rate, seizure frequency and adverse events were recorded at 3, 6 and 12 months after PER introduction. Sub-analyses by early or late use of PER, by age groups and by concomitant ASM were also conducted.

Results: 503 patients were included (age 36.5±19.9 years). About 80% had focal epilepsy. Retention rate was very high in the whole group (89% at 12 months). Efficacy measures were concordant. No major differences were observed in the sub-analyses, although patients who used PER as early add-on, as compared with late add-on, more often reached early seizure freedom at 3 months (66% vs. 53%, p=0.05). Adverse events were far less common than in randomized trials.

Discussion: This study confirms the good efficacy and safety of PER for focal or generalized epilepsy in real-life conditions.

Conclusions: This study provides robust data about PER effectiveness as only add-on treatment even in patients with a long-standing history of epilepsy and previously treated with many ASMs.

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NEWLY DIAGNOSED HEPATIC ENCEPHALOPATHY PRESENTING AS NONCONVULSIVE STATUS EPILEPTICUS: A CASE REPORT AND LITERATURE REVIEW

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Background: Hepatic encephalopathy is characterized by psychiatric and neurological abnormalities, including epileptic seizure, nonconvulsive and convulsive status epilepticus. Conventional brain magnetic resonance imaging is useful in supporting the diagnosis, since it can reveal specific radiological findings. In the literature, there is no description of hepatic encephalopathy onset as nonconvulsive status epilepticus; we provide the first report.

Case presentation: We report a case of a 67-years old woman, without history of cirrhosis, presenting altered mental state, normal brain computed tomography imaging and electroencephalography suggestive of epileptic activity. We suspected nonconvulsive status epilepticus and we administered diazepam and levetiracetam with clinical improvement. Thus, we made a diagnosis of nonconvulsive status epilepticus. Radiological study with brain magnetic resonance imaging showed bilateral hyperintensity on T1-weighted sequences of globus pallidus and hyperintensity of both corticospinal tracts on T2-weighted fluid-attenuated inversion recovery sequences. Blood tests revealed hyperammonemia, mild abnormality of liver function indices, chronic Hepatitis B and D virus coinfection. Hepatic elastosonography suggested liver cirrhosis. The patient started antiviral therapy with entecavir and prevention of hepatic encephalopathy with rifaximin and lactulose; she was discharged with a normal mental state.

Conclusions: Hepatic encephalopathy can present as initial manifestation with nonconvulsive status epilepticus. Electroencephalography is useful in differentiating nonconvulsive status epilepticus from an episode of hepatic encephalopathy and neuroimaging aids the diagnostic process.

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SARS-COV-2 PANDEMIC AND EPILEPSY: THE IMPACT ON EMERGENCY DEPARTMENT ATTENDANCES FOR SEIZURE

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Introduction: The need of reorganizing the Emergency Departments (EDs) to face the rising number of infected patients together with the risk of acquiring SARS-CoV-2 in hospital-based setting, which has deeply shaped the access of patients to the Health Care resources, have led to a reduction of ED attendances for non-infectious acute conditions and to a different management of chronic disorders.[1]

Materials and Methods: We performed a retrospective study evaluating the number and features of ED attendances for seizures during the lockdown period. We also reported the total number of ED attendances for all causes. We compared the lockdown period (March 10th – April 30th 2020) to a period of identical length immediately preceding the lockdown (January 18th – March 9th 2020) as well as to the same period in 2019 ("matched control").

Results: The total number of ED attendances dramatically decreased during lockdown (4664) compared to the matched control (10424) and to the pre-lockdown (9522) periods. A reduction of a lesser extent was detected also for seizure attendances to the ED: there were 37 during lockdown and 63 and 44 respectively during the two other periods. Interestingly, during the lockdown the percentage of known epileptics presenting to the ED for a seizure relapse was 54,1% during the lockdown, while they were the 77.8% and 65% during the "matched control" and "pre-lockdown" period, respectively.

Discussion: This is likely due to the fact that in chronic patients and their relatives, who had previously experienced seizures and know how to manage them, the fear of contagion outweighed the possible benefit of seeking medical aid. Surprisingly, during the "lockdown period" we found an increase in the admissions to the ward for seizures ($p = 0.043$) and a more severe triage code ($p = 0.027$) if compared to the "pre- lockdown period". Furthermore, comparison of the two control periods showed no differences, except for the number of EEG performed, which was higher in 2020 ($p = 0.005$). Finally, the percentage of EEGs ($p = 0,008$) and CT scans ($p = 0,018$) performed increased during the lockdown, probably due to the higher number of attending first seizure, which required further testing for diagnostic and therapeutic purposes. [2]

Conclusion: Our data suggest that the pandemic has affected the way patients with seizure access the Health Care System. In particular, patients with chronic epilepsy seek medical care for seizure to a lesser extent. On the other hand, the initial diagnostic work-up for patients with first seizures in the ED has not been affected by the pandemic and subsequent ED reorganization.

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TELEMEDICINE DURING THE SARS-COV-2 PANDEMIC LOCKDOWN: MONITORING STRESS AND QUALITY OF SLEEP IN PATIENTS WITH EPILEPSY

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Background and aims: SARS-CoV-2 pandemic heavily hit the western healthcare system rapidly saturating the hospital beds in wards and clogging the emergency departments. To avoid the collapse of Italian hospitals, office visits to outpatients were limited. Physicians had to approach new problems in the management of chronic patients who could not leave their homes. We explored the utility of telemedicine in the setting of lockdown in the evaluation of clinical stability of people of epilepsy and in assessing risk factors coming from isolation that could worse seizure control.

Materials and Methods: During the lockdown period our epilepsy clinic managed 38 outpatients with epilepsy via telemedicine. In addition to the standard clinical evaluation we administered to our patients 3 validated questionnaires testing sleep quality, daily sleepiness and stress level (PSQI, ESS and K6) and we collected data about daily habits during lockdown.

Results: We found that sleep quality was low ($PSQI \geq 5$) in 60% of patients and 37 % of the study population had high stress levels ($K6 \geq 14$). We found a strong association between those two items ($p<0,001$). Secondly, we found an increase in daily screen hours in comparison with a non-lockdown state and an association between screen hours and elevated daily sleepiness estimated with ESS ($p = 0,030$).

Discussion: Compared to a recent study [1] about the quality of sleep in people with epilepsy in pre-COVID-19 period, ESS was found similar but pathological PSQI was found with even a higher percentage. PSQI was also higher than the one of the normal population during the COVID-19 lockdown in Italy [2]. This result underline that people with epilepsy could be more susceptible than the general population to stressfull conditions. We found an increase in daily screen hours in comparison with a non-lockdown state and an association with elevated daily sleepiness estimated with ESS ($p = 0,030$). As we found an association of high stress levels and poor sleep quality we suggest that the lockdown state could facilitate sleep deprivation, which could trigger new seizures.

Conclusions: We report our experience in managing people with epilepsy during the lockdown, underlining the utility of telemedicine as a valid monitoring tool and the necessity of a psychometric and behavioral screening in patients with epilepsy during lockdowns.

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SUBCLINICAL SEIZURES: 24-H PERIODICITY AND SLEEP-WAKE CYCLE

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Background and Aims: To examine the sleep/wake distribution and 24-h periodicity of subclinical seizures (SS), recorded by 24-hour ambulatory EEG (AEEG) in adult patients affected by epilepsy and to compare focal subclinical sezures (FSS) versus generalized subclinical seizures (GSS).

Methods: SS, defined as ictal electrographic discharges with a temporal-spatial evolution lacking subjective or objective behavioral manifestations, with a duration longer than 6s, documented at AEEG, were retrospectively analyzed, and classified in FSS or GSS, based on EEG pattern. The occurrence of SS during wakefulness or sleep and within 3-h time blocks through a 24-h cycle (intervals I-VIII) was evaluated.

Results: A total of 295 SS (192 FSS, 103 GSS; mean duration 23.12±16.83s) from 30 patients (15F,15M) were studied. SS occurred more frequently during wakefulness than in sleep (242/295, 82% vs 53/295, 18%, $p<0.05$). Mean duration of FSS was significantly higher than GSS in every time block ($p < 0.001$). FSS occurrence was higher in the afternoon in time blocks VII and V (6-9pm, 39/192 and 12am-3pm, 35/192), meanwhile GSS showed a pick of presentation during morning awakening (6-9am, 34/103, $p<0.05$).

Conclusions: SS do not occur randomly but follow a specific circadian pattern and a particular sleep-wake distribution, depending on seizures type. In fact, FSS mainly tend to occur during wakefulness, and they have a significant propensity to

arise in the time slot 3-6pm, whereas GSS are more likely recorded on awakening. Relevance of SS arises from the potential effect on cognitive functions and their circadian pattern deserves interest in terms of chronotherapy.

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STATUS EPILEPTICUS IN PREGNANCY: LITERATURE REVIEW AND PROPOSAL OF A MANAGEMENT PROTOCOL

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Background and aims: Status epilepticus (SE) in pregnancy represents a life-threatening medical emergency for both mother and fetus. Pregnancy-related modifications may negatively affect seizure activity and anti-seizure medications (ASMs) pharmacokinetics [1]. No standardized treatment protocol for SE in pregnancy is available to date. The aim of this study was to review the current literature on management of convulsive SE in pregnancy and define an useful protocol that might ensure effectiveness in SE control and reduce maternal and fetal risks.

Material and methods: Original studies, systematic reviews and meta-analyses related to ASMs and anesthetic drugs used in SE during pregnancy were identified using PubMed and Google Scholar until November 2021. Based on available evidences, we developed a multidisciplinary-based protocol approach.

Results: Literature data are scarce and mainly generated from small observational studies, individual or case series reports [2]. A total of 39 women developing SE during pregnancy were found in the literature. Thirty-three out of 39 (84,6%) women had a good outcome; death occurred in two women and two fetuses. The limited available data suggest that the drugs commonly used for SE during pregnancy seem to be relatively safe for both mother and fetus. Benzodiazepines represent is the first-line drugs. If benzodiazepines are unsuccessful, levetiracetam and phenytoin are the preferred second-line ASMs, while valproic acid should be avoided during the first trimester of pregnancy due to its teratogenic risk and administered only if other ASMs failed. For refractory SE, anesthetic drugs (propofol or midazolam) are needed. Termination of pregnancy, via delivery or abortion, is recommended in case of failure of general anesthetics. Magnesium sulfate is the first-line treatment for SE in eclampsia.

Discussion: SE management during pregnancy is complicated by the lack of safety data on intravenous use of ASMs and anesthetic drugs in this population. Therapeutic choices mainly derive from literature on SE management in the overall population [3]. A multidisciplinary team (i.e. experts in neurocritical care, epilepsy, gynecology) is needed. Therapeutic approach depends on various factors such as the period of gestation, etiology and associated co-morbidities.

Conclusions: Prompt treatment of SE in pregnancy is mandatory. Multidisciplinary-based protocol is required for an appropriate management. Further studies are needed to identify the safest and most effective treatment protocol.

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DOES EPILEPSY CONTRIBUTE TO THE CLINICAL PHENOTYPE OF C9ORF72 MUTATION IN FRONTO-TEMPORAL DEMENTIA?

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Objective: Understand whether epilepsy contributes to the phenotype of patients with C9orf72 mutation, or it is part of the clinical spectrum of fronto-temporal dementia (FTD) itself.

Materials: C9orf72 mutation is the most common genetic cause of FTD and amyotrophic lateral sclerosis (ALS). To understand if epileptic manifestations are related to this mutation, we assessed epilepsy occurrence in patients with FTD with and without mutation.

Methods: We recruited 84 patients from the outpatient clinic of the Neurologic Clinic at University of Cagliari between 2013 and 2019. Patients were diagnosed and subcategorized in the variants of FTD according to the newest guidelines and underwent genetic screening for the C9orf72 mutation. Unprovoked seizures and epilepsy were assessed according to established clinical diagnostic guidelines.

Results: 84 patients (M=49; F=35) were diagnosed with FTD and checked for the C9orf72 mutation. Median age was 64.1 ± 9.8 years at the onset of FTD. Primary progressive aphasia (PPA) was diagnosed in 23 patients while behavioral variant (bvFTD) in 61 patients. The C9orf72 mutation was detected in 20/84 (23%) patients. Epilepsy was diagnosed in 6 patients (3 men and 3 women). Prevalence rate of epileptic manifestations in all FTD patients was 7.1% (6/84). Epilepsy was more frequent in patients with PPA than in those with bvFTD (4/23 vs. 2.61, $p = 0.045$), while the frequency did not differ according to family history (3/30 vs. 3/54, $p = 0.6$). Stratification for C9orf72 mutation showed epilepsy in 2/20 (10 %) patients who carried the C9orf72 mutation and in 4/65 patients (6.2%) who did not ($p = 0.6$).

Discussion: In our sample of FTD patients, 7.1% of cases reported epilepsy as unprovoked seizures. Epilepsy was more frequent in patients with PPA than in patients with bvFTD. By contrast, distribution of epilepsy did not significantly differ between patients with or without family history of FTD/parkinsonism/motor neuron disease (MND), or between patients who carried the C9orf72 mutation and those who did not.

Conclusions: Our data confirmed recent reports suggesting that epilepsy is part of the clinical spectrum of FTD. The lack of difference in the frequency distribution of epilepsy stratified for the presence of the C9orf72 mutation or family history of FTD/parkinsonism/MND, however, did not support the possibility that epilepsy represents a characteristic feature of the C9orf72 mutation. In agreement with recent studies showing that epilepsy is more common in PPA than bvFTD, we found a statistically significant difference between those two groups.

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COVID-19 VACCINATION IN PATIENTS WITH EPILEPSY: FIRST EXPERIENCES IN A ITALIAN EPILEPSY CENTER

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Objectives: To evaluate general side effects and side effects related to epilepsy of COVID-19 vaccines in a population of patients with epilepsy.

Materials and Methods: Consecutive patients attending the epilepsy outpatient clinic and receiving COVID-19 vaccines were asked about the type of vaccine, general vaccination adverse effects, epilepsy-related vaccination adverse effects (such as seizure frequency, seizure intensity, new seizures), and tolerance. Date were collected in a database and were used for statistical analysis. Demographics data were collected, including gender, age, age of onset of epilepsy, duration of epilepsy, etiology of epilepsy, type of seizures, antiseizure medications.

Results: COVID-19 vaccines are generally well tolerated in patients with epilepsy. Indeed such patients' population present similar side effects to the general population. The most frequently reported general side effects were fatigue, pain at the injection site and fever or low-grade fever. As concern the side effects related to epilepsy, only few patients reported an increased frequency of seizures occurrence. None of them required hospitalization. None of them presented with status epilepticus.

Discussion: Overall, tolerance of COVID-19 vaccines was good in most patients with epilepsy, with mild or moderate adverse effects. These data are in line with studies of the general population. [1-3] All reported adverse effects were already known. As for other vaccinations, that are generally recommended in people with epilepsy, the risk of increased seizure frequency is low or modest for patients with epilepsy undergoing COVID-19 vaccine. Therefore, when weighing the benefits and risks of vaccination, the recommendations are certainly in favor of vaccination.

Conclusion: Our data indicate that vaccines against COVID-19 in people with epilepsy are safe and well tolerated, particularly with regard to epilepsy-related adverse effects. Further studies in larger groups with sub-analyses for different vaccine types and with regard to efficacy of COVID-19 vaccination in people with epilepsy are needed.

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VAGUS NERVE STIMULATION IN SUPER-REFRACTORY STATUS EPILEPTICUS: THE EXPERIENCE OF A TERTIARY EPILEPSY CENTER

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Aims: The high mortality rate of super-refractory status epilepticus (SRSE) justifies the use of off-label therapies. Considering its low toxicity, a growing interest in neuromodulation has been observed. Current literature provides small evidence for the application of Vagus nerve stimulation (VNS) in SE. According to a recent review, VNS interrupted RSE and SRSE in 74% of cases. However, the incomplete description of concomitant treatments and stimulation protocols represents a strong limitation for the interpretation of these promising results [1].

Methods: We report our clinical experience with SRSE and acute VNS insertion.

Results: Case 1. A 16-year-old girl affected by Lafora Disease developed SRSE and underwent VNS implantation on the 66th day after SE onset. Within the 5th post-operative day, the parameters were set as follows: intensity 1.75 mA, 30" on-1.8' off, pulse-width 500 mcs, frequency 30 Hz, magnet 2mA. On day 3, the pharmacologically induced coma was successfully withdrawn, and EEG showed a progressive reduction of seizure activity. Only sporadic GTCS occurred during the next nine months, when tracheostomy-related complications caused her death [2]. Case 2. A previously healthy 20-year-old boy presented with new onset super-refractory SE (NORSE) in the aftermath of a febrile illness. On the 86th day from SE onset VNS was implanted. The following parameters were reached on the 6th post-operative day: intensity 2mA, 30" on-1.8' off, magnet 2.25 mA, pulse-width 500 ms. Sedation was interrupted and vigilance gradually recovered. On day 8, after recurrence of SE, the parameters were further modified to intensity 2.25 mA, 30" on-1.1' off. Afterwards, he has just presented isolated seizures with mild clinical manifestations until today, three months after implantation. Case 3. A 25-year-old lady with undiagnosed Medium-Chain Acyl-Coenzyme A Dehydrogenase and past unresponsiveness to VNS manifested SRSE. As a last resort, the VNS battery was replaced, and parameters were augmented to intensity 1.75 mA, 30" on–1.1' off, magnet 2mA (within 5th post-operative day). The next day, after sedation withdrawal, SE recurred, and she eventually died.

Discussion: In all patients we applied rapid titration by increasing intensity and then adjusting duration and amplitude, in the absence of side effects. In two out of three cases VNS was effective in resolving SRSE. However, the stimulation pattern that might lead to seizure termination needs further validation.

Conclusion: In our experience acute VNS implant and rapid titration to high stimulation parameters has proved to be a safe and effective procedure in SRSE.

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RISK OF HOSPITALIZATION AND DEATH FOR COVID-19 IN PERSONS WITH EPILEPSY OVER A 20-MONTH PERIOD: THE EPILINK BOLOGNA COHORT, ITALY

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Introduction: Data on COVID-19 outcomes in persons with epilepsy (PWE) are scarce and inconclusive. We aimed to study the risk of hospitalization and death for COVID-19 in a large cohort of PWE from 01 March 2020 to 31 October 2021.

Methods: Historical cohort design (EpiLink Bologna), comparing adult PWE grouped in people with focal epilepsy (PFE), idiopathic generalized epilepsy (PIGE), developmental and/or epileptic encephalopathy (PDEE), and a matched population cohort (ratio 1:10) for age, sex, residence, and comorbidity (assessed with the multisource comorbidity score), living in the local health trust of Bologna (about 800,000 residents). Clinical data were linked to health administrative data.

Results: In both cohorts (EpiLink N=1,576 subjects, 1128 PFE, 267 PIGE, 148 PDEE, 32 other; controls N=15,326 subjects), 52% were females, and the mean age was 50 years (SD 18). Hospital admissions for COVID-19 in the whole period were 49 (3.1%) in PWE and 225 (1.5%) in controls. The adjusted hazard ratio (aHR) in PWE was 1.9 (95% CI 1.4-2.7). The subgroups at higher risk were PFE (aHR 1.9; 95% CI 1.3-2.8) and PDEE (aHR 3.9; 95% CI 1.7- 8.7), while PIGE had a risk comparable to the controls (aHR 1.1; 95% CI 0.3-3.5). Stratified analyses of the two main epidemic waves (March-May 2020, October 2020–May 2021) disclosed a higher risk of COVID-19-related hospitalization during the first epidemic wave (March-May 2020) (aHR 3.8; 95% CI 2.2-6.7). Polytherapy with antiseizure medications contributed to a higher risk of hospital admission. 30-day risk of death after hospitalization was 14% both in PWE and controls.

Discussion: The hospitalization risk for COVID-19 in PWE may have been higher due to psychological, social, and healthcare-related issues, more prominent in the first wave. PDEE had the highest risk, likely for their vulnerability, whereas PIGE had the same risk as controls, possibly for the lower disease burden. The higher risk in PWE-P is attributable to the corresponding increased epilepsy severity, and to ASM-related adverse events. No higher mortality risk was noted in PWE after the matching with controls with the same burden of comorbidities.

Conclusion: During the first 20 months since the outbreak of COVID-19 in Bologna, PWE had a doubled risk of COVID-19 hospital admission compared to a matched control population, mostly attributable to epilepsy-related factors during the first epidemic wave. Conversely, epilepsy did not represent a risk factor for COVID-19-related death.

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RESILIENCE AND EPILEPSY: IMPACT ON PSYCHOSOCIAL FACTORS AND STIGMA

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Purpose: People with epilepsy (PWE) need to deal with seizure unpredictability and psychosocial prejudices as well as difficulties related to epilepsy. The tools that PWE use to cope with these challenges are still under discussion. Resilience is defined as 'a dynamic process that includes a positive adaptation in the context of significant adversity'. The aim of our study was to evaluate the resilience, through a dedicated scale, in a group of PWE and its impact on psychosocial factors, in particular the presence of feelings of stigmatization.

Methods: We consecutively enrolled 204 adult PWE (128 F/72 M; mean age: 42,4 y); 107 patients were seizure free (SF, 53,5%) and 93 not-seizure free (NSF, 46,5%). All subjects completed the Resilience Scale (RS)[1-2] and questionnaires for the assessment of depressive symptoms, anxiety and quality of life: respectively, Beck Depression Inventory-II (BD-II), Generalized Anxiety Disorder-7 (GAD-7) and QOLIE-31 (Q31). Finally, 57 patients in this group completed the Stigma Scale of Epilepsy (SSE) and Jacoby's Stigma Scale (JSS) for the assessment of the stigma associated with epilepsy. Therefore, we correlated RS values with all psychosocial aspects, in particular feelings of stigmatization.

Results: The results showed for the RS a significant direct correlation with the Q31 ($p = 0.001$) and inverse with the depressive and anxiety symptoms, evaluated with BDI-II ($p = 0.001$) and GAD-7 ($p = 0.001$). For the first time, a significant inverse correlation was evidenced between RS and the levels of stigmatization, assessed with SSE ($p < .001$) and JSS ($p = .006$). Patients with high Q31 despite persistent seizures (NSF_HiQ31) showed significantly higher levels of resilience than NSF patients with low Q31 values (NSF_LoQ31; $p = .005$) and SF patients with low Q31 levels (SF_LoQ31; $p < .001$). Compared to the same groups of patients, the 'resilient' group (NSF_HiQ31) showed fewer depressive and anxious symptoms. On the contrary, the most 'vulnerable' group (SF_LoQ31) showed low resilience values and greater depressive and anxious symptoms.

Conclusions: Our study showed that in PWE depressive symptoms, anxiety and quality of life were significantly associated with resilience, which was found to be able to decisively influence also the perception of stigma related to epilepsy.

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CANNABIDIOL AS ADD-ON TREATMENT IN DRUG RESISTANT EPILEPSY: REAL-LIFE EXPERIENCE IN A TERTIARY CENTRE

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Background: Cannabidiol (CBD) is a phytocannabinoid indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients two years of age or older. The efficacy and safety of CBD were clearly established in clinical trials and open-label extension studies, yet data regarding real-life experience are scarce. [1-2] The purpose of our study was to evaluate cannabidiol (CBD) safety and effectiveness in clinical practice in a tertiary center.

Methods: We retrospectively included all patients referred to the Epilepsy Center at the IRCCS Istituto delle Scienze Neurologiche in Bologna, Italy, who received a CBD prescription between March 2019 and May 2022. Epilepsy and seizure types were classified according to the ILAE classification. [3] Patients were assessed at baseline, and after 3 and 6 months of follow-up. Patients were defined as "responders" and "super responders" if reporting a reduction in seizure frequency >30% and >80% compared with baseline,

respectively. All adverse events reported by patients during the follow-up period were recorded to assess tolerability.

Results: A total of 35 patients were included (mean age 38 years, range: 15-57; 23 male and 12 females; 30 patients had an indication for treatment with CBD, 29 with a diagnosis of LGS and 1 with a diagnosis of DS, while 6 patients were trated off label, 3 had a diagnosis of Lafora disease, 1 patient had a diagnosis of Unverricht-Lundborg disease, 1 had polymicrogyria and 1 had a febrile infection-related epilepsy syndrome; everyone was in treatment with at least other 2 ASM). The retention rate at three months was 88,2%. 20 patients (58%) had a follow-up of at least 3 months and 11 patients (29%) of 6 months. At three months, 7 patients (35%) were responders, and 4 (20%) were super responders. 13 patients (65%) developed adverse effects: the most frequently reported adverse effect was somnolence (10 patients, 50%); 5 patients had to lower the initial target dose; 3 patients had to stop the treatment (1 for having developed jaudice, two for persistant somnolence).

Conclusions: In this monocentric real-world trial, CBD was a safe and effective therapeutic option for highly drug-resistant patients, and in a subset of these patients determined a dramatic reduction in seizure frequency.

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MANAGEMENT OF STATUS EPILEPTICUS IN ADULTS: A SYSTEMATIC REVIEW OF CLINICAL PRACTICE GUIDELINES

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Objective: Status epilepticus (SE) is a neurological emergency characterized by high mortality that has remained stable across decades. This stability could be partly explained by general aging of population but also by the gap between management based on clinical practice guidelines (CPGs) and clinical practice. CPGs for management of SE have been available for years, yet several studies have reported that recommendations are often not followed by clinicians. We hypothesized that lack of implementation of a formal treatment protocol was a possible explanatory factor. The aim of this systematic review is to appraise quality of CPGs, assuming that applicability domain may be particularly overlooked, and make an initial comparison of topics covered.

Materials: CPGs on diagnostic and therapeutic management of SE in adults, issued by recognized health authorities, published since 2010, were included.

Methods: This systematic review followed the methodology by Johnston et al. (2019). It was registered with PROSPERO database (CRD42022314153) and the protocol was published (10.5281/zenodo.6363325). We searched PubMed and EMBASE databases, guideline registries, EBM databases, point-of-care tools, websites of governmental organizations, websites of international neurologic societies. Quality of CPGs was assessed with the AGREE-II tool (Brouwers et al., 2010a).

Results: Fifteen CPGs were included. Regarding quality analysis, the AGREE-II domains 'Scope and Purpose' and 'Clarity of Presentation' were assigned the highest overall median scores of 69% and 78% respectively. The domain 'Applicability' was assigned the lowest median score of 10%. The domains 'Stakeholder Involvement', 'Rigor of Development' and 'Editorial Independence' were generally underreported (median score range 44-61%). Most CPGs simultaneously addressed pre-hospital management, treatment (antiepileptics and anesthetics) and EEG monitoring (60%). The first two coincide with the main topics discussed (87%-80% of CPGs) while those less considered were diagnostic investigation (40%), refractory/super refractory SE alternative treatments (47%) and timing for EEG registration (47%). Only 33% exploited tools/algorithms to implement CPGs.

Discussion: From a first analysis, it seems that CPGs deal extensively with some issues, leaving out others fundamental in clinical practice. Moreover, as hypothesized, applicability domain of CPGs is particularly neglected.

Conclusions: As a future prospect we will compare content of CPGs to draw common conclusions and outline discrepancies. All stakeholders involved in management of SE should improve implementation of CPGs in standard clinical practice.

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DETERMINATION OF BIOMARKERS IN EPILEPTOGENESIS AND DRUG-RESISTANCE IN EPILEPSY: FOCUS ON SPECIFIC MIRNAS AND STRESS PROTEINS

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Temporal lobe epilepsy (TLE) is one of the most common medically intractable disease, typically associated with hippocampal sclerosis (HS). miRNAs and the chaperone system (CS) are promising targets to understand pathogenic mechanisms and for developing novel therapies.

Objectives: 1) Evaluate circulating miRNAs levels in patients with focal lesional and non lesional drug-resistant epilepsy, to compare the results with the purpose to use specific miRNAs serum expression level as a biomarkers of drug-resistance. 2) Determine specific miRNA expression levels in specimens of hippocampus from patients with TLE-HS to compare it with specimens obtained from healthy subjects. 4) Determination of oxidative stress biomarkers, involved in epileptogenesis, and correlation of its levels with specific miRNAs expression.

Materials and methods: We have collected serum sample from 51 patients with a diagnosis of drug-resistant epilepsy according to the recent International League Against Epilepsy (ILAE) Classification (1) 26 (51%) with a focal idiopathic epilepsy and 25 (49%) with lesional focal epilepsy (12 focal cortical

dislpasya - 13 HS-TLE). Serum were processed to extract total miRNAs and the expression of specific miRNAs (miR-146a, miR-8071, and miR-663, MiR-1 and miR-206) was determined using quantitative real time PCR (qRT–PCR). Moreover, we obtained 10 surgical specimens of hippocampus from patients with HS-TLE matched for age and gender, and 5 control hippocampus obtained at autopsy from healthy controls. Hsp60 hippocampal tissue distribution was determined by immunohistochemistry.

Results and discussion: Among the investigated miRNAs, we observed a significant down-regulation of miR-146a, miR-8071,miR-663, MiR-1 and miR-206 in patients with idiopathic and lesional focal epilepsy compared to the controls.miR-146a and miR-8071 play an inhibitor role during the acute phase of an epileptic seizure explaining their down-regulation in our experiments. These miRNAs may be suggested as intrinsic marker of drug-resistance [2]. We determine the circulating levels of Hsp60 as a marker of oxidative stress, and we observed a significant decrease of its levels in patients with idiopathic epilepsy as well as in patient with lesional focal epilepsy compared with the controls. There was a positive correlation between Hsp60 and MiR-1 and miR-206 levels. Moreover, we observed a decrease of Hsp60 immunoreactivity in the hippocampus of TLE-HS patients. The protein has classically a role in the protection from oxidative stress [3], suggesting that it may be involved in epileptogenesis.

Conclusions: The data obtained should help in the identification of molecular targets which could be used as targets for therapeutic modulation in drug-resistant epilepsy.

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HEADACHES

THE CHRONIC MIGRAINE PHENOTYPE: ROLE OF POTENTIAL PERIPHERAL BIOCHEMICAL BIOMARKERS AND SPECIFIC CLINICAL FEATURES

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Title: In-depth profiling of chronic migraine phenotype: role of potential peripheral biochemical biomarkers and specific clinical features.

Aims: Chronic migraine with medication overuse headache (CM-MO) represents one of the most disabling phenotypes across the migraine spectrum. The progression from episodic migraine (EM) to chronic migraine is still an unclear process. The aim of this study is to better define the phenotype of CM-MO by means of peripheral biochemical markers and their correlation with specific clinical features.

Materials: We enrolled 13 CM-MO patients, 21 EM patients and 17 healthy controls (HC). All groups underwent a baseline blood sampling; in addition, CM-MO group was also tested 2 months after an in-hospital detoxification protocol. CM-MO and EM groups underwent psychodiagnostic evaluation.

Methods: In all subjects, we evaluated the expression of miR34a-5p and miR-382-5p in peripheral blood mononuclear cells, and plasma levels of CGRP and PACAP. Furthermore, we analyzed the clinical/demographic features and the psychological profile of migraine patients.

Results: CGRP and PACAP levels, miR34a-5p and miR-382-5p expression were higher in CM-MO group when compared to EM and HC ($p<0.05$ for all comparison). Headache frequency positively correlated with CGRP (Spearman's rho: 0.559, p=0.030), PACAP (Spearman's rho: 0.563, p =0.001) and miR-34a-5p (Spearman's rho: 0.496, p =0.003). Depression was more prevalent in CM-MO patients when compared to the EM group (61.5% vs 33.0%, p=0.001). Personality disorders and anxiety were equally distributed between the two groups. Two months after detoxification, we found in the CM-MO group decreased CGRP and PACAP levels (p=0.031 and p=0.008, respectively), as well as a reduction of miR34a-5p expression (p=0.004).

Discussion: In line with literature data, we found a relation between the studied peripheral biochemical biomarkers and the severity of migraine. Further analyses will evaluate the association of biochemical markers with the psychological profile of these patients.

Conclusion: Our findings deepen our knowledge about the CM-MO phenotype, which seems to be characterized by an alteration of peripheral biomarkers and of the psychological profile.

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MICROEMBOLIC SIGNALS IN EMBOLIC STROKE OF UNDETERMINED SOURCE and MIGRAINE AURA

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Introduction: Migraine is a complex neurovascular disorder whose triggers are not entirely understood. Similarly, the pathological mechanisms subtending the higher risk of stroke in patients with migraine with aura (MA) are still debated. Microembolisation has been theorized as a possible trigger for both aura and stroke. Microembolic signals (MESs) have been previously reported mainly in patients experiencing higher cortical dysfunction (HCD, i.e. language and memory impairment) during aura compared with visual aura. However, the incidental stroke seems to characterize patients with visual aura.

Methods: We considered for enrollment patients with MA, with embolic stroke of undetermined source (ESUS), and age and sex-matched controls (CTRLs) among subjects referred to our neurosonology unit to undergo bubble test to detect right-to-left shunt (RLS). Continous 45 minute monitoring with transcranial Doppler was performed bilaterally to insonate Middle Cerebral Artery (MCA) and Posterior Cerebral Artery (PCA) to detect MESs. A bubble test was performed thereafter.

Results: Transcranial Doppler monitoring was completed in 43 MA patients (38.8 SD 12.4 ys 77.3% females), 13 ESUS patients (46.4 SD 8.1 ys 64.3% F), and 12 CTRLs (38.6 SD 13.7 ys. 76.9% F). MESs were detected in 1 (2.3%) MA patient with visual aura, 3 (21.4%, p=.049) ESUS patients, and 1 (7.7%) CTRL participant, All MESs were detected in the MCA spectrum. Bubble test identified RLS in 8 (61.5%) CTRLs, 22 MA (52.4%), and 11 (78.6% p=.221) ESUS patients. MESs were detected in subjects with RLS in 4 out of 5 cases.

Conclusions: The present findings rebut the hypothesis that MES is a common observation in patients with migraine with aura and more specifically

in those with HCD. Further research in a larger cohort is needed to better understand the pathophysiological link between microemboli, aura and stroke.
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ONABOTULINUMTOXINA TREATMENT IN OLDER PATIENTS WITH CHRONIC MIGRAINE AND A LONG DISEASE HISTORY

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Introduction: Migraine prevalence decreases after the fifth decade of life, but some patients have high-frequency attacks or even chronic migraine (CM) in older ages. Comorbidities, polytherapy, and risk profile pose relevant challenges in these patients when considering the conventional preventive agents. Older patients were mostly excluded from trials testing new migraine preventatives. Establishing a preventive treatment in older patients is cumbersome. OnabotulinumtoxinA (OBT-A) represents an appealing strategy for the lack of systemic side effects and drug-to-drug interactions. Unfortunately, no studies specifically addressed the efficacy of OBT-A in the elderly population. This study aimed to investigate the outcome of OBT-A in the treatment of chronic migraine in the elderly.

Methods: This is a post-hoc retrospective analysis of real-life prospectively collected data at 16 European headache centers on patients treated with OBT-A for CM over the first three treatment cycles, including patients aged ≥65 years. The primary endpoint was the changes in monthly headache days (MHDs) from baseline to each treatment cycle (i.e., 3 (V3); 6 (V6), and 9 months (V9). The secondary endpoints were the frequency of "good response" (i.e., responder rate (RR) ≥50%), partial response (30-49% RR), and no response (<30% or drop-outs), the changes in days with medication intake and the discontinuation rate.

Results: In a cohort of 2789 CM patients, 235 were ≥ 65-year-old (8.4%, range 65-91 yrs, 69.6 SD 4.8; 73.5% females) with a migraine disease history of 47.2 years (SD 13.5), 15.2 (SD 13.8) with CM. At V9, the discontinuation rate was 32.3%. MHDs progressively decreased from baseline (24.8 SD 6.2) to V3 (17.5 SD 9.1, p<.000001), from V3 to V6 (14.8 SD 9.2, p<.0001), and from V6 to V9 (11.9 SD 7.9, p =.001). The percentage of patients with a good response increased from 30.7% at V3, to 34.5% at V6, to 38.7% at V9. At least a partial response of observed in 47.3% at V3, 52,8% at V6 and 51% at V9. Also, days with medication intake progressively decreased from baseline (19.2 SD 9.8) to V3 (11.9 SD 8.8, p<.00001), from V3 to V6 (10.9 SD 8.6, p=.012), and from V6 to V9 (9.6 SD 7.4, p =.049).

Conclusion: OnabotulinumtoxinA provided a significant benefit in the first three cycles of treatment in elderly patients with a long history of migraine with chronic frequency. The low discontinuation rate supports overall good tolerability. Our findings are in line with real-life data from young and middle-aged patients.
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GLYMPHATIC SYSTEM AND IDIOPATHIC INTRACRANIAL HYPERTENSION: AN OBSERVATIONAL CLINICO-RADIOLOGICAL STUDY

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Background: Glymphatic system is a recently discovered drainage structure that involves movement of cerebrospinal fluid (CSF) along perivascular space through cerebral tissue. CSF flows into the brain parenchyma through the periarterial space, it is transported to the interstitial space crossing blood–brain barrier and then flows out through the perivenous space and reaches the cervical lymphatic system [1]. The recent discoveries of glymphatic system have helped advance our understanding of CSF physiology and may allow new insights in the understanding of idiopathic intracranial hypertension (IIH), whose pathogenesis seems related to CSF dynamic disfunction [2].
Aim: To identify radiological sign of glymphatic system disfunction in patient with IIH.

Material and Methods: Patients with suspected IIH underwent to clinical, ophthalmological and radiological (brain MRI) along with lumbar puncture with intracranial pressure measurement. We evaluated the activity of the glymphatic system in cases with confirmed IIH with a post-acquisition

processing diffusion-based technique called "diffusion tensor image analysis along the perivascular space" (DTI-ALPS). Diffusion tensor images were acquired to calculate diffusivities in the x (Dx), y (Dy), and z (Dz) axes of the plane of the lateral ventricle body. We evaluated the diffusivity along the perivascular spaces as well as projection fibers and association fibers separately, to acquire an index for diffusivity along the perivascular space (ALPS-index, as mean (Dxpro, Dypro)/ mean (Dypro, Dzasc), where Dxpro and Dxasc are Dx values in the projection and association fiber areas, respectively) [3]. ALSP-index was calculated in both hemispheres and compared with age matched controls.

Results: From November 2021 to November 2022, 5 patients (all female) were consecutively enrolled, the age was 39 (mean, range 22–56) and the BMI 34 (mean, 26-51). All patients complaint headache and visual impairment; four disclosed papilloedema. Intracranial pressure was increased in all patients (22-40 cmH2O), and brain MRI showed signs of intracranial hypertension (tortuosity of the optic nerves n=4, poster globe flattering n=4, prominent perioptic nerve sheath n=5, empty sella n=4, enlarged Meckel cave n=2, transverse sinuses stenosis n=5). ALPS indexes of IIH cases and healthy control were 1,23±0.07 and 1,19±0,11 (mean ± sd) respectively, without significant differences among the groups.

Discussion and conclusion: To date this is the first study specially designed to analyze glymphatic system function in patients with IIH. The results of this preliminary study apparently do not reveal a primary dysfunction of glymphatic system in IIH. Anyway, further study with larger samples are mandatory before drawing conclusions.

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ANTI-CGRP ANTIBODIES EFFECTS ON MIGRAINE PSYCHIATRIC COMORBIDITIES

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Objective: To evaluate the effects of monoclonal antibodies (mAbs) acting on the calcitonin gene-related peptide (CGRP) or its receptor (anti-CGRP/R mAbs) on comorbid symptoms of depression, anxiety and fatigue in migraine patients resistant to traditional prophylaxis.

Materials and Methods: 48 patients (77% females, median age 48 years old) with chronic resistant migraine, studied in an open-label longitudinal study, were undergoing treatment with subcutaneous injection of anti-CGRP mAbs (46%) or with anti-CGRPR mAbs (54%). Psychiatric comorbid symptoms were evaluated with the Patient Health Questionnaire (PHQ-9), Generalised Anxiety Disorder (GAD-7) scales and Fatigue Severity Scale (FSS). Parameters were assessed at baseline and at 3-month follow-up. According to the European Headache Federation treatment guidelines, non-responders were defined as subjects that did not have a reduction of at least 50% in the frequency of migraine after the administration of drugs for at least three months.

Results: Non responders are 12 subjects (25%) and responders 36 subjects (75%). The first population is significantly younger (39 years old vs 51). However, two groups did not show significant differences in the distribution of psychiatric comorbidities and the burden of disease at the baseline. In responder population the reduction of disease severity observed, both in terms of headache frequency (median days/month 21 vs 6 $p < 0.001$), and allodynia (7.00 vs 4.74 $p = 0.002$), was associated with a significant decrease of the considered psychiatric comorbidities and with the improvement of the quality of life (GAD7 median 9.00 vs 6.83 p=0.001, PHQ9 median 9.50 vs 6.71 $p < 0.001$, FSS median 44.00 vs 31.91 p=0.001). Also in non-responder population a significant reduction of the headache frequency, (median 24.5 16.5 p=0.003), was observed as well as an almost significative trend in the reduction of ictal allodynia (median 7.5 vs 4.0 p= 0.05) and reduced migraine-related disability (MIDAS median 83.5 vs 39.5 p=0.002), but no significant improvement is registered for psychiatric comorbid symptoms.

Discussion: CGRP neurotransmission plays a pivotal role in migraine-specific pain perception. The relationship between anxiety, depression, fatigue, and migraine, especially chronic migraine has been established in several investigations and it is considered bidirectional though pathophysiological mechanism remains unclear. Whether the CGRP neurotransmission may have a role in determining modification of affective symptoms should be further evaluated. Additionally, chronic pain with multiple therapeutical failures is a trigger for psychiatric comorbidities.

Conclusion: Anti-CGRP/R mAbs treatment improves psychiatric symptoms only in responder subjects indicating that they are likely secondary to chronic pain condition. Further studies comparing anti-CHRP/R with other prophylaxis may help understand its potential specific role in psychiatric comorbidities.

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HEADACHE CHANGES IN MIGRAINE PATIENTS AFTER SARS-COV-2 INFECTION AND VACCINATION

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Aim of the study: The present study was aimed at verifying any changes in frequency and severity of headaches in migraine patients after Sars-Cov-2 infection and vaccination.

Materials and methods: In the period January-May 2022, about seven hundred patients visited the Headache Center of Perugia; during their visits they were questioned about the occurrence of Sars-Cov-2 infection in the past year, as well as their experience after the first, second and third dose of the vaccine for Sars-Cov-2, with particular attention to any changes in the headache pattern.

Results: 73 migraine patients reported Sars-Cov-2 infection in the past year; of these, 49 patients (67%) reported a persistent worsening of headache, both in terms of frequency (an increase of at least 50% of migraine monthly days) and intensity, in the months following the resolution of the infection. Among these, 14 patients (28%) reported a change pattern from an episodic to a chronic form of migraine and it was necessary to introduce or change the prophylactic therapy. The remaining 24 patients (33%) didn't report long-term changes in their usual migraine. It should be noted that among patients who

reported a headache worsening after the infection, only 32% were on prophylaxis, unlike the 54% of patients who didn't experience any headache changes. Regarding the vaccine, although many patients reported headache episodes soon after vaccine inoculation, only a small minority of interviewed patients reported persistent headache worsening after vaccine, independently of which vaccine was administrated.

Discussion: Headache occurs as one of the initial symptoms of infection in COVID-19 in a percentage that reach 60% of cases [1]; a persistent headache for at least six months, both as a clinical expression of new onset and as worsening/chronicization of a pre-existing migraine, has also been reported in literature [2]. Many possible pathophysiological mechanisms of this post-infection headache have been postulated, including the activation of peripheral trigeminal nerve endings by the SARS-CoV-2 directly or through the increased circulating pro-inflammatory cytokines; a deranged innate immune signaling and activation of inflammasomes is implicated in both COVID-19 headache and migraine [3].

Conclusions: In accordance with literature, Sars-Cov-2 infection is an important risk factor for worsening and chronicization of headache in migraine patients. The vaccine, on the other hand, does not appear to be related to a long-term change in headache in a significant percentage of patients.

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VESTIBULAR SIGNS IN EXPERIMENTALLY INDUCED MIGRAINE ATTACKS: A POST-HOC, EXPLORATORY ANALYSIS

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Aims: Vestibular migraine (VM) as defined in ICHD-3 represents one of the most common vestibular syndromes, although its pathophysiology is not fully understood. The acute phase of VM is characterized by transitory oculo-vestibular signs (OVSs) that usually disappear outside of the VM attack. The difficulty to study spontaneous migraine attacks led to inconsistent results, and we believe that the adoption of human migraine models can help overcome this issue.

Materials: We investigate the incidence of OVSs during experimentally induced migraine attacks in 24 episodic migraine patients without VM and 19 healthy controls exposed to sublingual nitroglycerin (NTG 0.9 mg).

Methods: A comprehensive oculo-vestibular examination was performed at baseline, at migraine-like onset and before hospital discharge (180 minutes after NTG).

Results: 16 out of the 24 migraine patients developed a migraine-like attack (66.7%). Three of them (12.5%) developed OVSs during the migraine-like attack. In line with previous results, we described a combination of central (down-beating nystagmus) and peripheral (bilateral deficit of vestibulo-ocular reflex) vestibular signs. Noteworthy, no patients with a negative induction test developed OVSs. No OVSs were detected in healthy subjects at any timepoints. Noteworthy, no subjects complained of vestibular symptoms throughout the study procedures.

Discussion: Human migraine models may indeed be appropriate tools to evaluate the vestibular dysfunction in migraine and in VM under well-controlled experimental conditions.

Conclusion: The present findings represent a starting point to design future ad-hoc and well-powered studies to deepen our knowledge on this topic.

REAL-WORLD PERSISTENCE RATES FOR ONABOTULINUMTOXINA VERSUS CGRP MABS AMONG PATIENTS WITH CHRONIC MIGRAINE: AN ANALYSIS OF ELECTRONIC HEALTH RECORD DATA

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Objective: Evaluate real-world persistence rates among patients with chronic migraine (CM) prescribed onabotulinumtoxinA (onabotA [BOTOX®]) or a calcitonin gene–related peptide monoclonal antibody (CGRP mAb).

Materials: Persistence for generic oral migraine preventive medications is reported to be low.

Methods: This was a retrospective, longitudinal, observational study that analyzed the Practice Fusion Electronic Health Record database (3/1/2018-2/28/2021). Adults were identified using prescription histories for either onabotA or CGRP mAb (index treatment) along with ICD-10 codes for CM and followed for 12 months. Persistence to index treatment was assessed at 6, 9, and 12 months. Sensitivity analyses evaluated the effects of COVID-19 on persistence using pre-COVID (follow-up ending before 3/2020) and COVID (follow-up ending in/after 3/2020) cohorts. For the sensitivity analysis, all patients with migraine were included.

Results: Of 28,323 patients with onabotA or CGRP mAbs prescriptions meeting all inclusion/exclusion criteria, 1974 were included in the final population (4812 in the sensitivity analysis). In the respective onabotA and overall CGRP mAbs populations, 88% and 86% were female and mean ages were 50 and 48 years with no notable differences for the individual CGRP mAbs. Significantly more patients with CM met persistence criteria with onabotA versus erenumab, fremanezumab, and galcanezumab at months 6 (80% vs 54%/59%/50%), 9 (73% vs 35%/40%/41%), and 12 (66% vs 27%/33%/24%; [all P<0.001]). In the sensitivity analysis, a greater percentage of patients met persistence criteria with onabotA versus erenumab, fremanezumab, and galcanezumab for both the pre-COVID (6 months: 76% vs 50%/56%/49%; 9 months: 67% vs 31%/40%/38%; 12 months: 61% vs 24%/34%/24%; [all P<0.001]) and COVID (6 months: 75% vs 50%/55%/45%; 9 months: 69% vs 32%/37%/37%; 12 months: 59% vs 25%/30%/24%; [all P<0.001]) cohorts.

Discussion: Patients with CM initiating onabotA treatment had higher persistence rates at 12 months compared to CGRP mAbs (66% vs 24%-33%). Results were similar among the pre-COVID and COVID cohorts.

Conclusion: These analyses estimate the treatment persistence rates for onabotulinumtoxinA and CGRP mAbs for the preventive treatment of chronic migraine, including the period prior to and during the COVID-19 pandemic. Comparisons of persistence rates for different preventive treatments for chronic migraine, including CGRP mAbs and onabotulinumtoxinA, are lacking in the literature and provide important information for clinicians.

ANTI-CALCITONIN GENE-RELATED PEPTIDE MONOCLONAL ANTIBODIES FOR THE TREATMENT OF VESTIBULAR MIGRAINE

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Aim: Vestibular Migraine (VM) is considered the most common cause of recurrent vertigo, with a prevalence of 2.7% in adults [1]. Monoclonal antibodies against CGRP are a new class of drugs that act by blocking CGRP receptor or ligand. Erenumab, galcanezumab and fremanezumab are suitable and safe in preventing episodic and chronic migraine. Since CGRP is also detected in human cochlear and vestibular organs it may also play a role in vestibular physiology and be effective in VM [2]. This study aims at evaluating the efficacy of anti-CGRP Mab for treatment of VM.

Materials: We evaluated fifty VM patients fulfilling the International Headache Society Appendix criteria for VM and with a history of multiple failed treatments with validated migraine preventatives at standard doses for at least 2 months.

Methods: Framenezumab, Erenumab or Galcanezumab were administered according to manufacturer recommendations for the study duration (12-month period). The mean monthly days with headache or vertigo occurring during the run-in period as well as during anti-CGRP MAb treatment were evaluated by reviewing standardized paper patient headache diaries at baseline and every three months in follow-up visit. Migraine-related clinical burden was assessed with the Migraine Disability Assessment (MIDAS) at baseline and every three months for twelve months [3].

Results: Statistically significant improvements were observed in migraine and vertigo frequency after three months and then confirmed at sixth, nine and twelve months follow-up. Migraine monthly frequency decreased from a mean of 22.4 ± 7.3 days at baseline, to 11.2 ± 6.6 days after three months ($p < 0.001$), to 7.4 ± 6.6 days after sixth months ($p < 0.001$), to 5.1 ± 6.2 days after nine months ($p < 0.001$) and to 3.4 ± 5.5 after 12 months ($p < 0.001$). Monthly days with vertigo decreased from a mean of 10.7 ± 9.4 days at baseline to 5.9 ± 7.2 days after three months ($p < 0.001$), to 2.8 ± 4.1 days after sixth months ($p < 0.001$), to 0.8 ± 1.9 days after nine months ($p < 0.001$) and to 0.4 ± 1.1 after 12 months ($p < 0.001$).

Discussion: Study findings show that monoclonal antibodies against CGRP or CGRP receptors seem to have a remarkable effectiveness also on VM vestibular symptoms. Since CGRP receptors are expressed in the vestibular system, our findings support that inner ear CGRP release might be causatively involved in vestibular symptoms associated to migraine.

Conclusions: Anti CGRP or CGRP receptor MABs show a high efficacy in the treatment of both headache and vestibular symptoms that characterize VM. This finding confirms the involvement of CGRP release in mechanism underlying VM and support the use of such new drugs in its treatment.

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MIGRAINE CHRONIFICATION AS AN ALLOSTATIC DISORDER: ASSESSMENT OF THE BOLOGNA ALLOSTATIC LOAD INDEX (BALI)

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Objective: In a bio-behavioural view, the migraine attack serves as an adaptive strategy to restore homeostasis (allostatic response), yet repeated and chronic stressors may result in a maladaptive remodelling of the central autonomic network (allostatic load) translating into chronification of the disease. The aim of this study is to investigate the role of the allostatic load in migraine to corroborate the evolutionary theory of migraine.

Methods: In this cross-sectional study, the allostatic load was measured with a composite multi-system index (BALI: Bologna Allostatic Load Index) evaluating 20 different biomarkers representing four physiological systems: immune, metabolic, cardiovascular and neuroendocrinological systems. BALI score was subdivided into high-score (≥6) and low-score based on the distribution in controls. Migraine patients were included and subclassified into low-frequency episodic migraine group (low-EM group) (1-9 headache days per month), high-frequency episodic migraine group (high-EM group) (10-14 headache days per month) and chronic migraine group (CM group) (≥15 days per month). Demographic and epidemiological characteristics, as well as psychological parameters, were gathered to investigate their relationship with BALI score and headache frequency.

Results: The distribution of BALI high-score increased in parallel with migraine attacks monthly frequency: 16% in low-EM group (n=10), 24% in high-EM group (n=12) and 40% in CM group (n=21) (p=0.017). In a multivariable analysis adjusted for confounding variables, the Odds Ratio to have a high-score BALI (vs low-score) in CM patients (vs Low-EM patients) was 2.78 (95% CI 1.07-7.22; p=0.036). Individual BALI biomarkers values which were significantly different among migraine subgroups included systolic blood pressure (p=0.018), diastolic blood pressure (p<0.001) and heart rate (p=0.019).

Conclusions: Our study revealed a potential pathogenic role of allostatic load in migraine chronification, corroborating the evolutionary theory of migraine. Future prospective and larger studies are warranted to confirm our results.

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DISABILITY AND IMPACT OF HEADACHE INFLUENCE SOMATOSENSORY ELECTROCORTICAL RESPONSES IN PATIENTS WITH MEDICATION-OVERUSE HEADACHE

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Objectives: Migraine is the most disabling nervous system disease in female patients under 50 years of age. When migraine becomes chronic due to medication overuse, the disability worsen at the same time as there are plastic changes in cortical somatosensory responses. It is not yet known how functional brain changes are related to the clinical disability associated with medication overuse headache (MOH).

Material and Methods: We prospectively enrolled 18 MOH patients who underwent a recording of somatosensory evoked potentials (SSEPs) from median nerve stimulation at the wrist. The same patients completed the Migraine Disability Assessment (MIDAS) questionnaire - the most frequently used questionnaire to assess migraine-related disability -, the Headache Impact Test (HIT-6) - measuring the adverse impact of headache on multiple domains -, and the 12-item Allodynia Symptom Checklist (ASC-12). We studied N20-P25 amplitude and habituation as well as high frequency oscillations (HFO) that most directly reflect thalamo-cortical (early) and primarily cortical (late HFO) activation.

Results: In patients with MOH, the higher the HIT-6 the more pronounced the habituation deficit (r=0.519, p=0.027), and the higher the ASC-12

(r=0.729, p=0.017). Furthermore, the higher the ASC-12 the higher the late amplitude HFOs (r=0.676, p=0.032). MIDAS scale score did not correlate with any electrophysiological variables.

Discussion: Using scales for assessing disability and impact of headache and recording neurophysiological tests, we were able to find a link between disability and altered central nervous system activity. Although disease perception is a subjective experience, identifying possible structures underlying its regulation allows us to gain a better understanding of both how the patient perceives the disease and migraine itself.

Conclusions: Our data show that habituation deficit and high-frequency cortical oscillatory activity of SSEPs may be biomarkers of the impact of headache in daily life and of its associated symptoms.

ABILITY OF A SET OF TRUNK ACCELERATION-DERIVED GAIT INDEXES TO CHARACTERIZE GAIT IMBALANCE IN SUBJECTS WITH MIGRAINE

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Objectives: It is not uncommon for subjects suffering from migraine to experience static and dynamic balance impairment, as well as a reduction in the limits of stability, which leads to a reduction in anticipatory postural adjustments and an increased risk of falling [1–3]. The aims of this study were: (i) to assess the ability of 16 gait stability indexes to identify gait instability in subjects with episodic migraine without aura (MO) regardless of age and gait speed and (ii) to investigate their correlations with clinical and kinematic variables.

Materials: This study included 23 walking trials from subjects with MO and 23 age, gender, and gait speed matched healthy subjects (HS) acquired using a single lumbar-mounted inertial measurement unit.

Methods: The harmonic ratios, percent recurrence, percent determinism (RQAdet), coefficient of variation, normalized jerk scores, and maximal Lyapunov's exponents for short time series (LLE) were calculated based on trunk acceleration patterns in the anteroposterior (AP), medio-lateral (ML), and vertical (V) directions. To assess the ability of the gait indexes to characterize the gait of MO, independent sample t-tests, Cohen's d, and the area under the receiver operating characteristic curves were calculated. To assess the correlations between clinical scales and gait parameters, partial Pearson's correlation coefficients were calculated, excluding the effects of gait speed.

Results: LLEML values ≥ 1.04, LLEV values ≥ 1.06, and RQAdetAP values ≥ 96.32 characterized MO with 78%, 70%, and 75% probabilities, respectively, regardless of gait speed. LLEML correlated with the duration of the migraine attacks (r = 0.48, p = 0.01), VAS (r = 0.42, p = 0.02), MIgraine Disability Assessment Score (r = 0.38, p = 0.03), Dizziness Handicap Inventory scores (r = 0.44, p = 0.04). LLEV correlated with Allodynia Symptoms Checklist scores (r = 0.46, p = 0.01) and pain intensity (r = 0.42, p = 0.02). RQAdetAP correlated with the Activities Balance Confidence scale scores (r = -0.40, p = 0.03).

Discussion: LLE can capture the subtle gait imbalance experienced by MO, reflecting a loss of local dynamic stability in ML and V directions, and a reduced ability to respond adequately to small perturbations during gait. As a result of their perceived imbalance, MO increase their gait regularity, particularly in the AP direction, as evidenced by higher RQAdet when compared to HS.

Conclusions: LLEML, LLEV, and RQAdet are accurate biomarkers of gait instability that reflect the severity and disability of migraine presentation.

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EFFICACY AND SAFETY OF ONABOTULINUMTOXIN A FOR CHRONIC MIGRAINE IN AN OVER 60 YEARS OLD POPULATION

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Objectives: Aim of the present study was to assess the safety and efficacy of onabotulinumtoxin A (BOTOX) in the treatment of chronic migraine (CM) in patients over 60 years of age.

Materials and methods: The present study was conducted at the Headache Centre of Spedali Civili of Brescia. Data were collected from June 2015 to May 2022. At baseline and at quarterly follow-up visits, the following variables were collected: number of headache days per month, analgesics consumption and migraine disability (MIDAS score). Patients comorbidities and reported side effects were gathered in order to assess treatment safety.

Results: Twenty-four consecutive CM patients were enrolled with a 12 month follow-up period. Patients mean age at the beginning of treatment was 64.9 years (SD 5.4), with a mean disease duration of 10.3 years (SD 6.6). On average patients had failed 5 previous oral preventive treatments.

At baseline, 46% of them suffered from hypertension and/or had a metabolic comorbidity (such as diabetes or hypercholesterolemia); one fourth had a psychiatric disorder and 17% presented with cardiovascular and/or neurological disease. A statistically significant reduction from baseline to 3-, 6- and 12-months' treatment cycles in total headaches' days (23.6 vs 17.1 vs 18.1 vs 15.7, p<0.0001), high intensity headaches' days (11.9 vs 9.2 vs 7.6 vs 3.5, p=0.002), analgesics consumption (36.1 vs 20.1 vs 22.4 vs 12.3, p=0.003) and MIDAS score (78.6 vs 48.6 vs 45,3 vs 36.2, p=0.05) per month was found. Six patients discontinued treatment following three treatment cycles due to lack of efficacy. BOTOX was a well-tolerated treatment: two patients reported mild neck pain, two had eyelid ptosis (spontaneously resolved) and one patient had an increase in creatinine level and developed systemic blood hypertension (not correlated to Botox treatment).

Discussion: Onabotulinumtoxin A was found to be safe, well tolerated and effective for the prevention of chronic migraine in patients with various comorbidities and over 60 years of age. Side effects were minimal, reported in 20% of patients, with no serious adverse event ever reported in our Centre.

Conclusions: In patients over 60 years old with chronic migraine, affected by systemic comorbidities, onabotulinumtoxin A seems to be a safe and well-tolerated therapeutic strategy. Further studies are needed to confirm these data in a larger cohort.

COMPARISON OF EFFICACY AND SAFETY OF ANTI-CGRP MONOCLONAL ANTIBODIES BETWEEN OVER AND UNDER 65-YEAR-OLD REFRACTORY MIGRAINE PATIENTS: A PILOT STUDY

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Objectives: Previous studies reported a positive effect of monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway in migraine prevention, either in over (O65) and under (U65) 65-year-old patients. [1] Aim of our study was to evaluate and compare real-life efficacy and safety of mAbs between young and elder migraine patients.

Materials: This observational real-life study was conducted on migraine patients, treated with erenumab, a full human mAb binding the CGRP receptor, for six months. Fifteen O65 and fifteen U65 patients were prospectively

enrolled and matched for sex, monthly headache days (MHD) and monthly migraine days (MMD) at baseline.

Methods: Within-group and between-group differences in MHD and MMD, number of pills and days of acute medication intake, HIT-6, MIDAS, Numeric Rating Scale (NRS) and Allodynia Symptom Checklist (ASC-12) scores were assessed after 3 (M3) and 6 (M6) months of treatment using Wilcoxon and mixed-effect ANOVA tests. The presence of adverse events was also investigated.

Results: In each group, thirteen patients (87%) were women and nine patients (60%) had chronic migraine. Baseline mean MHD and MMD of both groups was 20 (SD 9.6). Mean age was 70 (range: 65 – 76) and 45 (range: 19 – 55) in the O65 and U65 group, respectively. Before starting mAbs, patients have tried an average of 4 (range: 2 – 9) preventives in both groups. After 3 and 6 months of treatment, both groups had a reduction of MHD, MMD, MIDAS score, number of days and pills of acute medication intake, without statistically significant differences between two groups (M3: p=0.7, p=0.3, p=0.6, p=0.5, p=0.3; M6: p=0.1, p=0.4, p=0.4, p=0.3, p=0.9). Also, a similar proportion of patients in each group complained of adverse events at M3 (p=1.0) and M6 (p=1.0).

Discussion: Data about the efficacy and safety of mAbs in O65 migraine patients is poor. [2] This exploratory real-life study showed that treatment with mAbs is as effective as in O65 as in U65 migraine patients. Considering that oral preventive drugs can often be contraindicated in elder patients, these findings suggest a good handling of mAbs in this population of migraineurs, providing major confidence to physicians when prescribing these novel therapies to patients of advanced age.

Conclusion: Our real-life data showed that treatment with mAbs is as effective and safe in O65 as U65 migraine patients. Further studies are needed to confirm these findings.

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ROLE OF THE DEFAULT MODE NETWORK IN EPISODIC CLUSTER HEADACHE: CEREBRAL CONNECTIVITY ANALYSIS WITH HD-EEG

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Objectives: We aimed to define specific internodal connectivity patterns of the default mode network (DMN) in episodic cluster headache (eCH) patients, through advanced brain connectivity analyses with high-density EEG (HD-EEG).

Materials and Methods: Twenty-four patients with eCH and 19 healthy controls (HCs) were enrolled. Patients with eCH were evaluated during both the active (T0) and the remission (T1) phases of disease. Of these 24 patients, 8 were registered only at T0, 10 only at T1, while 6 completed both registrations. The DMN areas considered for the analysis were: the right and left angular gyrus (RANG and LANG), the medial pre-frontal cortex (MPC) and the posterior cingulate cortex (PCC).

Results: The study of internodal brain connectivity in patients showed lower connectivity at T1 (remission) when compared to T0 between PCC and MPC (T0=0.078±0.009 vs. T1=0.049±0.006, p=0.022) and between PCC and RANG (T0=0.076 ± 0.008 vs. T1=0.052±0.005, p=0.024). Furthermore, connectivity at T1 was lower when compared to HCs, specifically between PCC and MPC areas (CHe-T1=0.049±0.005 vs. HS=0.067 ±0.005, p=0.028).

Discussion: The pathophysiological mechanisms underlying eCH, particularly the shift between active and remission phases, are still not fully understood. Brain connectivity analysis with HD-EEG represents a novel method to characterize changes in connectivity between these two phases. Noteworthy, eCH patients evaluated during a remission phase of disease showed lower brain connectivity between specific areas of the DMN when compared with either eCH patients tested during an active phase and HCs.

Conclusion: The finding of altered brain connectivity during remission of eCH may represent a biological marker of disease, while the fluctuation in PCC connectivity may reflect pathophysiological mechanisms involved in the shift from one phase of disease to the other.

EFFECT OF ANTI- CGRP TARGETED TERAPY ON MIGRAINE AURA: RESULTS OF AN OBSERVATIONAL CASE SERIES STUDY

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Objective: Monoclonal antibodies directed against calcitonin gene-related peptide (CGRP) or its receptor (anti-CGRP mAbs) are clearly established as the disease-specific preventive treatment for both episodic and chronic migraine [1,2,3]. Limited clinical evidence is available on the potential effectiveness of anti-CGRP mAbs for preventive treatment of migraine with aura. This observational study is aimed to verify the changes in frequency of migraine aura attacks due to anti-CGRP mAbs treatment over one year.

Materials and methods: We retrospectively collected data of twelve migraine patients affected by both migraine with and without aura attending the Headache Centre of the Neurological Clinic of the University of Perugia. Seven were treated for one year with erenumab, two with fremanezumab and three with galcanezumab. Clinical parameters were recorded for each patient at baseline and at each trimester of treatment during one year treatment period, including the number of headache and migraine days/month, number of days with acute drug intake/month, number and characteristics of aura episodes, the scores of Migraine Disability Assessment (MIDAS) and those of Headache Impact Test-6 (HIT-6).

Results: Anti-CGRP mAbs induced a significant decrease in mean headache and migraine without aura days per months, number of days with medication intake, MIDAS and HIT-6 scores (p<0.0001). Conversely, they did not influence the frequency of migraine with aura attacks, but they determined a reduction in intensity and duration of headache phases of migraine aura. In addition, patients experienced aura attacks without headache more frequently.

Discussion and conclusions: Based on our findings we can speculate that anti-CGRP mAbs cannot influence neuronal and vascular events related to cortical spreading depression (CSD) considered the pathophysiological substrate of aura, but are able to counteract via their peripheral mechanism of action the sensitization of trigeminovascular pathway consequent to CSD, and this can explain why in our patients migraine aura attacks are unchanged in the frequency, but headache phase is reduced or abolished.

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BRAIN CONNECTIVITY MODIFICATIONS INDUCED BY MONOCLONAL ANTIBODIES TARGETING THE CGRP PATHWAY IN MIGRAINE PATIENTS: A PROSPECTIVE HD-EEG, OPEN-LABEL, STUDY

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Background: Monoclonal antibodies targeting the CGRP pathway (mAbs) proved effective and safe as migraine preventive treatment. The migraine pathophysiology is complex, involving peripheral and central mechanisms. Due to their heavy molecular weight, mAbs act outside of the blood brain barrier, namely in the peripheral component of the trigeminovascular system. Nonetheless, a reduced sensitization of the first order neuron in the trigeminal ganglion may induce secondary effects at central level. In the present study, we aim to study the changes induced by mAbs treatment in cortical brain connectivity recorded by means of high-density electroencephalography (HD-EEG).

Materials and Methods: We plan to perform 5 resting state HD-EEG recordings, namely at baseline (before mAbs treatment), and then every 3 months for one year. Here we present data regarding 16 migraine patients (age 44.7±10.6, 14 females, 11 with CM) who completed the first three months of mAbs treatment (T3). We aim to study the connectivity changes in the nodes of the default mode network (DMN): the right and left angular gyrus (RANG and LANG), the medial pre-frontal cortex (MPC) and the posterior cingulate cortex (PCC).

Results: At T3, mAbs treatment induced an inter-nodal connectivity reduction between MPC-PCC (p=0.025), MPC-LANG (p=0.020), MPC-RANG (p=0.043), and PCC-LANG (p=0.005). By contrast, the connectivity was enhanced between PCC-RANG (p=0.005) and LANG-RANG (p=0.003). At T3, 7 patients qualified as "Responder" to mAbs (reduction in monthly migraine days of at least 50% when compared to baseline). Responders were characterized by a baseline enhanced connectivity between MPC-PCC (p=0.042) and MPC-RANG (p=0.032), and by a reduced connectivity between LANG-RANG (p=.016).

Discussion: We described brain connectivity modifications in the DMN of migraine patients after three months of mAbs treatment. We hypothesize that a reduced sensitization of the peripheral component of the trigeminovascular system may account for the observed findings. If these changes represent a direct effect of mAbs treatment, or an indirect effect related to the clinical improvement is yet to be elucidated. In addition, Responder patients showed a specific baseline brain connectivity pattern.

Conclusion: mAbs may induce changes in HD-EEG cortical brain connectivity. A specific connectivity pattern may characterize Responder patients, further fostering the search for predictors of mAbs clinical outcome.

EVALUATION OF CEREBRAL VASOREACTIVITY IN MIGRAINE PATIENTS: A TRANSCRANIAL DOPPLER STUDY

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Objective: Transcranial Doppler (TCD) is a non-invasive technique, and it can be widely applied for the study of variations of cerebral blood flow. The relationship between systemic endothelial dysfunction and migraine remains debated. The aim of the study was to assess variations of cerebral blood flow and variation of vasoreactivity in patients affected by episodic migraine compared to healthy controls.

Materials and Methods: We presented a prospective observational study carried out in the Neurological Clinic at the A.O. Santa Maria (Terni) from October 2021 to December 2021. This study collected data of 49 patients matched by sex and age. The characteristics of enrolled patients were as follows: 27 migraine patients and 22 healthy controls. All patients underwent a clinical examination; specifically, the headache characteristics were collected as well as migraine related disability (MIDAS) and HIT6 scores. They also underwent TCD exam. The following parameters were recorded: pulsatility index (IP), resistance index (IR), systolic speed peak (PSV), telediastolic velocity (VTD), mean velocities of internal carotid artery (ICA), middle (MCA). anterior (ACA) and posterior (PCA) cerebral arteries, vertebral artery (VA) and basilar artery (BA) of both sides. Vasoreactivity index (VI) of the right and left middle cerebral artery was calculated after Valsalva maneuver.

Results: Our study had shown, in line with the literature, that the cerebral vasoreactivity measured at the level of the MCA in the interictal phase in migraine patients is lower than in healthy controls. A significant correlation was found between the VIs of left and right MCA and the frequency of attacks, MIDAS and HIT6 scores. In fact, the vasoreactivity index is reduced in the presence of some parameters of greater severity of migraine.

Discussion: The relationship between systemic endothelial dysfunction and migraine remains debated. Currently, there are several works that establish a relationship between migraine and cardio-cerebral-vascular disease [1,2,3]. These findings, observed in patients with no major cardio and cerebrovascular risk factors, correlate with the hypothesis of vascular damage in migraine patients predicting a major probability of cardio and cerebrovascular diseases.

Conclusions: TCD parameters can be used to non-invasively assess blood flow and vascular reactivity changes of the intracranial arteries in migraine patients. Higher is the gravity of migraine, greater will be the risk of vascular damage. Therefore, this concept underlines how it is important to start a prophylactic therapy in the case of severe forms of migraine: by improving migraine-related disability, vascular damage could also be reduced.

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KETOGENIC DIET INFLUENCES PREVALENCE AND SEVERITY OF POST-COVID-19 IN PATIENTS WITH MIGRAINE

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Objectives: To determine the prevalence and characteristics of post-COVID-19 (PC) in a group of patients with migraine, and the possible influence on PC of following a Ketogenic Diet (KD) as migraine prophylaxis.

Materials: It is a retrospective, multicentric, observational study on a group a patient with migraine who had previously contracted COVID-19, Inclusion criteria were diagnosis of migraine according to the International Classification of

Headache Disorders 3rd version, be between the ages of 18 and 65 years old, having been infected by SARS-CoV-2 as confirmed by specific tests (polymerase chain reaction or antigenic) positivity, acceptance to participate to the study. Diagnosis of PC was given in presence of persistence or increase of any COVID-19 symptoms after recovery by the acute phase of disease [1]. All the PC symptoms were collected. By clinical records, patients were segregated in 2 groups: who was following the diet during and after SARS-CoV2 infection, or not.

Results: On 364 consecutive patients with migraine, seventy-eight meet inclusion criteria. Of them, fifty-one resulted to be positive to PC (ranging from 1 to 8 simultaneous symptoms), twenty-seven not; twenty-seven patients were undergoing treatment by KD during and after viral infection. We collected 12 different groups of PC symptoms among our patients: Fatigue (72.54%); Dyspnea and other pulmonary symptoms (66.67%); Cognitive impairment and concentration difficulties (50.98%); Fibromyalgia, muscle pain and arthralgia (45.1%); Headache worsening/ Changes (43.14%); Thoracic pain (35.29%); Cough and other ear-nose-and-throat (ENT) symptoms (33.33%); Sleep disorders (21.57%); Postural orthostatic tachycardia syndrome (POTS), paroxysmal tachycardia, and other cardiac symptoms (15.69%); Dizziness (9.8%); Heartburn, diarrhea and other gastrointestinal symptoms (7.84%); Persistent fever (3.92%). Out of 51 patients with PC, 8 were following KD, 43 not (Yates's chi-squared test= 20.97; $p<0.001$; OR= 0.078; C.I.= 0.026-0.240). The mean number of symptoms was 1.50±0.76 for KD group, 4.53±1.47 for the others (t= 8.7; $p<0.001$).

Discussion: PC is very prevalent among migraine patients and KD seems to be protective against it, as already suggested for its anti-inflammatory activity and its capacity to taper acute COVID-19 symptoms [2], although it is also possible that a role is also played by nutraceuticals that are supplemented during KD.

Conclusions: PC is an emerging health issue also among subjects with migraine, and KD should be further studied to understand its promising role in the prevention of this syndrome.

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THE INFLUENCE OF SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO) IN MIGRAINE

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Objectives: Serotonin has a leading role in migraine pathogenesis, and many symptomatic and prophylactic drugs act on it. Its production is due to the assimilation in the small intestine of tryptophan, an essential amino acid, (we are unable to synthesize it endogenously). In case of small intestinal bacterial overgrowth (SIBO), bacteria assimilate tryptophan. This would result in 2 consequences: the decreased availability of tryptophan in the brain to produce serotonin; the presence of bacterial metabolites of tryptophan digestion, namely indole (indicating fermentative dysbiosis) and skatole (indicating putrefactive dysbiosis), 2 biogenic amines easily measured in urine. The aim of the study is to investigate the influence of these 2 tryptophan metabolites in a population of migraine patients comorbid with irritable bowel syndrome (IBS).

Materials: A total of 92 migraineurs comorbid with bowel disorders were referred to the gastroenterologist. Of these, 60 were diagnosed with IBS, and tested for urinary indole and skatole. According to values observed, dysbiosis was classified as absent, mild, moderate, or severe for each of the 2 metabolites. In addition, data were collected for each patient about the frequency of headache in the 30 days before the urine test was performed.

Results: Only 59 patients were analyzed since one did not fill the headache diary. Of them, 43 had an episodic migraine (EM; < 15 days/month) and 16 a chronic migraine (CM; ≥ 15 days/month). The mean number of migraine days/month was 12.64±7.26. According to indole: in 2 patients (2 EM) the dysbiosis was absent, in 15 was mild (15 EM), in 28 moderate (21 EM; 8 CM), in 14 severe (5 EM; 9 CM). According to skatole, 56 patients had absence of dysbiosis (40 EM; 16 CM), 2 had mild (2EM), 1 moderate (1 EM), none severe. By a univariate analysis of variance, indole emerged as significant predictor of headache days (F= 8.02; $P<0.001$). In a binary logistic regression, only severe indole dysbiosis emerged as independent predictor for presence of CM ($p=0.017$; OR= 0.185; CI= 0.046 – 0.742).

Discussion: The presence of fermentative dysbiosis emerged as influencing factor in migraine frequency. Indole can be also regarded as a serotonin receptor agonist, blocked by ondansetron (a 5-HT3 blocker) and pizotifen (a non-selective 5-HT1, 5-HT2A and serotonin2C receptor blocker, used for migraine prophylaxis).

Conclusions: Comorbidity with IBS in migraineurs should not be considered as a psychosomatic issue but rather as a probable SIBO, responsible for altered serotonergic homeostasis.

HYPEREXCITABILITY AND DYSFUNCTION OF CORTICAL EXCITATION / INHIBITION MECHANISMS IN MIGRAINE: A PAIRED PULSE TMS STUDY

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Introduction: Paired-pulse TMS paradigms can be used to test connectivity within the primary motor cortex. [1] Aim of the study was to provide additional information on short intracortical inhibition (SICI) and intracortical facilitation (ICF) using different intensities of the test stimulus (TS) in episodic and chronic migraine (CM, EM) patients.

Methods: We enrolled 24 patients with EM, 13 with CM and 24 healthy subjects. EM and controls were randomly assigned to two groups for assessment of SICI and ICF. While in patients with CM we tested both ICF and SICI during the same experiment. We assessed SICI and ICF at three different suprathreshold intensities of the TS (110%, 130% and 150% of the resting motor threshold). Interstimulus intervals of 2 ms and 10 ms were used for testing SICI and ICF respectively.[2]

Results: When testing ICF, maximum increase in conditioned MEP amplitude was observed in EM at the lower stimulation intensity of the TS($p<0.005$). This intensity was indeed to induce significant facilitation in the CM and healthy subjects. No significant differences were observed as regards SICI.

Conclusion: Our results strengthen the notion of altered tuning of cortical excitability in migraine. [3] The increased ICF cannot be detected at higher stimulation intensities in EM probably due to the induction of homeostatic regulatory mechanisms of cortical excitability that could aim to protect against the risk of neuronal damage. CM have have a greater cortical excitability than EM and the homeostatic regulatory mechanisms of cortical excitability are activated early, even at 110% of TS.

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MONTHLY MIGRAINE DAYS, ACUTE MEDICATION USE DAYS, AND MIGRAINE-SPECIFIC QUALITY OF LIFE IN RESPONDERS TO ATOGEPANT: A POST HOC ANALYSIS

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Objective: To characterize magnitude of treatment effect between atogepant responders and nonresponders.

Materials: In phase 3 ADVANCE trial, atogepant 60mg reduced mean monthly migraine days (MMDs) from 7.8 days at baseline to 3.0 at weeks 9-12 (Δ=-4.7) in overall episodic migraine population, including responders and nonresponders (ie, participants with marked benefit and with minimal benefit). This approach obscures clinically relevant information regarding magnitude of treatment effect in these populations.

Methods: This post hoc analysis used data from participants who completed 12-week ADVANCE trial. Mean MMDs, acute medication use days, Migraine-Specific Quality of Life-Role Function-Restrictive (MSQ-RFR) scores were calculated in responders (based on percentage reduction in MMDs) and nonresponders.

Results: During weeks 9-12, ≥50% improvement (ie, 50%-100% reduction in MMDs from baseline) was achieved by 71% (139/195) of participants. In these responders, MMDs were reduced from 7.6 at baseline to 1.3 at weeks 9-12 (Δ=-6.3). ≥75% response was achieved in 50% (97/195) of participants. In this group, MMDs were reduced from 7.7 at baseline to 0.6 at weeks 9-12 (Δ=-7.1). Atogepant 60mg nonresponders (<25% reduction in MMDs) comprised 15% (30/195) of participants and showed MMD change from 7.7 at baseline to 9.1 at weeks 9-12 (Δ=+1.4). Acute medication use days in ≥50% MMD responders decreased from 7.1 at baseline to 1.6 at weeks 9-12 (Δ=-5.5). In nonresponders (<25% reduction in MMDs), acute medication use days were 7.3 at baseline and 7.2 at weeks 9-12 (Δ=-0.1). Similar results were observed for mean MSQ-RFR score changes in responders and nonresponders.

Discussion: For 71% of participants experiencing ≥50% reduction in MMDs, substantial treatment effect (ΔMMD =-6.3) was observed, representing 83% reduction in MMDs.

Conclusion: Clinical trials usually report group mean data, representing average of those responding, and not, to treatment. This analysis evaluated efficacy of atogepant in subgroup of participants achieving at least 50% reduction in MMDs and examined magnitude of MMD reduction. Conditional analysis is useful for assessing treatment benefits in those most likely to continue treatment in practice, facilitating communication of benefits. For atogepant responders, substantial treatment effect was observed in MMDs, acute medication use days, MSQ-RFR scores. Clinical trials evaluate treatment outcomes in overall randomized population. In clinical practice, responders continue to treat while nonresponders do not. Based on these findings, 71% of people respond to atogepant and if so, on average they will experience 83% reduction in MMDs and very substantial improvements in health-related quality of life.

ADDITIVE INTERACTION BETWEEN ONABOTULINUMTOXIN-A AND ERENUMAB IN PATIENTS WITH REFRACTORY MIGRAINE

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Objective: In the last years significant progresses have been observed in the preventive treatment of chronic migraine. Nevertheless, onabotulinumtoxin-A (BTX-A) and monoclonal antibodies, both acting on the pathway of calcitonin gene–related peptide (CGRP-mAbs), should not be administered in combination, to date, due to the high costs. On the other hand, preclinical observations demonstrated that these therapeutic classes may act on different fibers: CGRP-mAbs prevent the activation of the Ad-fibers, BTX-A acts on C-fibers. Therefore, it can be argued that a combined therapy may provide an additive or synergistic effect on the trigeminal nociceptive pathway.

Materials: 10 patients meeting criteria for both chronic migraine and medication-overuse headache, with at least four oral preventive medication classes failure, underwent BTX-A therapy for at least 9 months. We observed a >30–<50% reduction in monthly headache days (MHDs) and/or severity of headache during attacks compared to the baseline. Because the migraine burden decrease was considered not satisfactory, BTX-A treatment was discontinued; whereupon, after 6-12 months, erenumab 140mg monthly administration was started and maintained for at least 6 months. After six erenumab 140mg monthly administrations, patients reported a >30–<50% reduction in MHDs and/or severity of headache during attacks compared to the baseline.

Methods: To achieve a putative additive or synergic interaction, a combined treatment with BTX-A (185 UI quarterly administration) and erenumab (140mg monthly administration) was started. Then, after 6 months of combined treatment, we evaluated MHDs, severity of headache during attacks, symptomatic drug intake per month, and migraine disability.

Results: We observed a statistically significant reduction of MHDs, intensity of headache attacks, and symptomatic drug intake per month, as well as migraine disability, during combined treatment with BTX-A and erenumab compared to baseline as well as BTX-A and erenumab treatments alone.
Discussion: Combined therapy with BTX-A and erenumab resulted in a statistically significant reduction in frequency and intensity of headache attacks, symptomatic drug intake and migraine-related disability probably related to a reduced need or also to a better responsiveness to rescue treatments.

Conclusion: Our results support, despite the limitation due to the low sample size, the concept that a combined therapy may provide an additive or synergistic effect on the trigeminal nociceptive pathway by acting on different comparts of the CGRP pathway.
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IMPROVING DISTRESS PERCEPTION AND MUTUALITY IN MIGRAINE PATIENTS' CAREGIVERS AFTER 6 MONTHS OF GALCANEZUMAB TREATMENT

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Migraine is a highly disabling chronic disease negatively impacting patients' and often their relatives' lives. While in several neurological conditions the

caregiver figure is highly considered, it has not been much regarded so far in defining the migraine burden. Caregivers are at risk of developing psychological distress and impacting their financial and social aspects in relation to patients' disease duration and disability. The present preliminary study investigated whether galcanezumab, a mAbs anti-CGRP ligand, can also reduce caregiver distress and improve mutuality perceived by patients and caregivers after 6 months of treatment. This preliminary prospective observational study enrolled consecutive migraine patients on treatment with galcanezumab at our headache center and their caregivers. Patients and caregivers were evaluated at baseline and after 6 months of treatment with galcanezumab (subcutaneous injections with a loading dose of 240 mg the first month, then 120 mg monthly). At the same intervals migraine disability was assessed Migraine Disability Assessment score (MIDAS) and the Headache Impact Test (HIT-6). Patients' caregiver distress was measured by the Relatives Stress Scale (RSS). At the same intervals, patients and caregivers filled out the Mutuality Scale (MS). Twenty-seven consecutive patient-caregiver dyads were evaluated. At V6 migraine burden significantly improved with a reduction in MMDs, pain intensity, MAMI, HIT-6 and MIDAS scores. Caregiver RSS score significantly decreased (baseline 20,70 + 13,70 vs V6 13,73 + 12,43, p= 0.027) while MS caregiver total score raised (baseline 3.04 + 0.61 vs V6 3.33 + 0.41, p=0.014). Moreover, in MS we observed no changes in caregivers' love domain (p=0.130) but a significantly improvement of shared pleasurable activities (p=0.02), shared values (p=0.035) and reciprocity (p=0.035) domains. This preliminary observational study demonstrated that patients' migraine improvement after 6 months of galcanezumab treatment could be favourably perceived also by caregivers, significantly reducing their distress with better reciprocity within the dyad. An educational program for migraine caregivers should be routinary in headache centers because taking into consideration the well-being of migraine caregivers could ameliorate the modality of care and management of patients.

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WHEN ACUPUNCTURE IS USEFUL IN MIGRAINE (THE WHAM PROJECT)

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Acupuncture is one of the therapeutic approaches of alternative complementary medicine (CAM). Although an US study described that approximately 50% of young adult migraine patients had used acupuncture for preventive purposes, other recent studies have underlined that its use in clinical practice is lacking. The use of acupuncture for the preventive therapy of migraine and tension-type headache is supported by Cochrane reviews and a recent meta-analysis. Despite the huge amount of favorable scientific data, in real life clinical practice patients admitted to the headache centers revealed they underwent acupuncture spontaneously and less frequently it was prescribed by the general practitioner or headache specialists. We retrospectively analyzed consecutive patients who had received the prescription of the antiCGRP monoclonal antibody at four Italian Headache Centers (Campus Bio-Medico of Rome, Italy; San Pietro Hospital, Rome; Asti Hospital, Asti, Italy and Woman's Headache Center, Turin, Italy). We found that 20% of patients declared to have used lifetime some complementary therapies for migraine (acupuncture, physiotherapy, osteopathy, massage therapy, ketogenic diet, nutraceuticals) and 40% of them reported that acupuncture was not effective. They used acupuncture after around 15 years of illness and after several drug therapies failures. It is still matter of debate when acupuncture can be effective in a migraine patient's history or when headache expert may recommend acupuncture or, finally, when on the contrary the acupuncturist could benefit from the headache expert collaboration. There is not a specific algorithm to follow so far about how acupuncture can be included in the therapeutic panel for headache. In Italy there are no acupuncture clinics within the headache centers (except in rare cases), and rarely acupuncturists are directly involved in the headache center. The collaboration between the headache specialists and the acupuncturist needs to be improved. From this background the idea of the WHAM project (WHen Acupuncture is useful in Migraine) raised up, a project aiming at prospectively analyzing patients with episodic or chronic migraine undergoing our headache centers who have already used acupuncture for migraine prevention, checking the effectiveness, the number and duration of therapy and the time of prescription in relation to migraine frequency.

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PERFUSION COMPUTED TOMOGRAPHY IN A CASE OF PERSISTENT FAMILIAL HEMIPLEGIC MIGRAINE WITHOUT INFARCTION

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Objectives: Reporting the results of a perfusion computed tomography (PCT) performed in a patient with clinical diagnosis of persistent familial hemiplegic migraine (FHM) without infarction.

Results: We describe the case of a 27-year-old male who have suffered from migraine without aura since he was 4-year-old. Since he was 15, a right hemibody strength deficit starting about 15 minutes after the onset of pain and during up to 12 hours has been associated. Since he was 21, a right hemibody hypoesthesia has also been associated to the motor symptoms with the same duration. Seldom, speech and visual disturbances were added. Patient's sister was diagnosed at the Headache Centre as having hemiplegic migraine. In 2016 the patient went to the Emergency Room (ER) due to the onset of more severe motor symptoms that alarmed him. The neurological examination objectified a right sensorimotor hemiparesis with pyramidal signs. The patient was subjected in urgency to our regional Stroke Protocol, inclusive of blood chemistry tests, cerebral CT and PCT within 4,5 hours after the onset of symptoms, while symptoms were still present. Results of blood tests and cerebral CT were normal. Mean Transit Time, Time To Pick, Cerebral Blood Volume and

Cerebral Blood Flow maps were analysed in PCT and no asymmetries were found between the different areas of the two brain hemispheres. Patient was discharged with an ER diagnosis of migraine with aura. Motor weakness and hypoesthesia of the right limbs persisted for three months; then he was evaluated at the Headache Centre of the University of Trieste and his disease was clinically diagnosed as a persistent FHM without infarction. Lamotrigine 50 mg bid, replaced by valproic acid 300 mg bid after two months, were prescribed, obtaining a resolution of aura symptoms. Specific genetic analyses are still ongoing.

Conclusions: For the first time, we described a PCT performed during pain and aura symptoms in a case of persistent FHM without infarction. No asymmetries nor altered patterns were found in PCT maps.

PERSISTENT FAMILIAL HEMIPLEGIC MIGRAINE WITHOUT INFARCTION: THE FIRST CASE REPORT

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Objectives: Familial Hemiplegic Migraine (FHM) is a rare genetical disease in which migraine pain is accompanied or followed by other disabling symptoms, such as hemiparesis, hemianopsia and aphasia, and at least one first- or second-degree relative has migraine aura including motor weakness. These disturbances can notoriously be long-lasting and correlate with a prolonged migraine aura up to a week. Nevertheless, until now a FHM-related persistent aura during more than a week had never been described. Aim of this study is to describe the first case of FHM with persistent aura.

Results: We analysed the case of a 27-year-old male migraineur afferent to the Headache Centre of Trieste. He suffered from migraine since he was 4-year-old. His mother, two maternal aunts and the maternal grandmother were migraineurs without aura. His sister was diagnosed at the Headache Centre as having hemiplegic migraine. There was not a history of migraine in paternal genealogy. No consanguinity between the patient's parents was reported. Since its onset, patient's migraine has presented with the unchanged pain characteristics of a bilateral orbito-temporal headache, throbbing, severe and lasting up to 3 days, associated with nausea, phono-photophobia and worsening with physical effort when more intense. Since he was 15, a right hemibody strength deficit starting about 15 minutes after the onset of pain and during up to 12 hours has been associated. Since he was 21, a right hemibody hypoesthesia has also developed. Then, strength and sensitive deficits have always been associated, starting with the first and continuing with the second after about 10 minutes. They had approximately the same duration, up to 12 hours. Seldom, speech and visual disturbances were added. Frequency of attacks were up to 3 days/month. At 27, he was evaluated because of weakness and hypoesthesia in the right limbs that started three months before. The neurological examination objectified a right sensorimotor hemiparesis. Cerebral CT, brain MRI and EEG were normal. Lamotrigine 50 mg bid was prescribed. For the appearance of suicidal ideation, this drug was replaced with valproic acid 300 mg bid two months later. Patient began to improve after one month of lamotrigine therapy and he reached the resolution of aura symptoms after two months of valproic acid treatment. Specific genetic analyses are still ongoing.

Conclusions: We described the first case of persistent FHM without infarction. Antiepileptic drugs such as lamotrigine and valproic acid were effective.

KETOGENIC DIET AS MIGRAINE PREVENTIVE TREATMENT: AN EFFICACY WHICH GOES BEYOND BODY MASS COMPOSITION CHANGES

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Aim: ketogenic diet (KD) is gaining attention as a possible non pharmacological approach for migraine prevention, supported by many observations [1]. This type of diet is also used for weight loss purposes, and there is a well defined relationship between migraine and weight excess [2]. KD efficacy on migraine is thought to depend on mechanisms which are specific for the ketogenic nature of the intervention, but there are few clinical observations to corroborate this hypothesis.

Materials: We conducted a retrospective observational study on patients suffering from migraine who received a KD as preventive treatment at the Clinical Neurology Unit Of Udine.

Methods: All the patients were evaluated at the baseline and after 3 months of diet both from a neurological and a nutritional point of view, including bioimpedance analysis.

Results: 23 migraine patients were considered in the analysis. 10 (43.5%) patients were affected by chronic migraine and 6 (26.1%) were suffering from medication overuse headache. The number of previously failed preventive treatments was 1.78±2.21. After KD, we observed a reduction in monthly headache days (12.5±0.5 v.s. 6.7±8.6; $p<0.001$) and in days of acute medication intake (11.06±9.37 v.s. 4.93±7.99; $p=0.008$). We also observed a decline in patients' weight (73.8±15.2 v.s. 68.4±14.6; $p<0.001$), BMI (26.9±6.2 v.s. 23.7±8.1; $p<0.001$) and fat mass (28.6±12.5 v.s. 20.6±9.8; $p<0.001$). Responders and non-responders to KD did not differ for weight (5.6±2.7 v.s. 6.2±5.1; $p=0.299$) or fat mass loss (6.1±2.1 v.s. 5.0±4.1; $p=0.120$). In addition, we observed no significant difference in the reduction of headache days between patients who had normal BMI or who were overweight or obese at baseline (9.2±11.5 v.s. 3.7±3.2; $p=0.545$).

Discussion: Adipose tissue does not just have a storage function, but it has also endocrine functions and a role in immune system regulation. As a consequence, weight loss is deemed effective in migraine amelioration [2]. However, KD does not only effectively reduce weight, but it is thought to ameliorate migraine also by restoring the metabolic imbalance present in these patients, by decreasing inflammation and oxidative stress and by neuronal transmission modulation [1,3]. Despite this hypothesized mechanisms, this is the first study to our knowledge to consider biompedance analysis in this setting and to consequently exclude that the effect of KD in migraine may be only due to body mass composition changes.

Conclusions: Our study corroborates the use of KD as a preventive treatment for migraine and suggests that its efficacy goes beyond weight loss.

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HEADACHE IN MINORS LIVING WITH HIV IN SUB-SAHARAN AFRICA

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Aims: Headache disorders are major contributors to the global burden of disease worldwide, including sub-Saharan Africa (SSA) countries [1]. HIV is highly prevalent in SSA and is a risk factor for neurological disorders. In a recent study in Malawi, a SSA country, conducted on a large HIV+ population a high 1-year headache prevalence and high attributable burden among these patients has been reported [2]. Minors are about 50% of SSA population and Malawi as well, and antiretroviral treatment (ART) has much prolonged their life expectancy. No data are available about headache occurrence in HIV+ minor patients. Special attention should be dedicated to this fragile young population. Aim of this study was to explore the prevalence and burden of headache in minors living with HIV in Malawi.

Methods: At the DREAM Centre in Blantyre, Malawi, a structured questionnaire was administered by a trained lay interviewer to consecutively attending HIV+ patients aged 6–65 years. All were monitored with regular viral load detection. For this study, we focused on patients <18 years. Details on the questionnaire and methods have been previously validated and published [2].

Results: Headache questionnaires were collected from 219 consecutive under 18 HIV+ patients (median age 16; 51.8 % females). All were on antiretroviral treatment, with viral load undetectable in 63%. The 1-year prevalence of headache was 72.6% (females 78.1%, males 66.7%); one subject (0.5%) had ≥ 15 headache days/month, none had probable medication-overuse headache (2). Mean overall headache frequency was 3.4 days/month. Thirty-eight (17.4%) had lost at least one day of school in the previous month (mean 3.2 days/month) because of headache. Only 54 (24.7%) had sought advice for their headache. Analgesics were used by 54.8% (mostly paracetamol).

Discussion: This is the first study investigating headache occurrence and its burden in minors living with HIV in a SSA country. Our study showed high headache prevalence among HIV+ minors in Malawi. Given the very low number of neurologists in the country (3 neurologists for 19,5 million population) the question arises about the proper diagnosis and management of these patients including integration of headache medications and ART.

Conclusions: These data disclose a large unmet need for headache care in young HIV+ patients requiring a multilevel innovative approach for the country. The management of young HIV+ headache patients challenges the WHO Intersectoral Global Action Plan on neurological disorders in developing countries [3].

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DISINHIBITION AND PATHOLOGICAL CRYING IN BRAIN SAGGING DEMENTIA: A CASE REPORT OF SPONTANEOUS INTRACRANIAL HYPOTENSION

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Introduction: Spontaneous intracranial hypotension (SIH) is determined by a reduction of cerebrospinal fluid (CSF) volume and/or pressure. Although the etiopathology is not fully resolved yet, the syndromic phenotype has been extensively portrayed as a cause of orthostatic headache, its most common manifestation. Herein, we report a case of acute onset of pathological crying, behavioural changes and memory loss as a rare presentation of SIH.

Case Presentation: A 64-year-old male presented to the emergency department claiming recent onset of neck pain irradiated towards the frontal areas, unresponsive to drugs and without recent history of traumas. Moreover, his siblings noticed a progressive occurrence of memory impairment for recent events and severe mood swings. At examination, the patient was alert but disoriented in time and partially in space. He showed slow thinking and gave confused answers. Furthermore, he presented severe emotional lability with involuntary crying and exhibited disinhibited behaviours such as wandering underdressed or entering forbidden areas of our inpatient ward. At magnetic resonance imaging (MRI) of the brain, the presence of extensive bilateral subdural haematomas, diffuse contrast enhancement of the meninges, drooping splenium of the corpus callosum and reduction of the ponto-mesencephalic angle suggested a diagnosis of SIH. Myelo-MRI did not show CSF leaks. Two blind epidural blood patches (EBPs) were performed respectively one week and two weeks after admission. Afterwards, behaviour markedly changed to be coherent and more appropriate, memory impairment and headache fully remitted. Pre-procedural MMSE and FAB scores were respectively 24/30 and 9/18 and then rose to normal values in the post-procedural administration. The patient was discharged after complete recovery.

Discussion: SIH is characterised by a wide range of symptoms. Among the least frequent ones, cognitive impairment is often mentioned and, lately, has gained an ever-increasing attention since its implications as a treatable form of dementia (brain sagging dementia, BSD). Above all, differential diagnosis with behavioural variant of frontotemporal dementia is crucial, as the symptoms, the age of onset and the male prevalence found in both BSD and bvFTD can easily lead to misdiagnoses. Usually, cognitive symptoms occur with a mean interval of 26 months from the onset of headache. In this case, headaches and memory loss appeared almost simultaneously and just a month prior to hospitalisation. EBPs might have been so effective in consideration of the recent onset of cognitive symptoms. Therefore, a correct and prompt identification of BSD is essential to prevent misdiagnoses and wrong therapeutic decisions.

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EFFICACY OF THERAPEUTICAL SHIFT FROM ONABOTULINUMTOXIN A TO ERENUMAB IN MULTIDRUG-RESISTANT CHRONIC MIGRAINE WITH MEDICATION OVERUSE: A CASE SERIES

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Objectives: Assessing the efficacy of a direct shift from onabotulinumtoxin A (BoNTA) to erenumab in a cohort of multidrug-resistant migraineurs suffering from chronic migraine with medication overuse not responding to BoNTA.

Methods: A twenty-one-month prospective study of multidrug-resistant patients with chronic migraine with medication overuse not responding to BoNTA and shifting to erenumab were analyzed. Subjects had to have received at least 4 different ineffective prophylaxes in the past. All subjects performed 3 unsuccessful sessions of treatment with 195 U of BoNTA. Then they stopped BoNTA and received erenumab at the dosage of 70 mg at time 0 (T0), incrementable to 140 mg after three months (T1) in case of poor effectiveness. Therefore, they were clinically re-evaluated after sixth (T2) and twelve months (T3) after the first administration of erenumab. Patients did not use other prophylactic drugs. Demographic data, previous ineffective prophylactic treatment, medication overused, response rate, headache days, headache duration, symptomatic drug intake and MIDAS were analyzed with SPSS 24.0.

Results: Eleven patients (3 males, 8 females, mean age 44±11) were enrolled. Chronic migraine developed from 3±1 years. Subjects had used 7±1 previous ineffective migraine prophylactic drugs, most frequent being anticonvulsants (100% of cases) and calcium antagonists (91%). Symptomatic medications overuse were triptans (63.6% of cases), analgesics combinations (18.2%), analgesics in association (9.1%), non-steroidal anti-inflammatory drugs (9.1%). 50%, 75% and 100% responders were 54.6%, 18.2% and 9% of patients respectively. All the headache outcomes improved from T0 to T3 (days of headache/month: 20±5 at T0, 7±6 at T3; attacks duration [hour]: 7 ±1 at T0, 4 ±2 at T3; symptomatic drugs/month: 23±7 at T0, 9±6 at T3; MIDAS: 95±38 at T0, 44±40 at T3).

Conclusions: A direct shift from Onabotulinumtoxin A to erenumab is effective in multidrug refractory chronic migraine with medication overuse and should be considered as an effective therapeutical option.

EVALUATION OF THE LONG-TERM SAFETY AND TOLERABILITY OF ORAL ATOGEPANT 60 MG ONCE DAILY FOR PREVENTIVE TREATMENT OF MIGRAINE: A PHASE 3, 40-WEEK, MULTICENTER EXTENSION TO THE ADVANCE TRIAL

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Objective: To evaluate the long-term safety and tolerability of atogepant over 40 weeks in participants who completed the pivotal 12-week ADVANCE trial.

Materials: Atogepant is an oral small molecule calcitonin gene-related peptide (CGRP) receptor antagonist under investigation as a preventive treatment of migraine. Daily atogepant administration was shown to be safe and effective at episodic migraine prevention via 2 placebo-controlled, double-blinded, randomized clinical trials (Phase 2b/3, NCT02848326; and, Phase 3 ADVANCE, NCT03777059).

Methods: Participants in this open-label extension trial (NCT03939312) were rolled over from the lead-in ADVANCE trial and were treated with atogepant 60 mg once daily for 40-weeks, with a 4-week safety follow-up period. Only safety data were collected.

Results: 685 participants took at least one dose of study drug, 74.6% completed the 40-week treatment period; mean age of 41.8 years, 88.2% female, 84.4% white, and mean BMI of 30.58 kg/m2. Mean (SD) treatment duration was 233.6 (89.32) days. Overall, 62.5% of participants experienced a treatment-emergent adverse event (TEAE), with 8.8% considered treatment-related by the investigator; serious adverse events (SAEs) occurred in 3.4% of participants, none were treatment-related. The most frequent AE leading to discontinuation was nausea (0.4%, n=3), and the most frequent TEAEs observed included upper respiratory tract infection (5.5%, n=38) and urinary tract infection (5.3%, n=36). No deaths and no hepatic safety issues were observed.

Discussion: These safety results are consistent with the known safety profile of atogepant from previous trials.

Conclusion: This study supports the long-term safety and tolerability of once daily dosing of atogepant 60 mg.

REAL-WORLD EVIDENCE FOR CHRONIC MIGRAIN TREATMENT WITH ANTI-CGRP ANTIBODIES: AN ITALIAN TERTIARY CENTER EXPERIENCE

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Objectives: Monoclonal antibodies targeting the calcitonin gene-related peptide pathway (anti-CGRP mAbs) are promising therapies for Chronic Migrain (CM) prevention and randomised clinical trials (RCTs) assessed their safety and efficacy. As a real-life study, we investigated anti-CGRP mAbs efficacy in CM patients from our center.

Materials: We selected patients diagnosed with CM (IHS 2018 criteria) who were candidate to erenumab, fremanezumab or galcanezumab based on AIFA guidelines and had a ≥ 6-months follow-up. We collected patients anamnestic characteristics, the Monthly Headache Days (MHDs), the Migrain-related Disability Assessment (MIDAS) questionnaire and the status of medication overuse at baseline and after 6 and 12 months.

Methods: We reported the median values of the included variables and analized the mean difference between baseline and after-treatment MIDAS and MHDs with a paired T-test. We defined a clinically meaningful response as ≥50% decrease in MHDs and quantified anti-CGRP mAbs responders and super responders (MHDs decrease ≥80%).

Results: We included 62 patients (53 females), whose median migrain onset age and chronicization age were respectively 16.50 (IQR 10-24) and 40 years (IQR 30-45). At baseline, the median MIDAS was 66.50 (IQR 49.75-91.25), the median MHDs was 20 (IQR 12-25) and 45 patients (72.6%) were overusing medications. 18 patients were treated with erenumab, 22 with fremanezumab and 22 with galcanezumab. After six months of treatment, only seven patients (11.3%) were overusing medications. Either considering the whole cohort of patients or each different antibody treatment group, the mean differences between baseline and 6-months MIDAS and MHDs values were highly significant (both pMIDAS and pMHDs < 0.001). 56 patients (90.3%) were labeled as responders and 32 (51.6%) as super-responders. The values tended to keep constant or furtherly decrease at the 12-months follow-up (when available). Three patients (4.8%) suspended treatment since ineffective. No severe adverse effect was reported.

Discussion: Erenumab, fremanezumab and galcanezumab showed statistically significant reduction in MIDAS and MHDs in most of the included CM patients. The rate of medication overusers dramatically decreased, too. Only three patients did not experience clinical benefits and interrupted treatment. No severe adverse effect was reported.

Conclusion: This real-world study demonstrated and confirmed the optimal efficacy and safety of anti-CGRP mAbs as prophylactic treatment in CM patients.

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SUBCLINICAL CEREBRAL LESIONS IN MIGRAINE AND PLATELET AGGREGATION

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Introduction: Migraineurs have lesions of the white matter of the brain (WMLs) more frequently than the general population. The etiology of these lesions is not yet known but it is hypothesized that they may be micro-ischemic. Platelet function has long been studied in migraineurs; however, no studies have so far evaluated platelet function in brain-injured migraineurs. Our aim was to evaluate platelet aggregation in migraineurs with WMLs.

Materials: All consecutive patients diagnosed at the tertiary Headache center of the 'Sapienza' University of Rome with episodic and chronic migraine, with and without aura, were enrolled (ICHD3 criteria). All patients taking antiplatelet therapy or with hereditary platelet defects or thrombophilia, as well as those taking preventive therapy for migraine, were excluded from the study.

Method. All patients underwent magnetic resonance imaging with 3D T1 weighted, DP T2, and 3D T2 FLAIR sequences. A neuroradiologist, blinded to clinical data, evaluated the images to identify the WMLs and quantify their volume in mm3. Platelet aggregation was assessed in response to agonists (ADP, collagen, adrenaline, and arachidonic acid) in migraineurs, who were free of attack, compared to a group of age- and sex-matched healthy volunteers (HV).

Results: Forty-two migraineurs were enrolled, of which 26 with and 16 without WMLs. We found that platelet aggregation in response to adrenaline was lower in migraineurs than in HV. Migraine sufferers with a lesion load greater or equal to 150 mm3 (median total WMLs volume) had increased adrenaline-induced aggregation than those with lesion load <150 mm3 or no lesion ($p < 0.001$).

Discussion: This study shows that migraine is associated with reduced platelet responsiveness to aggregation stimuli compared to HV. By grouping migraineurs according to lesion load, patients with a greater WMLs load had increased platelet aggregation compared to those with a lower load.

Conclusion: The data collected show for the first time a correlation between platelet aggregation and WMLs load. On the one hand, migraineurs show reduced platelet aggregation at the group level; this might be interpreted as a protective factor from continuous vascular insults. Supporting this notion is the finding that reduced platelet aggregation is not present in migraineurs with greater WMLs damage. The mechanisms linking migraine to ischemic vascular disease remain uncertain and are likely to be complex. In this light, our finding has translational relevance since, if WML-related ischemic pathophysiology is confirmed in migraineurs, those patients should probably be offered stroke as well as migraine prophylaxis.

THE REGIONAL OUTREACH PROGRAMME OF THE INTERNATIONAL HEADACHE SOCIETY IN SUB-SAHARAN AFRICA: PARTNERSHIP WITH THE DREAM PROGRAM AND RESULTS FROM THE FIRST SURVEY ON HEADACHE TRAINING

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Background: In recent years, headache in sub-Saharan Africa (SSA) has been shown to be as prevalent as in Western countries [1]. However, healthcare facilities providing headache services are almost absent in SSA, partly because of the lack of neurologists. Hence, neurological care is mainly delivered by non-physician healthcare professionals (np-HCPs) who frequently lack adequate training. Here we report the results of a survey conducted to evaluate training, needs, and knowledge about headache of a representative group of np-HCPs in Malawi (MW).

Methods: The Regional Outreach Programme of the International Headache Society (ROPE-IHS) promotes headache education worldwide. In SSA a big proportion of patients with neurologic disorders are managed in primary care by np-HCPs. Hence ROPE-IHS decided to develop an education program at that level in partnership with the Disease Relief through Excellent and Advanced Means (DREAM) program, a recognized primary care health programme that has activated healthcare facilities in 10 SSA countries [2]. In order to customize the training program on the specific needs of local np-HCPs, we performed a survey among np-HCPs working in different primary care including DREAM centres in MW. For this purpose, we created a specific questionnaire to test the level of preparation and interest on headache.

Results: Fifty-one np-HCPs (23 women) participated in the survey (median age 37 years; median duration of education 3 years). All of them delivered care to patients at healthcare facilities: 26 were clinical officers, 6 nurses, 5 clinicians, and 14 had other roles. The survey showed that all subjects agreed on the importance to receive education and training on headache; 84% never attended a full headache course. Past headache courses were mainly delivered by np-HCPs including clinical officers (29%), health care providers (27%) or other clinicians (25%). Only 2% of headache patients are referred to doctors while the vast majority (84%) are seen by clinical officers or local healers (57 and 27%, respectively); 94% of participants recognized that headache is a frequent disorder and 41% correctly indicated that migraine can be prevented with beta-blockers (61%).

Conclusions: Insufficient education among healthcare providers is the main barrier to care for headache patients in SSA. A partnership between international societies and recognized local providers is a valid tool to provide bottom-up tailored education on headache at primary care level in difficult contexts as in SSA. The partnership also accomplishes the WHO Intersectoral Global Action Plan [3].

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EFFECTIVENESS, SAFETY AND IMPACT ON BLOOD PRESSURE OF ERENUMAB AND FREMANEZUMAB AMONG OVER-60 MIGRAINE PATIENTS

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Objective: Cardiovascular safety is a major concern of anti-CGRP therapies, especially in patients older than 60. On the other hand, chronic migraine affects 0,5% of females and 0,25% of males older than 601, but older patients have been excluded from most RCTs2–4. Evidence is needed to safely use these drugs among these patients. We compared the effectiveness and safety of erenumab and fremanezumab among patients younger than 60 and older than 60 years, and their possible effect on blood pressure (BP).

Methods: We selected high-frequency episodic/chronic migraine patients who started a prophylactic therapy with either erenumab or fremanezumab, without major cardiovascular or cerebrovascular events. Data regarding efficacy (50% responder rate and MIDAS score reduction), incidence of adverse events, and BP values before and after 9 months of therapy, were compared between two groups: under 60 and over 60.

Results: 45 patients were included, 23 under 60 and 22 over 60. 50% responder rate and incidence of cardiovascular adverse events did not differ between the groups, the latter being sparse in all of them. Blood pressure values did not change significantly before and after both anti-CGRP use. Anti-hypertensive therapy needed to be adjusted in 13.6% (3/22) of the older patients and none of the younger patients.

Discussion: In our cohort of migraine patients with no previous major cerebrovascular/cardiovascular events, anti-CGRP molecules proved to be effective and safe, with no difference between young and older patients. Mean arterial blood pressure did not increase significantly, however a limited percentage of older patients needed anti-hypertensive therapy adjustment.

Conclusion: Anti-CGRP(r) monoclonal antibodies seem to be effective and safe among over-60 migraine patient. However, larger studies are warranted to confirm these results.

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OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY (OCTA) IN PATIENTS WITH MIGRAINE: A POTENTIAL BIOMARKER?

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Objectives: Migraine is third most common disorder in the world. It is reported to be associated with massive changes in cortical and retinal perfusion and has been proposed as a risk factor for systemic and ocular ischemic complications. Optical coherence tomography-angiography (OCTA) processes three-dimensional images of retina and choroid vasculature. We aim to compare OCTA findings between patients with episodic migraine (EM) and chronic migraine (CM) and between migraine patients and healthy controls (HC). Moreover we evaluate structural parameters of macula and optic nerve through optical coherence tomography (OCT).

Materials/Method: In this pilot study, 15 patients with EM or CM and 12 HC were recruited from Umberto I Hospital (Rome). Neurological and ophthalmological examinations, OCTA and OCT analysis were conducted. Migraine patients had never been on therapy and were evaluated during intercritical phase. HC reported no headaches. Exclusion criteria consisted in: ocular or systemic disorders; current or previous treatment with potentially interfering drugs, refractive defect greater than 3 diopters. Due to OCTA artefacts, some eyes were excluded. Therefore, we eventually evaluated 24 eyes of migraine patients and 22 eyes of HC.

Results: There is a trend of retinal thinning in migraine patients, particularly in macular and perifoveal retinal thickness (p=0.02), and patients with EM show significantly lower values compared to subjects with CM (p=0.005). Superficial, deep and total Foveal Avascular Zone (FAZ) values are significantly higher in patients with EM than in patients with CM (p=0.005).

Discussion: Retinal thinning in migraineurs is consistent with other studies, which describe decreased thickness localized in some areas. Selective involvement may be associated with different vulnerability of retinal axons to ischemia. Some authors associate lower thickness to a greater risk of developing neurological diseases. Moreover it has been showed that OCTA findings correlate with severity of neurodegenerative diseases. Increase in FAZ suggests possible presence of retinal microangiopathy damage, which could be correlated with potential increased vascular risk in migraine.

Conclusion: There is still no marker that could predict course of migraine, its possibility of progression to a chronic disorder, nor therapeutic response of patients. We have established a 1-year follow up to monitor progression from EM to CM and investigate whether there is a link between OCTA alterations and worst outcomes. If further studies confirm this association, it will lead to possibility of using the OCTA as a fast, non-invasive, and unexpensive biomarker for migraine patients.

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AN ALTERED HYPOTHALAMIC-PONTINE FUNCTIONAL INTERPLAY COULD AFFECT MIGRAINE DISEASE PROGRESSION OVER THE YEARS

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Objective: Functional magnetic resonance imaging (fMRI) studies showed a significant pontine-hypothalamic interaction during the pain phase of migraine. We aimed to explore resting state (RS) effective connectivity (EC) abnormalities between the pons and hypothalamus in interictal migraine patients and investigate their association with disease progression over the years.

Materials: RS fMRI scans were acquired from 92 headache-free episodic migraineurs and 73 controls. Twenty-three migraineurs and 23 controls were reexamined after 4 years.

Methods: RS EC of bilateral pons and hypothalamus was performed using SPM12 and dynamic causal modelling. Cross-sectional and longitudinal RS EC differences between groups were investigated using parametric empirical bayes models.

Results: At baseline, compared to controls, migraine patients had higher inhibitory EC within the left pons and from the right and left pons to the ipsilateral and contralateral hypothalamus. Migraine patients experienced also a lower inhibitory left hypothalamic-left pontine EC, as well as a lower excitatory EC from the right pons to the left pons. During the follow-up, 35% of patients reported an increased migraine attack frequency. Over the follow-up, migraine patients developed a higher inhibitory EC within the left pons, from the right pons to the ipsilateral hypothalamus, from the left hypothalamus to the ipsilateral and contralateral pons, and from the left pons to the ipsilateral and contralateral hypothalamus. Migraine patients experienced also a higher excitatory EC from the right pons to the left pons. At follow-up, greater headache impact correlated to higher inhibitory EC from the left pons to the ipsilateral and contralateral hypothalamus, while higher migraine attack frequency was associated with higher inhibitory left hypothalamic-left pontine EC. During the follow-up, the increased left pontine-right hypothalamic inhibitory EC was significantly associated to an increased migraine attack frequency. Lower inhibitory RS EC from the left pons to the left and right hypothalamus at baseline predicted clinical worsening at follow-up.

Discussion: Interictal migraine patients experience a prominent inhibitory influence of the pons over the hypothalamus that is strengthen after 4 years. The influence of the hypothalamus over the pons is reduced at baseline and reinforced over the time. The higher pontine inhibitory activity on the hypothalamus could facilitate the transition into the acute phase of the migraine attack, thus increasing the migraine attack frequency. An altered pontine-hypothalamic inhibitory activity may be a prognostic marker for migraine worsening over time.

Conclusions: The hypothalamic-pontine functional interplay could significantly affect migraine progression over the years.

IS THERE A SUSTAINED CLINICAL RESPONSE FOLLOWING DISCONTINUATION OF LONG-LASTING ERENUMAB TREATMENT? A PILOT REAL-LIFE STUDY

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Objectives: Previous studies showed progressive migraine deterioration after 3-month discontinuation of anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies [1,2]. In this real-life study we aimed to investigate whether long-lasting treatment with erenumab, a monoclonal antibody targeting the CGRP receptor, could lead to a sustained clinical response after 3-month treatment discontinuation in migraine patients.

Materials: Fifty-four patients with migraine, who attended the Headache Center of San Raffaele Hospital, were prospectively enrolled. Twenty-nine patients were treated with monthly erenumab for 12 months (A-group), while 24 patients received erenumab for more than one year (B-group).

Methods: Demographical data were collected at baseline. Clinical variables, including monthly headache days (MHD) and migraine days (MMD), monthly acute medication pills (AMP) and days (AMP), headache intensity on NRS, HIT-6, MIDAS and ASC-12 scores were recorded at baseline (T0), after one year or more of therapy (T1) and after minimum 3-month discontinuation period (T2). Within-group changes of clinical outcomes from T0 to T1 (T0-T1) and from T1 to T2 (T1-T2) were assessed using Wilcoxon test. Between-group differences were investigated using mixed-effect ANOVA tests.

Results: In A-group, 24 patients were women, 20 patients had chronic migraine and the mean age was 48 (range: 19 – 74). In B-group, 17 patients were female, 15 patients had chronic migraine and mean age was 54 (range: 31 – 70). Baseline mean MHD and MMD were 18 (range: 7-30) and 17 (range: 7-30) in A-group; 19 (range: 6-30) and 18 (range: 6-30) in B-group. At T0-T1 both groups showed a significant reduction of MHD, MMD, AMD, AMP, NRS, HIT-6, MIDAS and ASC-12 scores. Even if between-group comparison was not statistically significant, we observed a higher reduction in MHD, MMD, AMD and AMP in B-group. At T1-T2, both groups showed a significant clinical worsening for all outcomes. We observed a worse clinical deterioration in B-group compared to A-group, even if differences were not statistically significant except for ASC-12 score (p=0.01).

Discussion: Long-lasting therapy with erenumab leads to a slight higher clinical improvement during treatment administration, as well as a more pronounced rebound effect during treatment discontinuation. No significant carry-over effect was found in patients receiving erenumab for more than one year, similar to what has been shown for patients undergoing one-year therapy of erenumab.

Conclusion: Discontinuation of erenumab leads to an important clinical worsening regardless the duration of treatment. Further real-life studies with a larger sample size are needed to confirm our results.

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FEASIBILITY AND EFFECTIVENESS OF HOME-WITHDRAWAL PROGRAM COMBINED WITH BEHAVIOURAL APPROACH (BE-HOME) IN PATIENTS WITH CHRONIC MIGRAINE AND MEDICATION OVERUSE DURING COVID-19 EMERGENCY: PRELIMINARY RESULTS

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Objective: Chronic Migraine (CM) is a disabling condition affecting 2% of the general population, in particular if combined with Medication Overuse (MO). The detoxification program is an essential step in the treatment strategy (4, 5). Aim of this pilot study was to assess the feasibility and the long-term effectiveness of a specific protocol, designed during the COVID-19 pandemic emergency, consisting of a home withdrawal plus behavioral treatment (mindfulness) delivered by web.

Materials: Twenty patients with diagnosis of CM-MO (according to IHS criteria) were enrolled into the study.

Methods: Our patients performed the withdrawal program at home, (oral administration of steroids and benzodiazepine) for 5 days, including education to manage pain, combined with six weekly1-hour-video mindfulness sessions. Home-practice was encouraged by 12-minutes mindfulness sessions on smartphone; follow-up visits scheduled at 3-6-12 months after withdrawal. Percentage of patients with absence of MO at 6 months from withdrawal (assessed by Daily Diary Card), and percentages of patients obtaining a decrease of at least 50% in the number of migraine days/month and medications/month were considered.

Results: Twenty patients enrolled: 16 females and 4 males, (mean age 44 ±12; mean duration of disease 19,5±12,7). Results showed a significant decrease in medications/month (18±8,3 at baseline vs 6±3.8 at 6 months), and migraine days/month (15±6,4 at baseline vs 8±4,1 at 6 months). None of the patients recorded a MO condition at 6 months follow-up.

Discussion: Clinical results are significant, the "BeHome" program seems to be effective, and sustainable in particular during the COVID-19 pandemic emergency, also at a medium-term follow-up.

Conclusion: Our "BeHome" program can be considered as a new and valid approach to drug detoxification in MOH.

HEADWORK AS INNOVATIVE TOOL FOR MONITORING MABS EFFECT ON MIGRAINE-RELATED DISABILITY

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Objectives: Monoclonal antibodies (MABs) are a game changer for migraine treatment since their approval; in addition to the well-known metrics for assessing treatment efficacy, HEADWORK has been recently developed specifically to assess the impact on work-related migraine disability.

Materials: Thirty patients from our Headache Center at IRCCS C. Besta, with diagnosis of migraine without aura, eligible for MABs treatment, were enrolled and followed up to 3 and 6 months (3M and 6M).

Methods: Were collected data on monthly headache frequency, medications intake and MIDAS. Employed patients were also asked to complete the HEADWORK questionnaire, consisting of two sections: "Work-related difficulties" (HW1), and "Factors contributing to work-related difficulties" (HW2). The effect size (ES: mean difference divided by baseline SD) was calculated.

Results: Seven males and 23 females were enrolled: mean age (50±8), mean disease duration (34y±13). Monthly headache frequency decreased from 12.5±4.2 to 5.8±3.7 (3M) and 5±4.1 (6M – ES 1.8); medications/month from 14±5.3 at baseline to 5±3.7 (3M) and 5±3.1 (6M – ES 1.7); MIDAS from 42 ±54 at baseline to 5.5±13.4 (3M) and 1±11 (6M – ES 0.7); HW1 from 23 ±8.9 at baseline to 11±9.6 (3M) and 1±7 (6M – ES 2.5); HW2 from 11±6.1 at baseline to 7±4.4 (3M) and 1±4.8 (6M – ES 1.7).

Discussion: The effect of MABs on monthly headache frequency and medications intake is impressive, but even larger the effect on migraineurs' work-related disability, as evidenced by the ES in both HW1 and HW2.

Conclusion: HW can be considered as a new and effective parameter to evaluate the effectiveness of treatments in migraine, especially in improving the impact of work disability.

THE HYPOTHALAMUS IN CHRONIC CLUSTER HEADACHE: INVOLVEMENT OF THE IPSILATERAL HYPOTHALAMIC PARAVENTRICULAR NUCLEUS AND PREOPTIC AREA

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Objectives: In the pathophysiology of cluster headache (CH), the cyclic nature of attacks and the presence of numerous neuroendocrinological abnormalities has led the hypothesis of a potential central role of the hypothalamus. Although May et al. [1] demonstrated a volumetric increase in a region described as the posterior hypothalamus ipsilateral to the cranial pain, subsequent studies failed to replicate these findings. A recent study [2], using a manual segmentation approach showed an increase volume of the bilateral anterior nuclei of the hypothalamus in different CH conditions (chronic, episodic, and probable) with a prevalent involvement of the suprachiasmatic and paraventricular nuclei. Although manual segmentation provided this remarkable result, the small size of this structure and its low-contrast in MRI may limit reproducibility. This, coupled with the bilateral findings, conflicting with the unilateral clinical and neuroimaging features of CH, and with the previous inconsistencies with the results of the morphological studies, does not allow robust conclusions to be drawn about structural alterations of the hypothalamus in CH.

Methods: We applied a new convolutional algorithm to high-resolution T1-weighted MRI images acquired in a sample of 28 chronic CH patients and a control group matched for age and sex to confirm morphological abnormalities of the hypothalamus and identify subnuclei involved in the pathophysiology of CH.

Results: Patients exhibit increased volume in the ipsilateral to the cranial pain anterior superior hypothalamic region, where the paraventricular nucleus, the main synthesizer of the neuropeptide oxytocin, and preoptic area, where sleep-promoting neurons have been identified, are located.

Discussion: Our finding, coupled with the results of our previous investigations, supports the hypothesis of robust interactions between the identified abnormal nuclei (i.e., the paraventricular nucleus and the preoptic area) and the dopaminergic system, possibly via the neuropeptide oxytocin.

Conclusions: Taken together, our results link the diverse findings in CH from neuroimaging, animal, and clinical studies into a coherent framework.

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HEADACHE AND COVID-19 VACCINATION: DATA FROM ONLINE QUESTIONNAIRE IN PATIENTS WITH MIGRAINE

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Objective: Vaccines represented the breakthrough in the fight against COVID-19 allowing a reduction of COVID-19 related hospitalizations and deaths. Based on high frequency of headache attacks reported in the days following vaccination, both in randomized controlled trials and in our clinical experience, we focused on the effects of COVID-19 vaccine administration in migraine population and we speculated on the putative pathophysiological mechanisms.

Materials: A self-administered electronic 15 points questionnaire was developed to collect in patients with migraine: i) demographic and clinical parameters; ii) data related to previous COVID-19 infection and vaccination; and finally iii) headache episodes occurring in the days immediately following COVID-19 vaccination focusing on the differences between these headache attacks and those generally experienced by patients in terms of intensity, duration, and response to pain-killers.

Methods: An on-line questionnaire was created using "Google questionnaires" form and administered to 20 non-headache healthy subjects, to assess its readability. Subsequently, the questionnaire link was published on Italian Facebook groups oriented to headache patients with at least 1000 members for 10 days, and the answers were collected in an online database.

Results: Among 841 migraine patients filling-in the questionnaire, 66% and 60% experienced a headache attack within 7 days after, respectively, the first and the second vaccine dose. Over the half of patients perceived the

headache attacks as more severe, long-lasting, resistant to symptomatic treatment compared to usually experienced episodes.

Discussion: Headache worsening following COVID-19 vaccination could be related to the production of inflammatory mediators such as type Iβ-interferon known to be involved in migraine occurrence or worsening, along with IL-6, NO pathway activation and cortical dysexcitability, altogether recognized as critical moments of migraine pathophysiology.

Conclusion: Considering the high prevalence of migraine in the general population, the awareness of the possibility of headache worsening following COVID-19 vaccine administration in these patients could make a reduced waste of resources employed in an inappropriate healthcare.

BILATERAL ALTITUDINAL HEMIANOPSIA AND BITEMPORAL HEMIANOPSIA CAN BE CLINICAL FEATURES OF IDIOPATHIC INTRACRANIAL HYPERTENSION

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Background: Altitudinal Hemianopsia is the loss of visual sensation of the upper or lower half of the visual field. Typically, it can be caused by both, prechiasmatic and retro-chiasmatic lesions of visual pathways, such as occipitals infarctions, occipital lobes trauma or anterior ischemic optic neuropathy. Requiring for anatomical reasons a bilateral and simultaneous damage of the optical nerves, a bilateral altitudinal hemianopia is only rarely observed. Instead, Bitemporal Hemianopsia is the heteronymous defect of the external part of the visual field, mostly caused by optic chiasm injury.

Methods: We reported 2 cases of women with diagnosis of Idiopathic Intracranial Hypertension (IIH) and of Idiopathic Intracranial hypertension without papilledema (IIHWOP) in which the visual impairment presented as Bilateral Altitudinal Hemianopsia (BAH) and Bitemporal Hemianopsia (BH) respectively.

Results: Diagnosis of IIH/IIHWOP was based on the clinic and radiologic features. Both patients had a lumbar puncture (LP) with the demonstration of an elevated cerebrospinal fluid (CSF) pressure. BAH and BH were confirmed by Computerized Visual Field Test.

Conclusions: We described two cases of BAH and BH in IIH patients, proposing a possible underlying pathogenetic mechanism and reviewed the literature on the topic. Ophthalmologists and neurologists should be aware about the likely visual field defects in IIH/IIHWOP patients.

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GENDER-DEPENDENT DIFFERENCES IN PATIENTS WITH MIGRAINE TREATED WITH ANTI-CGRP MONOCLONAL ANTIBODIES: A REAL LIFE PILOT STUDY

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Introduction: Calcitonin Gene-Related Peptide (CGRP) has a central role in the pathophisiology of migraine and monoclonal antibodies (mAbs) blocking CGRP function are known to be effective as preventative treatments for migraine. Recent evidence highlights a divergence in the features of migraine between male and female populations, but data comparing the treatment response to anti-CGRP mAbs related to gender are lacking [1].

Aims: We compared the efficacy of anti-CGRP mAbs for migraine treatment between males and females in order to understand if gender differences have a role on treatment response.

Methods: We investigated the treatment efficacy after a year in migraine patients treated with mAbs blocking CGRP function. The outcomes were: decrease in monthly headache days (MHDs), rate of treatment stopping, monthly days of acute medication use, Headache Impact Test-6 (HIT-6) score and intensity of headache pain assessed with the visual analogue scale (VAS 0-10). Decrease of MHDs was evaluated basing on percentage of decrease and classified in four classes of response: 0-29% (low responders), 30-49% (medium-low responders), 50-74% (medium-high responders) and ≥75% (high responders). Patients who interrupted treatment were considered as non-responders.

Results: We recruited 83 migraine patients (61 F; 22 M) treated with anti-CGRP mAbs. After a year of treatment we found: 18,18% of men were low responders, 9,09% were medium-low responders, 22,73% were medium-high responders, 22,73% were high responders, while 22,27% interrupted the treatment. Whereas 18,03% of women were low responders, 9,84% were medium-low responders, 31,15% were medium-high responders, 26,23% were high responders, while 14,75% interrupted the treatment. Data analysis showed a difference of 35% between females and males in non-responders group. While considering the classes of response to mAbs we found a sex difference of 27% and 14% respectively in groups of medium-high and high responders.

Discussion: Our data suggest un high rate of treatment failure and poor response to treatment in male respect to female patients. These results are consistent with evidence that demonstrated a difference in CGRP expression between males and female linked to hormones levels and hormones fluctuations during different life stages [2]. Hence CGRP levels could also have a greater role in the response to mAbs treatment of migraine.

Conclusions: Our pilot study demonstrates the presence of gender differences on response to mABs treatment for migrain.

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HEADACHE AND DEPRESSION

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Objectives: Find an adeguated therapy.

Material: Female 63 year old, headache frontal and parietal pain, resisting to pharmacological therapy. Cerebral RM negative for neoplastic pathology and hemorragic foci. Few expansion of lateral ventricula; ansius and depressive syndrome.

Method: Therapy with rizatriptan, vertioxetina, lorazepam. after 2 weeks it substitutes rizatriptan with indometacina/caffeine/cloroproperazina.

Result: Headache improved, but there is depression and generalized ansia. She continues therapy at all.

Discussion: Headache can be associated with depression, but it is not the expression.

Conclusion: It is not always possible to complete headache therapy, because of the varying implication.

EFFICACY, SAFETY AND SLEEP EFFECT OF ERENUMAB IN CHRONIC MIGRAINE: IS CGRP IMPLICATED IN CIRCADIAN RHYTHM?

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Background and aims: Erenumab, human monoclonal antibody directed against CGRPr, is first approved specific treatment for migraine. [1] No study has been conducted yet about Erenumab and sleep. The only experimental data deriving from Drosophila models, a homolog of the CGRP was created by observing that the "loss function" animal acquired better sleep especially in the second half of the night. [2] In this real-life study, we evaluate the efficacy and safety of erenumab associated with a multidisciplinary impact including sleep and circadian effect in 12 months treatment.

Methods: Data are collected From Headache Center in Policlinico of Palermo and Messina, IRCSS Neurolesi Center "Bonino Pulejo". Patients with chronic refractory migraine received 140mg or 70mg of Erenumab every 28 days. Neurologist administrate MIDAS, HIT-6 and BDI and scales to study sleep impact of erenumab (MEQ-SA, PSQI, SCI, ESS), every month for first 3 month treatment, and then every 3 months.

Results: We enrolled 88 patients: 38 migraineurs underwent to 140mg and remaining to 70mg. Erenumab reduce significantly monthly-migraine-days (MMD) from 1stmonth to 12-month treatment (Graph1,2), improving disability and depression (Graph3). Drug overuse is eliminated in 80% of patients as early as 3-month treatment. Dosage of 140mg is more effective than 70mg up to 6-month treatment in reduction of MMD (Graph2). At 3month there is a reduction of the morning chronotype in favor of the intermediate one (Graph4) and in insomnia. Most common adverse event is constipation, which is observed in 9 patients (10%). No adverse events led to withdraw.

Conclusions: Our real-life data confirm the efficacy and safety of erenumab in chronic migraine up to one year treatment with a significant improve on quality of life. It is the first study that evaluate the effect of Erenumab on sleep: a result of improvement in headache or the result of the action in CGRP, that is implicated in circadian rhythm?

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BONT-A EFFICACY IN MIGRAINE: A REAL-WORLD SINGLE-CENTRE STUDY APPLYING MACHINE LEARNING TO PREDICT THERAPY RESPONSIVENESS

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Background: OnabotulinumtoxinA (BoNT-A) reduces the frequency of migraine attacks in a significant portion of patients when administered according to the PREEMPT paradigm. [1] Despite large clinical trials and numerous real-world studies, there are no clinical predictors of response BoNT-A. [2]

Objective: In this single-centre, real-life study, we applied machine learning algorithms to a relatively large database of patients who underwent treatment with BoNT-A to identify baseline clinical characteristics capable to predict response to treatment.

Methods: We collected baseline demographic and clinical data of consecutive patients who started BoNT-A at IRCCS Mondino Foundation from January 2017 to March 2022. All patients had a diagnosis of chronic migraine or high-frequency episodic migraine and underwent at least one treatment cycle with BoNT-A according to the PREEMPT paradigm. Patients were classified as responders or non-responders according to the monthly migraine days (MMD) reduction from the 28-day baseline in the 12-week period after the fourth BoNT-A treatment. More specifically, responders were the patients who experienced an at least 50% reduction in MMD, non-responders were those who experienced a MMD reduction of $\leq$25% or terminated the treatment early due to inefficacy. Other classifications in responders or non-responders were defined using secondary endpoints such as migraine disability assessment (MIDAS) score and acute medication use. We ran different kinds of supervised and unsupervised machine learning (ML) algorithms, including support vector machine, artificial neural network, clustering and random-forest (RF) with a ten-fold Monte Carlo cross-validation to predict responders.

Results: Of the 212 patients included in the evaluation, 35 qualified as responders to BoNT-A administration and 91 as non-responders (38 did not report sufficient improvement with the 4 BoNT-A cycles, while 53 were early terminators). The remaining 86 patients were excluded from the analysis: 18 because they experienced an improvement in MMD >25% but <50%, 68 because of missing data. Not a single, or panel, of anamnestic characteristics, proved capable to discriminate responders from non-responders. All ML models coherently reached good accuracy but underperformed and lacked specificity (low area under the curve). An acceptable level of discrimination was reached only when a high number of clinical features (>20) were considered simultaneously.

Conclusions: Overall, ML findings suggest that routine anamnestic features acquired in real-life settings cannot accurately predict the patients that will benefit from BoNT-A treatment. A deeper phenotyping of patients' features, possibly combined with multimodal parameters, is probably required to identify features predictive of response to BONT-A.

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RESTING-STATE EEG FUNCTIONAL CONNECTIVITY IN THE INTER-ICTAL PHASE OF MIGRAINE WITH AURA

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Background and aim: Migraine with Aura (MA) is a common neurological disorder affecting about 5% of the population. The condition is driven by an imbalance between excitatory and inhibitory neural systems, ultimately leading to cortical spreading depression, the neurophysiological substrate of aura. The EEG is a non-invasive and accurate tool to investigate changes in the brain's functional connectivity (FC) with high temporal resolution. Previous neuroimaging studies documented altered coupling of brain regions and abnormal network functioning in migraineurs. However, little attention has been

paid to migraine subtypes and to the distinction between ictal/inter-ictal phases. We here investigated FC-EEG features of MA subjects and compared them with healthy, age- and sex-matched controls (HC).

Methods: Subjects suffering from MA and HC were recruited. In addition to the primary diagnosis, the inclusion criteria were age between 18 and 50 years and the absence of any significant systemic, neurological, or psychiatric condition. The study subjects underwent clinical evaluations, MIDAS assessments, neuropsychological testing (svMMSE-2, BDI-II, BAI, CFI), and a 20-minute resting-state EEG recording (10 with open eyes and 10 with closed eyes) with 10:10 International Standard System placement of the 64 electrodes. EEG signals were divided into 2-seconds epochs. Coherence, as measured by weighted lag index (wPLI, wPLID, and imCoh), was employed for the FC analysis. Connectivity matrices for each epoch and for each FC function were built and then averaged across epochs to get subject-level connectivity matrices.

Results: 20 MA subjects and 20 matched HC were enrolled. All subjects were cognitively normal, but migraineurs presented more subjective cognitive complaints as assessed by the CFI-self report (p=0.006). These problems were also confirmed by the study partner (p=0.008). Migraineurs also presented more prominent anxiety (p=0.04) than controls. The FC-EEG analysis documented a hypoconnectivity in the theta band, especially in parietal areas (wPLI p=0.01, imCoh p=0.009, wPLID p=0.06), as well as hyperconnectivity in the beta band in centro-parietal regions (wPLI p=0.017, imCoh p=0.007, wPLID p=0.006).

Discussion: MA Patients exhibit anxiety and subjective cognitive deficits, which were not associated with impaired global cognition as assessed by the svMMSE-2. Migraineurs showed FC-EEG findings that are compatible with other chronic pain conditions (e.g., fibromyalgia, temporomandibular joint pain).

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REVERSIBLE MORPHOMETRIC CHANGES OF BRAINSTEM AND REM SLEEP BEHAVIOR DISORDER IN PATIENTS WITH SPONTANEOUS INTRACRANIAL HYPOTENSION

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Aim: To longitudinally evaluate effects of epidural blood patch (EBP) treatment on brainstem morphometric changes and behavioral sleep disorder with rapid eye movements (RBD) in patients with spontaneous intracranial hypotension (SIH).

Methods: MRI morphometry on 3-Tesla scanner was performed in 10 SIH patients at baseline and 3 months after first EBP treatment. Midbrain and pons areas were calculated on T1-weighted MRI images in patients. Ten controls were included in morphometric analysis to determine any structural differences with SIH patients before treatment. RBD Single-Questionnaire was used to assess clinical RBD. Subjects who were positive on RBS1Q underwent polysomnographic confirmation (PSG).

Results: After EBP treatment at brain MRI, a substantial change in midbrain and pons morphometry associated with complete remission of RBD was observed in SIH. In fact, 8 patients who presented with deep brain swelling at baseline had complete restoration of brainstem configuration associated with complete remission of clinical and PSG-symptoms in 5 patients with PSG-confirmed RBD. Morphometric analysis of cross-sectional MRI revealed that midbrain and pons areas were significantly larger in SIH than in controls. A cut-off value of 200 mm2 for midbrain area correctly distinguished patients from controls on an individual basis. Finally, longitudinal morphometric analysis in SIH showed significantly lower midbrain areas at follow-up than at baseline.

Discussion and Conclusions: There are brainstem morphometric changes in SIH patients, these are reversible after the EBP treatment and are associated with clinical remission of RBD. Morphometric measurement of midbrain area can be used as a dynamic biomarker of SIH in clinical practice.

INTERICTAL BURDEN IMPROVEMENT DURING TREATMENT WITH GALCANEZUMAB: REAL-WORLD EVIDENCE

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Aims: Aim of the present study was to assess migraine disability outcome in terms of interictal burden following six months of prophylactic treatment with galcanezumab in patients with chronic migraine and medication overuse.

Material and Methods: This is a retrospective observational study, conducted at the Headache Centre – ASST Spedali Civili Brescia. All patients in monthly treatment with galcanezumab with a 6 month follow-up at April 2022 and a diagnosis of chronic migraine were included. The following markers of interictal burden were evaluated: scores of depression and anxiety scales (Beck Depression Inventory and Zung Anxiety Scale), work productivity and leisure time. These following two variables were inferred from the first and last items of Migraine Disability Assessment Score Questionnaire (MIDAS).

Results: Fifty consecutive patients were enrolled. All patients had a diagnosis of chronic migraine and medication overuse. From baseline to T3 and T6, a significant improvement in terms of BDI (12.7±2.1 vs 9.4±1.2 vs 8.7±1.1; p=0.004) and Zung Anxiety (37.1±5.6 vs 32.9±5.02 vs 31.3±4.1; p=0.002) scale scores was found. On average, at baseline, patients lost 7.4±6.3 working days quarterly. At T3 and T6, respectively, the number of working days lost decreased to 2.5±5.8 and 2.1±3.5 (p<0.001). Similarly, at baseline, patients lost 18.3±14.1 days of leisure acitivities quarterly. At T3 and T6, respectively, the number of days of leisure activities lost decreased to 3.8±3.3 and 3.4±2.3 (p<0.001).

Conclusions: The present study confirms previous reports from post-hoc analyses regarding galcanezumab efficacy beyond migraine frequency. A significant and sustained improvement from the beginning of treatment was found in terms of depressive and anxiety symptoms, work productivity and leisure activities. These latter variables were indirectly inferred from the MIDAS scale (item 1 and 5). Although this might partially bias our results, it could be a feasible and easily achievable measure of work and leisure activities, in order to facilitate data collection in different settings.

LONG-TERM TREATMENT WITH ERENUMAB IN HIGH-FREQUENCY EPISODIC MIGRAINE

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Aims: Aim of the present study was to assess migraine outcome in patients with high frequency episodic migraine (HFEM) in prophylactic treatment with erenumab during discontinuation and subsequent re-treatment.

Materials and Methods: the present study involved three Headache Centres at the ASST Spedali Civili Brescia, ASST Franciacorta and ASST Papa Giovanni XXIII. Data were collected between January 2019 and June 2022. Inclusion criteria were the following: age ≥ 18 years old, migraine frequency ≥ 8 migraine days per month, MIDAS score ≥ 11, ongoing second cycle of treatment with erenumab 70 mg or 140 mg every 4 weeks. The following variables were evaluated: mean monthly migraine days (MMDs), analgesics consumption, MIDAS and HIT-6 quarterly scores.

Results: Twenty-five consecutive patients were enrolled, of whom 20 were females. Mean age at baseline was 36.6 (SD 9.8) years old. From baseline to end of treatment (T12) a significant reduction in MMDs (10.5±2.4 vs 5.7 ±1.04; p=0.02), analgesics consumption (11.7±4.2 vs 5.8±3.6; p=0.008) and MIDAS score (72.5±36.5 vs 13.5±11.4; p=0.005) was found. As per national guidelines a discontinuation period followed (on average 3.6±2.3 months). At retreatment, patients documented a significant worsening in MMDs and MIDAS score compared to T12 (respectively 8.6±1.6; p=0.03 and 30.1 ±18.4; p=0.05), yet significantly better compared to baseline (respectively p=0.05 and p=0.01). Analgesics consumption at retreatment was comparable to baseline (10.1±5.7; p>0.05) and significantly higher compared to T12 (p=0.02). Following 3 and 6 months of retreatment, MMDs (respectively 6.1 ±0.9 and 6.0±1.3), analgesics consumption (5.5±3.3 and 5.4±2.8) and MIDAS score (22.4±8.9 13.0±11.4) improved as T12 (all p<0.05).

Conclusions: Erenumab discontinuation following the first 12 months treatment cycle resulted in a significant migraine worsening in patients with HFEM, although not as baseline. Migraine outcome, in terms of frequency and disability, during the second treatment cycle was comparable to the former.

REAL-WORLD PERSISTENCE AND COSTS AMONG PATIENTS WITH CHRONIC MIGRAINE TREATED WITH ONABOTULINUMTOXINA OR CGRP MABS: A RETROSPECTIVE CLAIMS ANALYSIS STUDY

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Objective: Evaluate real-world persistence rates and costs among patients with chronic migraine (CM) treated with onabotulinumtoxinA (onabotA [BOTOX®]) or calcitonin gene–related peptide monoclonal antibody (CGRP mAb).

Materials: Persistence with oral migraine preventive medications (OMPMs) is reportedly low. Real-world data on treatment persistence and costs associated with recently approved preventive CM treatments are limited.

Methods: This retrospective, longitudinal, observational study analyzed the IBM MarketScan® Commercial and Medicare Supplemental databases (7/1/2017-2/29/2020). Adults treated with either onabotA or CGRP mAbs (based on overall migraine ICD-10 codes) and having continuous coverage ≥6 months before and ≥12 months after treatment initiation were included. Persistence to index treatment was assessed at 6, 9, and 12 months, and all-cause and migraine-related costs were evaluated during the 12-month follow-up period. Persistence and costs were adjusted for potential confounders (demographics, comorbidities, OMPM use) using generalized linear model regression.

Results: Of 66,303 patients with onabotA or CGRP mAb claims, 2697 patients with CM met inclusion/exclusion criteria. In the total population, patients were primarily female (86%) and their mean age was 44 years, which was consistent among the individual CGRP mAbs. Persistence was higher among those treated with onabotA versus the combined CGRP mAbs group at 6 (67% vs 47%; P<0.001), 9 (51% vs 37%; P<0.001), and 12 (40% vs 27%; P<0.001) months. OnabotA and CGRP mAbs were associated with comparable 12-month all-cause ($16,681 vs $16,666) and migraine-related ($8198 vs $8518) costs. Compared to CGRP mAbs, onabotA was associated with lower 12-month acute medication ($763 vs $1240; P<0.001), OMPM ($685 vs $993; P<0.01), and migraine-related inpatient ($224 vs $728; P<0.01) costs. Migraine-related emergency department costs were comparable between onabotA and CGRP mAbs ($149 vs $129). Findings were sustained after regression adjustment for confounders.

Discussion: CM patients initiating onabotA treatment had higher persistence and comparable all-cause and migraine-related costs over 12 months compared to CGRP mAbs.

Conclusion: Comparing treatment persistence rates and healthcare costs associated with the use of onabotulinumtoxinA and CGRP mAbs for the preventive treatment of chronic migraine can help guide clinical decision-making. Limited data are available that compare treatment persistence rates and healthcare costs associated with more recently approved preventive treatments for chronic migraine, including onabotulinumtoxinA and CGRP mAbs.

THE HYPOTHALAMUS PLAYS A ROLE IN MODULATING MIGRAINE ATTACK DURATION: INSIGHTS FROM A MICROSTRUCTURAL AND FUNCTIONAL MRI STUDY

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Objectives: Neuroimaging studies have shown an involvement of the hypothalamus in the premonitory phase of a migraine attack. Little is known about the role played by the hypothalamus and the brain networks with which it is interconnected during a migraine attack.

Materials and method: We scanned 15 patients during a spontaneous migraine attack without aura and, for comparisons, 20 control subjects. We analyzed diffusion tensor imaging (DTI) metrics of the entire hypothalamus and its anterior and posterior regions of interest (ROIs) bilaterally. In addition, we estimated Higuchi fractal dimension (FD) from resting-state functional MRI data as a non-linear measure of neural activity complexity. All MRI data were correlated with clinical disease variables.

Results: In comparison to healthy subjects, patients during the attack had altered diffusivity metrics of the hypothalamus, particularly of the posterior ROIs, and higher FD values in the salience network (SN). Correlation analysis revealed a direct correlation of axial diffusivity of the hypothalamus with disease severity and FD of the SN. Furthermore, the mean duration of the migraine attack correlated positively with the metrics of the anterior hypothalamus bilaterally.

Discussions: Our results show plastic structural changes in the hypothalamus related to the attacks severity and the complexity of the salience cortical network involved in the multidimensional neurocognitive processing of pain.
Conclusions: Our data suggest that the hypothalamus may play an important role in modulating migraine attack duration.
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PAIN CATASTROPHIZING SCALE AND MONOCLONAL ANTIBODIES AGAINST CGRP: A REAL-LIFE EXPERIENCE

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Objectives: Catastrophic thought, defined as a negative cognitive and emotional response to pain, plays a crucial role in pain chronification, anxiety, and depression in chronic migraine. We aimed to evaluate how pain catastrophizing, measured using the Italian version of the "Pain Catastrophizing Scale (PCS)", could influence clinical response to anti CGRP monoclonal antibodies (Erenumab, Galcanezumab, and Fremanezumab) in-patient with chronic migraine.

Materials/Methods: We collected sociodemographic and clinical data from patients attending at our secondary hospital headache ambulatory from July 2021 since now. We assigned randomly patients, diagnosed with chronic migraine according to ICDH III criteria, between Galcanezumab (120 mg), Erenumab (140 mg) and Fremanezumab (125 mg) treatments. We measured PCS at the beginning of therapy (T0) and repeated at three (T1) and six months (T2). Clinical impact was measured by the HIT-6 "Headache Impact Test-6" scale and the MIDAS "Migraine Disability Assessment Test" scale. Comorbid depression and anxiety were assessed by BDI II "Back Inventory II" scale. All patients were treated by a psychologist.

Results: The study included 11 patients (1 men and 10 women) with or without medication overuse. Migraine impact was moderate (HIT-6≥56) except for one case (HIT-6 44), with severe disability (MIDAS ≥ 21) and mild to severe lever of anxiety and depression (BI II ≥ 10). PCS median values at T0 were 31, 45, meanwhile at T1 and T2 PCS scoring decreased at 17, 9 and 17,6 respectively. After 6 month of treatment all patient reached better quality of life, lowest levels of anxiety (MIDAS and BDI II median scores of 18.9 and II 9.7 respectively). No correlation was found with monoclonal antibodies treatment or among scales ($p>0.005$).

Discussion: In our cohort, the higher PCS scoring at T0 seems to correlate to the better clinical sustained response, but more data are needed to better explain these results.

Conclusions: To our knowledge this is the first real life experience describing the impact of PCS scoring on monoclonal CGRP clinical response in patients with chronic migraine.

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EFFECTIVENESS AND SAFETY OF CGRP-MABS IN MENSTRUAL RELATED MIGRAINE: A REAL-WORLD EXPERIENCE

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Objective: Migraine prevalence is significantly higher in women especially during reproductive age when menstrual related hormonal fluctuations represent the most common migraine trigger. Indeed, over 50% of patients report a higher occurrence of migraine attacks during the perimenstrual window. Menstrual migraine attacks are consistently referred as more disabling, less responsive to symptomatic treatments, longer in duration, and more prone to relapse than non-menstrual migraine attacks. We aimed to evaluate whether mAbs blocking CGRP-ligand or receptor (CGRP-mAbs) could represent an effective and safety preventive treatment for menstrual migraine attacks in patients with menstrual related migraine (MRM) with previous treatment failures.

Materials: This is a report of our real-life experience focusing on the effectiveness and safety of mAbs anti-CGRP in the prevent treatment of migraine attacks occurring during the perimenstrual window in patients with menstrual related migraine with at least three previous preventive treatments failures.

Methods: Forty patients with menstrual related migraine with at least three previous treatment failures received monthly CGRP-mAbs. At the baseline and after six CGRP-mAbs administrations, patients underwent to extensive interviews to assess frequency, duration, intensity and responsiveness to painkillers intake of migraine attacks occurring during the perimenstrual window.

Results: After 6 administrations of CGRP-mAbs we observed a reduction of median menstrual migraine frequency (from 5 to 2 days per month), pain intensity (from 8/10 to 6/10) and attacks duration (from 24 hours to 8 hours) ($p<0.001$). Nevertheless, a significant increase in the percentage of responding to migraine painkillers was observed from 42.5% at baseline to 95% at T1 ($p<0.001$).

Discussion: Several evidences strongly suggest that estrogen fluctuations are involved in migraine attacks worsening during the perimenstrual window through several mechanisms directly or indirectly involving the CGRP pathway. Specifically, it has been argued that estrogens act in strategic areas of central as well peripheral central nervous system (as the trigeminal ganglion) to increase migraine thresholds. In this context, a sharp decline in estrogens levels would shift the balance towards a pro-migraine state, thereby increasing the susceptibility to initiation of attacks. Therefore, the observed significant reduction in menstrual migraine attacks burden findings could be related to the modulation of signalling balance at the trigeminal ganglion induced by CGRP-mAbs administrations.

Conclusion: CGRP-mAbs could represent a safety and effective preventive therapeutic strategy able to reduce the disabling burden of menstrual migraine attacks frequency, duration, intensity and significantly improve the response to painkillers.

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GALCANEZUMAB EFFECT ON "WHOLE PAIN BURDEN" AND MULTIDIMENSIONAL OUTCOMES IN MIGRAINE PATIENTS WITH PREVIOUS UNSUCCESSFUL TREATMENTS: A REAL-WORLD EXPERIENCE

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Background: Clinical trials have demonstrated galcanezumab as safe and effective in migraine prevention. However, real-life data are still lacking and overlook the impact of galcanezumab on those different migraine facets strongly contributing to migraine burden. Herein we report the clinical

experience from an Italian real-world setting using galcanezumab in patients with migraine experiencing previous unsuccessful preventive treatments.

Materials: This was an observational, prospective, non-randomized, open-label study evaluating the efficacy and safety of galcanezumab as preventive treatment in migraine patients with failure of at least 3 previous preventive strategies.

Methods: Forty-three patients with migraine and failure of at least 3 migraine preventive medication classes received monthly galcanezumab 120 mg s.c. At the first administration and after 3 and 6 months, patients underwent extensive interviews to assess clinical parameters of disease severity to assess a composite score defined as "whole pain burden", derived from the product of headache frequency (mean of attacks per month in the last three month) per headache intensity (mean of NRS values) per headache duration (mean headache hours when treated). Furthermore, validated questionnaires were administered to explore migraine-related disability, impact, and quality of life as well as symptoms of depression or anxiety, pain catastrophizing, sleep quality and the ictal cutaneous allodynia.

Results: After the third and the sixth administration of monthly galcanezumab 120 mg s.c., headache attacks frequency reduced from 20.56 to 7.44 and 6.37 headache days per month, respectively. Moreover, a significant improvement in headache pain intensity (from 8.95 to 6.84 and 6.21) and duration (from 9.03 to 3.75 and 2.38) as well as in scores assessing migraine related disability and impact, depressive and anxious symptoms, and pain catastrophizing was observed. Furthermore, we demonstrated a significant reduction in the values of "whole pain burden".

Discussion: Real-world data support monthly galcanezumab 120 mg s.c. as a safe and effective preventive treatment in reducing headache frequency, intensity, and duration as well as comorbid depressive or anxious symptoms, pain catastrophizing and quality of life in both episodic and chronic migraine patients with previous unsuccessful preventive treatments. Furthermore, we demonstrated that monthly galcanezumab 120 mg s.c. is able to induce a significant improvement in the scores of "whole pain burden".

Conclusion: The "whole pain burden" is a reliable and easy-to-handle tool to be employed in clinical setting to evaluate the effectiveness of preventive drugs (in this case, galcanezumab) or when the decision of continuing the treatment with anti-CGRP mAbs is mandatory.

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INFODEMIOLOGY OF CLUSTER HEADACHE SEASONALITY: A PROOF OF CONCEPT BY A GOOGLE TRENDS ANALYSIS

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Objectives: Cluster headache (CH) is a primary headache disorder characterized by cluster bouts periods with almost daily attacks separated by pain-free remission periods lasting more than 3 months. Although with conflicting results, CH is reported to follow an annual pattern with a peak in the spring (March–April) and a second peak in autumn (September–October). Headache patients frequently use search engines, such as Google, to look for terms related to their disease creating trend data which can be analysed with Google Trends.

Materials: Google Trends has been used for surveillance studies and can provide indirect estimates of the burden of diseases and symptoms. The present study is aimed to investigate the seasonality of Google Trends last 10-year search volumes for the search term 'cluster headache', in the Northern and Southern hemispheres.

Methods: The search term "Cluster Headache" was translated into the 10 most spoken languages in the world and searched on Google Trend. Google Trends automatically normalized data for the overall number of searches and presented them as relative search volumes (from 0 to 100), to compare variations of different search terms across periods. Subsequently, in order to avoid the noise from populations with fewer Internet searches and/ or with lower relative interest in CH, countries were selected according to the following criteria: (1) presence of a relative search volume >70 for CH; (2) presence of at least 20 million inhabitants. For statistical purposes, countries were grouped in relation to the hemisphere (Northern or Southern). Relative search volumes for "cluster headache" were extracted from January 2012 to January 2022. Generalized linear models were employed to assess possible differences in relative search volumes for 'cluster headache", between seasons.

Results: A seasonal trend for the search of 'cluster headache' was found worldwide with higher relative search volumes presented higher levels in meteorological seasons of spring (March, April and May) and autumn (September, October and November) compared with summer (June, July and August) and winter (December, January and February).

Discussion: Google trend is a web facility which provides access to search term relative volumes which have been proven to be highly predictive of present behaviours providing reliable information into disease experiences and, indirectly, about disease burden.

Conclusion: Our data showing higher search volumes for the term cluster headache during meteorological seasons of spring and autumn, clearly reflect the circannual pattern of CH occurrence representing new evidence for its seasonality.

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DIFFERENT PERSONALITY PROFILES IN PATIENTS WITH CHRONIC CLUSTER HEADACHE: A DATA-DRIVEN APPROACH

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Background and Aims: Cluster headache (CH) patients are usually comorbid to mood spectrum disorders, but the role of psychopathological aspects is poorly explored. We aimed at identifying, by a data-driven approach, if CH patients may be classified according to their psychological functioning.

Methods: We applied a Principal Component Analysis (PCA) to identify psychological patterns of functioning of 56 CH patients, based on values of the clinical personality pattern scales of the Millon Clinical Multiaxial Inventory-

III (MCMI-III). A hierarchical cluster analysis (HCA) was further run to cluster patients according to patterns found. Subgroup comparisons on demographical data (age, sex, education), clinical features (headache frequency, laterality) and MCMI-III scores were performed.

Results: PCA found two bipolar personality patterns: the Psychological Dysregulation, positively correlated with illness duration and the Social Engagement, negatively correlated with age. HCA found three groups of patients with different personality traits but similar demographical and clinical features. The most psychologically compromised group had high Psychological Dysregulation and low Social Engagement scores.

Conclusions: Our data-driven approach revealed different psychological patterns in CH. Combining medical and psychological information may help clinicians to identify tailored-based therapeutic interventions for a better management of the CH population health.

AUTONOMIC EVALUATION IN MIGRAINE: A STUDY WITH HEART RATE VARIABILITY

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Objectives: Migraineurs show symptoms suggesting an involvement of autonomic nervous system (ANS) both during attacks and interictally [1]. Heart rate variability (HRV) study is a simple tool able to identify ANS alterations. We aim to study HRV in migraineurs, comparing data with healthy subjects.

Materials: We included episodic migraineurs (EM) from two Italian headache centers and healthy subjects (HS) of same age. Electrocardiographic (EKG) signal was collected using Polar H10 thoracic band and data were analyzed using Kubios HRV software.

Methods: EM were included during the interictal phase. All measurements were acquired in standardized environmental and subjects' conditions. EKG signal was recorded during the following conditions: i) basal (resting respiratory rate at 12-16bpm, 15min recording); ii) deep breath test (DBT, 6 deep breaths in 1min). HRV was studied in the frequency domain, analyzing total power, high frequencies (HF, influenced by parasympathetic system), low frequencies (LF, influenced by sympathetic system) power, total power and LF/HF ratio. Moreover, we calculated HRV in basal and DBT conditions with the formula: ((Fcmax–Fcmin)/Fcmean)*100. Statistical analyses were performed using Mann-Whitney U test.

Results: We included 11 EM (36+/-10 years old, 8 females) and 11 HS (30+/-10 years old, 5 females). We found a significant difference in basal HRV between the two groups (EM 19.6+/-5.6%; HS 29.7+/-8.0%, p=0.005). About frequency domain analysis, we found a significant difference in total power (EM 1128.6+971.0ms^2; HS 1677.2+872.8ms^2 p=0.040) and LF one (EM 383.69+/-275.0ms^2; HS 864.0+/-468.8ms^2; p=0.007). Conversely, HF power, LF/HF ratio and DBT HRV did not show any significant difference.

Discussion: ANS involvement in migraine is described both during the attack and interictal phases [1, 2], but there are just few studies on HRV [3]. Here, we observed a reduction of basal HRV compared to HS; basal HRV depends mainly on parasympathetic tone, but a similar reduction in HF power was not appreciated. Differently, the reduction of LF power in migraineurs may suggest a reduced sympathetic tone.

Conclusion: Our data confirm that migraineurs show differences in ANS compared to healthy subjects, but more studies and wider samples are needed to better understand such aspects of the disease.

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POST COVID19 HEADACHE: A MULTICENTRIC ITALIAN CASE SERIES

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Objectives: To describe patients with new onset headache after COVID19 infection.

Materials: We analyzed data from patients coming for evaluation at three Italian headache centers for new onset headache after COVID19 infection. We investigated headache onset latency after the infection, its location, intensity, duration, quality, and concurrent symptoms. Moreover, we collected data regarding the efficacy of preventive and acute treatments. Lastly, we took note of imaging exams performed.

Methods: Data were collected during routine neurological evaluations at the headache centers, and, in some cases, we got follow-ups. Non-parametric variables were analyzed using Mann-Whitney U-test.

Results: 11 women (33+/-22 years old), without previous history of headache were included. Headache onset was 4.5+/-5.8 days from the infection beginning (54.5% started concurrently). The localization of the pain was: frontal (27.3%), fronto-temporal (18.2%), temporal (9.1%), parietal (9.1%), occipital (9.1%), periorbital (9.1%), holocranic (18.2%); in 90.9% pain was bilateral. Headache was pulsating (54.5%) or tightening (45.5%) and presented a mean intensity of 7.5+/-1.0/10VAS. Associated symptoms were nausea (54.5%), photophobia (27.3%), phonophobia (18.2%), tearing (18.2%), burning eye (18.2%), stabbing pain (18.2%), worsening with physical activity (18.2%), vomit (9.1%), concentration difficulties (9.1%), tinnitus (9.1%). Headache was persistent and daily in 8 patients (72.7%), while presented in episodes of 16.7+/-8.1 hours duration with a frequency of 16.3+/-5.5 days/month in the remaining ones (27.3%). About acute treatment, 3 patients (27.3%) were responsive to acetaminophen, while the remaining ones got partial (45.5%) or scarce (18.2%) relieve from NSAIDs. Ten patients received one or more preventive treatments: amitriptyline (36.4%), magnesium (36.4%), corticosteroids (27.3%), topiramate (18.2%), B-vitamins drugs (18.2%). Five patients (45.5%) showed improvement after the therapy (25.6+/-6.4 vs 8.6+/-7.9 headache days/month, p=0.016). Eight patients (72.7%) underwent a brain MRI that showed no significant alterations.

Discussion: Headache is a common symptom of COVID19 infection [1]. We described 11 patients without clinical history of headache, presenting with a new onset headache associated to COVID19 infection. Headache characteristics were migraine-like in most cases or tension-type-like. In 4 cases, ICHD-3 criteria for new daily persistent headache (NDPH) were met and other 4 patients showed criteria for "probable NDPH"[2]. A pathogenetic hypothesis may lay on CNS inflammation lasting after the infection [3], supported by the positive response that some patients got from corticosteroids and not from anti-migraine drugs.

Conclusion: Headache following COVID19 infection is a common condition that can become persistent and severe, with a variable treatment response.

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DURAL ARTERIOVENOUS FISTULAS IN SPONTANEOUS INTRACRANIAL HYPOTENSION: A REPORT OF 2 CASES

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Background: Spontaneous intracranial hypotension (SIH) is an uncommon cause of headache related to low cerebrospinal fluid (CSF) pressure caused by spinal CSF leaks. Cerebral venous thrombosis (CVT) rarely complicate SIH natural history. Dural arteriovenous fistulas (DAVFs), vascular abnormalities connecting branches of dural arteries to dural veins/venous sinus, are associated with several conditions including CVT. DAVFs have been exceptionally observed in SIH.

Aim: We report two cases of SIH complicated by DAVFs.

Cases: Patient n°1. A 59-year-old man presented with a 4-week history of occipital headache and tinnitus relieved assuming the recumbent position. Brain-MRI with gadolinium showed diffuse pachymeningeal enhancement (DPE), cerebellar tonsillar descent, and a suspected left transverse/sigmoid sinus dural arteriovenous fistula (DAVF). Brain-MRV revealed left transverse/sigmoid sinus thrombosis. Digital Subtraction Angiography (DSA) confirmed the finding of left transverse/sigmoid sinus DAVF. Lumbar EBP treatment with an autologous blood volume of 30 ml was performed; ortostathic headache disappeared the day after. Three days after EBP, DAVF was treated adopting endovascular embolization [180cm of platinum coils and 2,5ml of ethylene-vinyl-alcohol-copolymer(onyx®)-glue]. After 14 months, DSA showed successful DAVF closure treatment and complete recanalization of the left sigmoid sinus and left transverse sinus thrombosis, unchanged from baseline. Patient n°2. A 75-year-old man presented with orthostatic headache started seven days before. He was taking warfarin for management of deep venous thrombosis. Brain-MRI showed DPE, brain sagging, bilateral subdural haematomas and a probable right-transverse DAVF, subsequently confirmed by DSA. After 12 days, because the patient presented comatose status (GCS=5), an urgent endovascular DAVF embolization [9ml of ethylene-vinyl-alcohol-copolymer-(onyx®)-glue] was performed with subsequent coma awakening and headache disappearing. After 38 days, he reported non-postural headache, imbalance and left-hand weakness. Brain-MRI showed subdural hematoma enlargement, right cortical fronto-parietal subarachnoid haemorrhage (SAH) and DAVF disappearance. DSA showed a parietal cortical venous thrombosis, which was absent in the previous scans. Lumbar EBP was performed 47 days after orthostatic headache onset. Within 3 months the patient became asymptomatic. Brain-MRI returned normal 8-months later.

Conclusion: DAFV expands the neuroradiological spectrum of SIH. Patient n°2 may be the first case in which occurrence of SDH, CVT, SAH and DAVF following SIH have been described. Moreover, in patient n°2, DAVF developed before CVT, so we speculate that microscopic vascular channels' formation within the dura mater, secondary to extreme venous dilation by SIH may be the start of a cascade of events that results in DAVF development. Further studies are needed to explore this hypothesis.

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WHAT HAPPENS TO HEADACHE FEATURES DURING ERENUMAB RESUMPTION AFTER MANDATORY INTERRUPTION? ASSESSMENT IN CHRONIC MIGRAINE PATIENTS TAKING A PREVENTIVE THERAPY

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Aim: The subsidization of antibodies targeting CGRP pathway (mAbs) in Italy is regulated by specific rules dictated by AIFA. These provide a 1-year-cycle of monthly mAbs administrations followed by a mandatory interruption period of at least 1 month. Data from the literature suggests that headache frequency tends to increase after mAbs cessation, while limited data is available on headache pattern after restarting. Our primary aim was to compare migraine response during the initial three months of treatment (T3) of the first erenumab cycle and the corresponding period after treatment resumption (II cycle) in chronic migraine patients.

Materials and Methods: Data are extracted from a population of 63 patients who resumed erenumab after a mean of 5.9±3.0 months of interruption (mean age 49.2±8.6yrs, years of chronicity 10.7±8.5yrs, 92% with baseline diagnosis of medication overuse headache). We prospectively collected monthly migraine days (MMDs), headache intensity score (Numerical Rating Scale 0-10), days of intake and numbers of acute drugs during the first three months of the I and II erenumab cycles (C1 and C2). For each parameter, we calculated mean of data reduction at T3 compared to baseline for both C1 and C2 (delta).

Results: MMDs, headache intensity, doses and days of acute drug intake significantly improved at T3 both during C1 and C2. All parameters worsened during suspension, though they were still better than baseline C1 values. Mean MMDs reduction at T3 compared to baseline values was greater during C1 than C2 (C1: MMDs prior starting erenumab 21.7±5.5, T3 9.6±6.8, T13 7.6±6.0; C2: prior resumption 17.5±6.5, T3 9.6±6.1; deltaC1: 12.1, deltaC2: 7.8, p=0.003). The same was true for headache intensity, doses and days of drug intake (NRS: deltaC1 1.4, deltaC2 0.7, p=0.009; number of acute medications: deltaC1 19.5, deltaC2 9.2, p=0.005; days of intake of acute medications: deltaC1 11.1, deltaC2 6.0, p<0.001).

Discussion: Erenumab effectiveness persists across two subsequent 1-year cycles separated by the mandatory treatment interruption. The size of the effect is however less marked during the second cycle. Data interpretation should consider the different starting points for the two cycles, due to persistence of erenumab efficacy after interruption. Future data are needed to assess migraine trend in the long term and after multiple resumptions.

Conclusions: Erenumab maintains an early significant improvement in migraine pattern after resumption. Evidence of migraine trend after restarting could help clinicians for decision making in the real-world setting.

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INSIGHTS INTO MIGRAINE PATIENT CHARACTERISTICS AND TREATMENT PATTERNS: INTERIM BASELINE RESULTS FROM THE TREATMENT OF MIGRAINE: OUTCOMES FOR PATIENTS IN REAL-WORLD HEALTHCARE SYSTEMS ITALY (TRIUMPH [ITALY]) STUDY

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Objectives: Describe baseline demographic and clinical characteristics of patients with migraine in routine clinical care who are switching or initiating pharmacologic treatment for migraine prevention within the TRIUMPH [Italy] study with a focus on patients initiating galcanezumab.

Materials and Methods: TRIUMPH is an ongoing, 24-month observational study investigating migraine prevention treatment in the United States, Japan, Germany, Italy, Spain, United Kingdom, and United Arab Emirates. Eligible patients are ≥18 years, have a diagnosis of migraine, and are switching or initiating pharmacologic treatment for migraine prevention. Interim cross-sectional baseline demographics, disease characteristics, current and historical migraine treatment patterns, and Migraine Disability Assessment (MIDAS) were collected from July 5, 2021 to March 11, 2022 and are presented as percentages or Mean±standard deviation (Min;Max).

Results and Discussion: Currently, 89 patients aged 42.8±13.23 (19;67) years are enrolled in Italy, among which 75 are females. Patients initiated galcanezumab (n=30), other calcitonin gene-related peptide monoclonal antibodies (CGRP mAb, n=12), oral standard of care preventive treatments (n=34), botulinum toxin A or B (n=3), other locally approved treatments (n=9), and drugs within these classes that were yet to be classified (n=1). On average, patients were diagnosed with migraine for 6.2±11.38 (0;42) years and first experienced migraine symptoms 24.7±14.89 (0;60) years prior to enrolment. The number of monthly headache days was 16.9±7.99 (4;30) for all patients and 19.6±7.6 (8;30) for patients initiating galcanezumab. The number of monthly migraine days was 16.4±7.74 (4;30) for all patients and 18.9±7.53 (8;30) for patients initiating galcanezumab. Enrolled patients reported 1.7 ±1.87 (0;8) prior preventive treatments at baseline. The most frequently reported prior preventive treatments by patients initiating galcanezumab at any time before enrolment were anticonvulsants (n=26), beta blockers (n=18), and botulinum toxin A or B (n=13). At baseline, the overall MIDAS summary score was 52.1±41.44 (0;225, Grade IV-B) with patients initiating galcanezumab 67.5±45.9 (17;225, Grade IV-B).

Conclusions: At baseline, patients initiating galcanezumab utilized a numerically greater number of previous preventive treatments and reported more headache days and migraine headache days than the overall enrolled cohort. Moreover, the MIDAS summary score for patients initiating galcanezumab was also numerically higher compared to the overall cohort. Together, these observational data suggest higher migraine severity in the galcanezumab group within the TRIUMPH [Italy] study.

HOW MUCH DISABLED ARE VERY DISABLED MIGRAINE PATIENTS? A COHORT ANALYSIS IN CHRONIC MIGRAINE PATIENTS WITH MULTIPLE PREVENTIVE TREATMENT FAILURES

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Introduction: The arrival of the new calcitonin gene related peptide (CGRP) targeted therapies opened new horizons in migraine management; however, because of their high costs, it has posed new questions on patients' selection. In Italy, the Migraine Disability Assessment Questionnaire, MIDAS, was identified as the parameter to select the candidates for receiving these new treatments. Nevertheless, the range of MIDAS scale is quite widespread, from 0 to 270, while the cutoff score for high disability (MIDAS grade IV) is >20. In fact, the highest category is divided into grade IV-A, severe disability (scores of 21–40) and grade IV-B, very severe (scores of 41–270). The present study aimed at assessing the distribution of MIDAS scores in chronic patients with multiple treatment failures.

Methods: We retrospectively evaluated the MIDAS and Headache Impact Test 6 items, HIT-6, scores, pain intensity (Numeric Rating Scale, NRS), and monthly acute medication intake (MAMI) of consecutive chronic patients with multiple treatment failures.

Results: We enrolled 487 patients (84.2% females, 45.3±11.7) with 4 (IQr 3) failed preventive therapies. The Median HIT-6 score was 68 (IQr 6), median NRS was 8 (IQr 2). The MIDAS grade IV was observed in 90.6% of patients, grade IVB in 73.5%. The median MIDAS score in grade IVB patients resulted in 86 (IQr 60). Accordingly, we divided patients into MIDAS grade IVB1 (i.e. 41-85) and IVB2 (≥86). For a preliminary test of the criterion validity of this portioning, patients with grade IVB2 presented higher HIT-6 (69 (6) vs. 67 (42); p=.0003) and MAMI (30 (105) vs. 20 (24) p=.046) than those with grade IVB1. They did not differ for age, BMI and number of failed preventives, and disease history.

Conclusion: Chronic patients with multiple treatment failures are most often very disabled (more than 70% with MIDAS grade IVB). However, among them, those with a MIDAS score of 86 or higher are characterized by an even higher disability as expressed by higher HIT-6 scores and MAMI. We propose to distinguish patients with MIDAS grade IVB into two subsets, accordingly.

THE 4-D MIGRAINE SCALE: A COMPOSITE SCORE EVALUATING MIGRAINE SEVERITY AND TREATMENT EFFICACY

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Introduction: Different measures are currently used to evaluate the migraine frequency and disability. However, a single measure may represent only partially the burden of migraine. A composite measure, including a weighted approach and the most relevant parameters, would fully evaluate migraine load and treatments efficacy.

Methods: We chose 4 of the most used endpoints: monthly migraine days (MMDs), acute medications intake (MAMI), attack pain intensity (by

Numerical Rating Score, NRS) and Migraine Disability Assessment (MIDAS) Score, to design the composite 4-D migraine scale. Each parameter was scaled into definite levels: 7 for migraine frequency, i.e. 0 as level 1, 3 intervals for episodic (1-3, 4-7 and 8-14 MMDs), 3 for chronic migraine (15-20, 21-25 and 26-30 MMDs); 6 levels for MAMI: 1-4 as level I, 5-9, 10-14, 15-20, 21-30 and finally ≥31 drugs/months as level VI; 4 grades for pain intensity (level I=0 at NRS, II=1-3, III=4-7 and finally level IV=8-10); and 5 intervals for MIDAS, grade I=0-5, II=6-10, III=11-20, IVA=21-40 and IVB=41-270, according to current literature. First, the relative weight of each level per parameter was rated by 100 patients and 100 headache experts according to the Conjoint Analysis, which is based on how respondents choose among specific, hypothetical, but plausible options. Secondly, we applied the 4-D migraine score to a sample of 205 episodic and chronic migraine patients treated with galcanezumab. We assessed its concurrent validity with respect to HIT-6.

Results: There was strong agreement between clinicians and patients about the weight of each parameter: MIDAS was the most important attribute (weight 33%), followed by MMDs and MAMI which resulted equally important (weight 23%), while NRS was slightly less relevant (weight 21%). A definite score was attributed to each level of the 4 parameters and finally the total 4-D score was calculated summing up each of the 4 parameters score for each patient. Since MAMI and MIDAS were log-normally distributed, a log transformation was applied before obtaining z-score for each of the 4 measures. Then, the Conjoint Analysis based 4-D migraine score was computed according to the formula (0.23* Z-MMDs+0.23* Z-MAMI+0.33* Z-MIDAS+0.21* Z-NRS). In our sample, the correlation with HIT-6 resulted higher (Spearman rho=0.31) for 4-D score than for each single measure (MMD: rho=0.18; NRS: rho=0.25; MAMI: rho=0.16; MIDAS: rho=0.22).

Conclusion: Such composite score based on the preferences weights of clinicians and patients could be useful as a Clinician- and Patient-Reported Outcome in clinical trials and Real-World studies.

OBSESSIVE-COMPULSIVE TRAITS AMONG CHRONIC MIGRAINE PATIENTS: GENDER DIFFERENCES

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Objectives: Psychiatric illnesses are often associated to headache, especially to severe forms as chronic migraine (CM) with medication overuse headache (MOH). Both migraine and some psychiatric traits are more common among females, with relevant repercussion on therapeutical and clinical aspects. Few data are available about obsessive-compulsive disorders (OCD) in migraine patient. Aim of this study was to establish the quote and the characteristics of OCD traits in CM with MOH patients and its impact on migraine therapy.

Methods: We enrolled all consecutive patients with CM and MOH undergoing treatment with onabotulinum toxin A (OBT-A) in our Headache Centre. Each subject was submitted to the Obsessive-Compulsive Inventory-Revised (OCI-R) test at the start (T0) and after four sessions of therapy (T1). Statistical analysis compared OCI-R results at T0 and T1 according to sex with chi-squared test.

Results: We analysed a sample of 60 subjects, with 40 females (66,7%). According to OCI-R scores at T0 we observed that 5% of the males and 27,5% of the females were borderline for OCD traits at T0; 10% of the males and 12,5% of the females showed psychological distress. Last, 60% of males and 22,5% of females had scores compatible with pathologic OCD traits. The difference in the distribution of OCI-R was significant at T0 (p=0,016). At T1, we observed 30% of normal males and 60% of normal females. 5% of the males and 12,5% of the females were borderline, while 25% of the males and 12,5% of the females remained with psychological distress. 40% of males and 15% of females were frankly pathologic. The difference in the distribution of OCI-R was significant at T0 (p=0,041). Both males and females underwent a significant increase in normalization rates at T1 (males: from 25% to 30%; females: from 37,5% to 60%, p<0,05).

Conclusion: Our data showed a significant rate of OCD traits at baseline (till to 60% among men). Females showed a more significant improvement in OCD traits between T0 and T1. These data partially confirmed literature, that reported a major quote of OCD traits among men. The two genders showed different response to therapy based on their OCI-R scores. OBT-A confirmed its high efficacy on CM, with an improvement in migraine severity in both gender and in all the OCI-R classes. The role of psychological attitude could be relevant in management of CM with MOH and should be better investigated in future studies.

EFFECTIVENESS AND SAFETY OF MONTHLY VERSUS QUARTERLY FREMANEZUMAB IN MIGRAINE PATIENTS: A REAL-LIFE PIVOTAL STUDY

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Objectives: Previous randomized controlled trials (RCTs) showed that monthly (225 mg) and quarterly (675 mg) fremanezumab, a monoclonal antibody targeting the calcitonin gene-related peptide, are effective and safe for migraine prevention. [1,2] The aim of our study was to compare the effectiveness and safety of monthly versus quarterly fremanezumab in a real-life setting.

Materials: Twenty-nine patients, attending the Headache Clinic at San Raffaele Hospital, were prospectively enrolled. All patients completed a three-month treatment period, receiving subcutaneous fremanezumab monthly (Mth) or quarterly (Qtly) (12 Mth versus 17 Qtly patients); twenty-three patients completed a six-month treatment period (13 Mth versus 10 Qtly patients). Three patients switched from Qtly to Mth fremanezumab after three months due to a possible end-of-dose effect.

Methods: Demographical data were collected at baseline. Clinical variables, including monthly headache days (MHD) and migraine days (MMD), monthly acute medication days (AMD) and pills (AMP), headache intensity on NRS, HIT-6, MIDAS and ASC-12 scores were recorded at baseline and after three (M3) and six (M6) months of treatment. Adverse events (AEs) were also investigated at M3 and M6. Within and between-group differences in treatment effectiveness were assessed at M3 and M6 using Wilcoxon and mixed-effect ANOVA tests.

Results: Women were 11 (92%) in the Mth group and 13 (76%) in the Qtly group (p=0.286); the mean age was 51 (range: 31 – 64) and 48 (range: 27 – 65), respectively (p=0.647). Ten patients (83%) in the Mth group and 11 (65%) in the Qtly group had chronic migraine (p=0.269). Baseline mean MMD was 18 in both groups (Mth range: 10 – 30; Qtly range: 8 – 30), while MHD was 18 (Mth range: 10 – 30) and 19 (Qtly range: 8 – 30) (p=0.947). After 3 and 6 months of treatment, both groups had a significant reduction of MHD, MMD, AMP, HIT-6 and MIDAS scores, without statistically significant differences between the two groups (M3: p=0.335, p=0.318, p=0.560, p=0.805, p=0.217; M6: p=0.598, p=0.755, p=0.821, p=0.902, p=0.255). Three patients of the Qtly group reported AEs at M3 and one patient of the Mth group reported AEs at M6.

Discussion: Our real-life findings are in line with previous RCTs, showing that both patients treated with monthly and quarterly fremanezumab achieved clinical improvement after 3 and 6 months of treatment, with no significant AEs.

Conclusions: Fremanezumab effectiveness and safety is similar between the two dose regimens. Further real-life studies with a larger sample size are needed to confirm our results.

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NEUROCOVID

MUSK MYASTHENIA GRAVIS AFTER SARS-COV2 INFECTION IN A CMT PATIENT: A CASE REPORT

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Charcot-Marie-Tooth disease (CMT) is a genetic sensory-motor neuropathy, which affects peripheral nerves and leads to progressive weakness of extremities. Myasthenia gravis (MG) is an autoimmune disease in which autoantibodies are directed against post-synaptic complexes of proteins in the neuromuscular junction: mostly acetylcholine receptors (AChR) and in lower cases muscle specific kinase (MuSK) or LDL receptor related protein 4. It is well acknowledged that Sars-CoV2 infection may trigger a wide variety of neurological diseases. Several cases of MG have been described after Sars-CoV2 infection in the last two years. We report a case a MG triggered by Sars-CoV2 infection in a patient with CMT1 disease. A 20 years old woman with a CMT1 disease was referred to us with a generalized proximal muscle weakness, marked ophthalmoparesis, dysphagia, dysphonia and mild respiratory failure for which it was prescribed CPAP. Despite COVID vaccination, these symptoms had occurred one month after Sars-CoV2 infection and were markedly different from those experienced in CMT1 disease. In our Institution, blood tests were unremarkable; nerve conduction studies showed a polyneuropathy. Cerebrospinal fluid tests did not show albumin-cytological dissociation. Anti-ganglioside antibodies were negative. A brain MRI was unremarkable. As muscle weakness appeared fluctuating a neuromuscular transmission disorder was hypothesized. Repetitive nerve stimulation test performed to accessory nerve showed a decremental pattern with a typical U-shape. AChR antibodies were negative while MuSK antibodies assay was markedly positive: 19.42 nMol/l (<0.40: negative) and patient was diagnosed with MuSK MG. As patient's respiratory conditions worsened, orotracheal intubation and then tracheostomy were required. At the same time intravenous immunoglobulins were administered with mild benefits. A course of pyridostigmine was ineffective and then withdrawn. After the introduction of steroid and plasma-exchange patient's conditions improved. MuSK MG after Sars-CoV2 infection were described in a 77 years old man and a 24 years old women so far. This will be the third case. Even the co-occurrence of MG and CMT had been described in two cases so far. However, to our knowledge, this is the first case in which a co-occurrence of CMT and MuSK MG triggered by Sars-CoV2 infection have been described.

Sars-CoV2 may trigger many neurological conditions mediated by T-cell or B-cell. It is well acknowledged that MuSK MG is mostly a B-cell related disease mediated by IgG4. Despite the pandemic and scientific effort little is still known about neurological diseases after Sars-CoV2 infection and it warrants further studies.

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BILATERAL OPTIC NEURITIS AFTER AZD1222 COVID VACCINATION AND REVIEW OF LITERATURE

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Background: Optic neuritis (ON) has been described in COVID-19 infection disease [1]; ON has been observed to be the most common isolated inflammatory syndrome of the central nervous system (CNS) and most frequent serious ocular adverse event following vaccinations.

Objective: We report the case of a patient who developed a bilateral retrobulbar optic neuritis after exposition to Oxford/AstraZeneca ChAdOx1 (AZD1222) vaccine for COVID-19 and we reviewed scientific and grey literature.

Case report: A healthy female, two weeks after the first dose of inactivated virus vaccine (Oxford/AstraZeneca ChAdOx1), experienced headache and painful blurred vision worsened by movement in both eyes and decreased l vision acuity. The patient denied previously contracting COVID-19 or suffering from any COVID-19 typical symptoms and repeated nasopharyngeal swabs were negative. Brain CT scan and CT venogram intra- and extra-cranial showed no abnormalities. Neurological examination revealed bilateral loss of vision and decreased color perception and cephalalgia. On initial ophthalmology examination, she had a visual acuity of 6/10 in both eyes, with ring bilateral scotoma and normal-appearing optic nerves in both eyes. Optical coherence tomography was normal. Visual evoked potential observed bilateral latency delay (greater on the left eye). Brain and spinal magnetic resonance imaging revealed increased signal of the left optic nerve. Laboratory and sierological tests have not showed any active infection, autoimmune or paraneoplastic disorder. Determination of aquaporin 4 (AQP4)-IgG and MOG-IgG has been observed as negative. Cerebrospinal fluid (CSF) was normal, and no oligoclonal bands were found. Real-time PCR for neurotropic viruses was negative. A total body CT scan with contrast and a mammogram have been performed, and no neoplastic lesions and sarcoidosis granulomas have been observed; after treatment with methylprednisolone (1000 mg for 5 days), the patient's symptoms were greatly improved. Ophthalmologic revaluation with campimetry test and evoked visual potential reported a full recovery. The patient was then discharged with regular neurology follow-up and the diagnosis was "optic neuritic after recent AstraZenecaCOVID-19 vaccination." We have carried-out a review of literature and Elnhary et al. [2] described a female with unilateral ON after AstraZeneca vaccine. Alvarez et al. [3] in their series (69 ON) collected in 15 countries reported that most events (67%) occurred after vaccination with AstraZeneca.

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CLINICAL AND NEUROPHYSIOLOGICAL EVALUATION OF THE BRAINSTEM IN NON-COVID-19 AND COVID-19 PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

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Introduction: The aim of our study was to explore the brainstem function in patients with COVID-19 and non-COVID-19 Acute Respiratory Distress Syndrome (ARDS), by neurophysiologically assessing the Blink Reflex (BR) and the Masseter Inhibitory Reflex (MIR). BR and MIR share quite similar brainstem pathways, comprising the pons and medulla, which are directly (reticular activating system) or indirectly (reticular formation and nuclei of XI and XII cranial nerves) involved in respiratory control. To date, a comprehensive neurophysiological approach to the respiratory function of the brainstem is still lacking in humans.

Materials & Methods: 25 healthy volunteers (15 males, mean age 29.6 ± 10 years), 5 non-COVID-19 ARDS patients (4 males), and 9 COVID-19 ARDS patients (9 males, mean age 55.2 ± 7.1 years) were enrolled in the study. First, a Bayesian comparison of BR latencies (RI and RII) was performed in healthy volunteers undergone three different experimental conditions: normal breathing, maximal inspiration, and maximal expiration. Second, differences in RI and RII latencies were assessed among healthy volunteers, non-COVID-19 and COVID-19 ARDS. Finally, a Bayesian comparison was used to compare differences in silent periods (SP1 and SP2) onset latency and duration of the MIR between healthy volunteers and non-COVID-19 ARDS. The three groups were also analyzed with parametric comparisons, post-hoc t-tests.

Results: At the time of the clinical and neurophysiological assessment, no patient showed a pathological pattern of human-ventilator interaction. Among healthy subjects, a significant value emerged from the comparison between basal condition and maximal expiration for the latency of direct RII (BF10>3). Analyzing the three different groups of subjects, almost all the values from the Bayesian and parametrical comparison of the BR among healthy volunteers and COVID-19 ARDS patients were statistically significant (BF10>3 and p-value<0.05). There was no statistical evidence between the two groups of ARDS patients (BF10<3 and p-value>0.05) nor among healthy patients and non-COVID-19 ARDS subjects (BF10<3 and p-value>0.05, except for RI latencies, with BF10>3 and p-value<0.05). The examination of the MIR showed no statistical significance (BF10<3 and p>0.05).

Discussion: This is the first study evaluating possible neurophysiological changes in the brainstem functions of patients with ARDS, as well as differences between the inspiratory and expiratory phases in healthy controls.

Conclusions: Our data provide a neurophysiological involvement of the brainstem function in COVID-related ARDS, thereby playing a possible role in the acute respiratory failure as observed in these patients, but not in non-COVID ARDS.

MANAGING NEURO-COVID AND POST-INTENSIVE CARE SYNDROME SYMPTOMATOLOGY AMONG SEVERE SARS-COV2 SURVIVORS: THE EXPERIENCE OF THE FOLLOW-UP OUTPATIENT SERVICE TEAM FROM THE NORTH-WESTERN TUSCANY LOCAL HEALTH UNIT, LUCCA, ITALY

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Aims: There is growing evidence suggesting that severe SARS-CoV2 infection may crucially impact the morphological and functional characteristics of the Central Nervous System, with a subsequent detrimental effect on patients' cognitive status and overall functional abilities. Accordingly, a proper "Neuro-COVID" syndrome, with specific disease stages and features, has been described [1]. Plus, Post-Intensive Care Syndrome represents another critical issue which requires early detection and treatment in order to avoid severe cognitive and functional sequelae for patients who have undergone acute and intensive care and ventilator reliance [2]. Given such scenario, a systematic, multidisciplinary evaluation of post-intensive SARS-CoV2 survivors becomes mandatory. The present study aims at describing the implementation of the Follow-Up Outpatient Service by the multidisciplinary team of the North-Western Tuscany Local Health Unit based in Lucca, Italy, along the three main peaks of the SARS-CoV2 pandemic.

Materials: Seventy patients (M:F=53:17, mean age=60.43+9.42 years) were recruited and underwent a composite battery of physical, cognitive and psychopathological measures (including the Barthel Index, the Brief Cognitive Status Exam, the Hospital Anxiety and Depression Scale, and the Impact of Event-Scale-Revised), which was set up by a multidisciplinary team. The team was coordinated by a Neuropsychologist and an Intensivist and consisted of Neuropsychologists, Psychologists, Intensivists and Intensive Care Nurses.

Method: This is a prospective study. Follow-up screening evaluations were carried out jointly once a month on post-intensive SARS-CoV2 survivors, about three months after their hospital discharge.

Results: Specific acute and intensive care procedures (i.e., intubation, mechanic ventilation, and sedation) significantly correlated with specific subtests of the Brief Cognitive Status Exam, namely "Orientation" (that investigates semantic and episodic memory) and "Inhibition" (that assesses speed, visual scanning and selective attention), but not with psychopathological measures. Plus, the presence of delirium during hospitalization significantly correlated with anxiety and depression measures, on the one hand, and with subjective cognitive complaints and the overall Brief Cognitive Status Exam, on the other one. To end with, functional abilities at follow-up significantly correlated with depression measures and with cognitive performance at the Brief Cognitive Status Exam, concerning both overall and specific scores.

Discussion: During the visits, patients exhibited a wide range of physical, cognitive, and psychopathological symptoms, which in turn impacted their overall functional abilities.

Conclusions: Implementing a Follow-Up Outpatient Service for post-intensive SARS-CoV2 survivors may effectively contribute to the early detection of physical, cognitive, and especially functional decline, thus promoting a Public Health approach.

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NEUROLOGICAL DISORDERS THROUGHOUT ACUTE SARS-COV2 INFECTION: A COMPARATIVE STUDY BETWEEN VACCINATED AND NON-VACCINATED PATIENTS

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Background and Objectives: Neurological disorders have been largely associated with SARS-CoV-2 infection, but the role of vaccination on Covid-19 severity in neurological patients is still unknown. The aim of this study was to describe the clinical characteristics of breakthrough and unvaccinated cases, as well as to evaluate the progression to death or intensive treatments between vaccinated and unvaccinated Covid-19 patients hospitalized for neurological disorders.

Materials and Methods: In this retrospective study, we included all adult COVID-19 patients admitted to a Neuro-COVID Unit from January 2021 till February 2022. Demographic, clinical and laboratory data were extracted from medical records and compared between vaccinated and un-vaccinated patients.

Results: 232 patients were included in this study, of whom 158 un-vaccinated and 74 with a full-dose SARS-CoV2 vaccine. Breakthrough cases were older (years 72.4+16.3 vs 67.0+18.9 years, p=0.029), showed higher pre-morbid CIRS (1.59+0.3 vs 1.38+0.3, p<0.0001) and Clinical Frailty scale score (4.46+1.6 vs 3.75+2.0, p=0.008), and exhibited greater severity of inflammatory parameters, as expressed by C-reactive protein level. Nevertheless, unvaccinated subjects showed worse systemic parameters with no differences in terms of mortality rate (16.2% vs 15.2%) and number of ventilated patients, compared to full-dose vaccinated patients. Cox-regression analysis showed age and systemic parameters as the variables with a significant relation to mortality between the two groups, independently from pre-morbid conditions and inflammatory response.

Discussion and Conclusions: Full-dose vaccinated Covid-19 patients admitted for neurological disease were older, exhibited higher comorbidity index and inflammatory parameters compared to unvaccinated cases, with no differences regarding the progression to intensive treatments and death. Although vaccines are very effective at preventing severe cases of COVID-19, this study on breakthrough infection could help identify vulnerable neurological patients with higher risk of poor outcomes.

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POST COVID-19 TRANSVERSE MYELITIS SHOWS SUBTLE RADIOLOGICAL FINDINGS AND STEROID-RESISTANT COURSE: A CASE REPORT

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Background: Post COVID-19 acute transverse myelitis (ATM) is an uncommon neurological complication, with annual incidence ranging from 1.34 to 4.60 cases per million [1], characterized by acute or subacute spinal cord dysfunction, typically occurring after 15 days to 6 weeks from infection symptoms onset [2]. Due to its variability in MRI diagnostic characteristics and treatment response, post COVID-19 ATM management may be challenging. We report a case of post SARS-CoV2 infection myelitis with dissociation of clinical and neuroradiological picture, as well as treatment-resistance.

Case report: A 48-year-old man presented to our emergency department with subacute onset of paraparesis, lower body hypoesthesia, and urinary dysfunction. He was SARS-CoV2 unvaccinated and reported COVID-19 infection, occurred paucisymptomatically, started 10 days before the ATM onset. Infection was completely recovered when spinal cord syndrome started, documented by negative SARS-CoV2 RNA PCR nasal swab. His past medical history was unremarkable. Neurological examination evidenced gait difficulty, severe hypoesthesia with T4 sensory level and decreased proprioception in the legs. Magnetic resonance imaging (MRI) showed a very slight T2-hyperintensity at level T8-T9 with no contrast enhancement. Screening for autoimmune diseases (including anti-MOG, anti-AQP4 antibodies) and vasculitis was negative. Detailed microbiological screening in blood and CSF resulted unremarkable. CSF examination showed mild lymphocytic pleocytosis (11 mononucleated cells/μL), normal protein count and oligoclonal bands absent. High dose of intravenous (IV) methylprednisolone was administrated for 5 days, followed by slow tapering, with poor clinical response. After 20 days a lower limb strength worsening occurred, constraining the patient to use walking frame. Thereby, a new MRI scan was performed disclosing clear multiple short T2-hyperintensity (in C1, C3, C7-C8, T1-T2, T2, T3, T4, T5, T6, T7 metameres) with post-contrast enhancement. A new high dose IV steroid cycle was administrated, with no substantial clinical changes, hence the patient was treated with IV human immunoglobulins (IVIG) 0.4 g/kg for 5 days. A slight clinical improvement in his lower limb strength was observed, although sensory deficits and neurogenic bladder remained unchanged, and he was transferred to a neurorehabilitation hospital.

Conclusion: Our case points out two possible characteristics of post COVID-19 ATM which might make challenging the diagnostic and therapeutic management: 1) the clinical-neuroradiological mismatch which can occur at the onset; 2) the unresponsiveness to corticosteroids, which may be related to the short time lag between infection end and ATM start, assuming a residual activity of the virus.

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THE ROLE OF ANTITHROMBOTIC THERAPY IN COVID19 RELATED STROKE-PRELIMINARY OBSERVATIONS FROM CHIETI'S HOSPITAL

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Radiological data from patients with Covid19 infection and cerebral stroke show the involvement of multiple vascular territories and occlusion of large vessels. Hence the hypothesis of cardioembolism and thrombosis of large vessels as possible causes of stroke. The high inflammatory response found above all at the level of the vascular endothelium has led to the emergence of vasculitis and platelet hyperreactivity as a further mechanism. Finally, the concomitant presence of deep vein thrombosis rises the hypothesis of a paradoxical embolism, especially in young patients and without cardiovascular comorbidities. The objective of this study is to evaluate whether antithrombotic prophylaxis previously prescribed as secondary prevention can protect patients from the onset of stroke during Covid-19. We investigated a cohort of 240 patients with Covid 19 infection in the period between March 2020 and March 2021, identifying a subgroup of patients with cerebral ischemia. Demographic, clinical, radiological data (CT and MRI) and comorbidities, pharmacological therapies in progress were analyzed from this subgroup. Eleven patients (mean age 79 years, 2 men and 9 women) developed ischemic stroke, with an estimated prevalence of 4.5%. Among these 11 patients, 9 had severe lung disease by the time they developed stroke. A clear cardioembolic genesis was found in 4 patients, 1 had a vasculitic cause. The outcome was

unfavorable in almost 50% of cases. Among therapies in progress we found that: 2 patients treated with acetylsalicylic acid (ASA), 1 with a new oral anticoagulant (NOAC) plus ASA, 1 with warfarin, 2 with low molecular weight heparin (LMWH) at prophylactic dose (SA), 2 ASA plus LMWH at prophylactic dose, 1 LMWH at anticoagulant dose (BD), 2 untreated. Diabetes and hypertension were more common comorbidities in the Covid19 positive stroke population than in the general one (ie Covid19 positive population without stroke). LMWH SA is significantly more represented in the non-stroke group, suggesting a potential beneficial role in preventing stroke in Covid19 infected patients. ASA alone did not show any protective role against stroke development. We conclude that EBPM (SA) currently represents the most used and potentially more effective strategy for thromboprophylaxis of cerebral stroke than alone antiplatelet therapy. Hypertension and diabetes mellitus are the two comorbidities that tend to be most represented in the population of Covid-19 patients with stroke. Heparin therapy with an anticoagulant dose in selected hospitalized Covid19 patients (elevated D-dimer level) could be useful as a preventive strategy

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NEUROPSYCHOLOGICAL SYMPTOMS, PSYCHOLOGICAL WELL-BEING AND QUALITY OF LIFE MORE THAN ONE YEAR AFTER SARS-COV-2 INFECTION

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Aim: SARS-COV-2 infection has been associated to long-lasting neuropsychiatric sequelae [1]. Indeed, recent evidence suggests that neuropsychological deficits may still be observable after 1 year [2]. Here, in a sample of previous COVID patients, we investigate cognitive, psychological and quality of life-related profiles up to 18 months from hospital discharge.

Materials and Method: Out of 657 COVID patients screened at the Manzoni Hospital (Lecco), 22 were referred, following neurological evaluation, to neuropsychological testing because of subjective cognitive disturbances. Here, we report preliminary data in 12 patients (4 females, age range: 19-83) who completed a neuropsychological evaluation after 6 months (t0), 12 months (t1) and 18 months (t2) from hospital discharge. The evaluation at t0 included tests for memory, attention, and executive functioning. At t1 and t2, we additionally administered tests of computerized reaction times and speed of processing. Questionnaires for depressive (BDI) and PTSD-related symptoms (IES-R), as well as psychological well-being (PGWBI) and quality of life (WHO-QoL-BREF) were also administered. Repeated-measures, non-parametric analyses were carried out.

Results: According to the Equivalent Scores (ES) method or cut-off values, 42% of patients (n=5) at t0 and 33% of patients at t1 and t2 (n=4) showed pathological (ES=0 or below cut-off) or borderline scores (ES=1) in at least one cognitive domain. However, by introducing additional measure at t1 and t2, we highlighted pathological or borderline performances in 58% (n=7) of patients lasting up to 18 months after the infection. In particular, 3 patients showed slowed RTs. Non-parametric analyses highlighted an overall improvement, from t0 to t1, in visuospatial long-term memory ($p<.001$). From t1 to t2, we observed enhanced selective attention ($p<.001$), verbal long term memory ($p<.001$), speed at RTs ($p=.040$), and verbal shifting ($p=.019$). Moreover, from t1 to t2, we observed a reduction of depressive symptoms ($p=.038$) and a trend of reduction of PTSD-related symptoms ($p=.061$). Patients generally reported low psychological well-being (PGWBI) and decreased quality of life as compared to pre-pandemics, especially in the physical domain at t1 ($p=.011$) which remained stable at t2.

Discussion: In line with previous literature, despite some cognitive and psychological improvements, our preliminary data confirm that some patients may still show deficiencies in their cognitive profile associated with reduction of quality of life and psychological well-being over 1 year after COVID-19. Here, we highlight that the psychological profile and quality of life should be considered besides cognitive testing.

Conclusions: Long-term neuropsychological and psychological monitoring is advised.

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COVID-19 NEUROPATHOLOGY: EVIDENCE FOR SARS-COV-2 INVASION OF HUMAN BRAINSTEM NUCLEI

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Objectives: Neurological manifestations are common in COVID-19, the disease caused by SARS-CoV-2. Despite reports of detection of SARS-CoV-2 in the brain and cerebrospinal fluid of COVID-19 patients, it's still unclear whether the virus can infect the central nervous system, and which neuropathological alterations can be ascribed to viral tropism, rather than immune-mediated mechanisms. In the present study, we assess the neuropathological alterations occurring in COVID-19 subjects deceased during the acute stages of the disease and compare these findings with the neuropathological alterations occurring in pneumonia / respiratory failure patients.

Materials: 24 COVID-19 patients and 18 sex- and age-matched controls who died due to pneumonia / respiratory failure were included in the study. Clinical and demographical data was retrospectively obtained. The brain was sampled and underwent extensive neuropathological sampling, with particular focus on the brainstem.

Methods: Immunoperoxidase and immunofluorescent staining for 20 different antibodies (CD3, CD20, CD61, CD68, TMEM119, HLA-DR, pTAU, Beta-Amyloid, Beta-III Tubulin, GFAP, ACE2R, TMPRSS2, etc) was performed to assess the neuropathological alterations and two SARS-CoV-2 specific antibodies were employed to assess viral tropism. RT-PCR analyses for SARS-CoV-2 genomic sequences was performed to complement these findings. Morphometrical evaluation of brainstem regions of interest was performed to asses microglial activation and density.

Results: Aside from a wide spectrum of neuropathological alterations, including hypoxic/ischemic damage, perivascular lympho-monocytic cuffing and other aspecific findings, SARS-CoV-2-immunoreactive neurons were detected in the vagal nuclei of the medulla and in the substantia nigra of 5 COVID-19 subjects. Viral RNA was also detected by real-time RT-PCR. Quantification of reactive microglia revealed an anatomically segregated pattern of inflammation within affected brainstem regions, and was higher when compared to controls.

Discussion: These findings suggest that while acute fatal COVID-19 is characterized by neuropathological alterations, such as hypoxic / ischaemic

damage, microthromboses and microgliosis, mediated mainly by systemic infection and the ongoing cytokine storm, SARS-CoV-2 neurotropism is a possible, yet not frequent, consequence of infection without immediately appreciable neuropathological alterations, at least in the acute phases of the disease.

Conclusions: These findings indicate the need to further investigation of the role of SARS-CoV-2 neurotropism in the general population, not only in severe / fatal COVID-19 cases, including whether SARS-CoV-2 neurotropism may determine specific neuropathological sequelae in cases of prolonged infection or in patients suffering from the long-term effects of COVID-19.

COGNITIVE DEFICIT IN POST-ACUTE COVID-19: AN OPPORTUNITY FOR EEG EVALUATION?

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Aim: Among the most common post-COVID symptoms, many patients experienced subjective cognitive deficit, commonly named brain fog, that might be present also in those individuals without severe acute COVID-19 respiratory involvement. Some studies have investigated some of the mechanisms that might be associated with the brain fog with objective techniques including transcranial magnetic stimulation and neuroimaging. Aim of this study was to investigate the presence of electroencephalographic (EEG) alterations in people with post-COVID self-reported cognitive deficit.

Materials and Methods: Out of the 90 patients attending the post-COVID neurology ambulatory service, twenty patients presenting brain fog at least 4 weeks after acute non-severe COVID-19 infection, and without previous history of epilepsy, were investigated with 19-channels EEG, Montreal Cognitive Assessment (MoCA), and magnetic resonance imaging (MRI).

Results: EEG was found altered in 65% of the sample, among which 69% presented a slowing activity and 31% were characterized by epileptic discharges principally in the frontal areas. None of the patients showed DWI MRI lesions.

Conclusions: These findings highlight the usefulness of EEG analysis to objectively describe possible neurophysiological abnormalities in post-COVID patients presenting subjective cognitive deficit.

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NEUROLOGICAL LONG-COVID IN THE OUTPATIENT CLINIC: TWO SUBTYPES, TWO COURSES

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Introduction: Symptoms referable to central and peripheral nervous system involvement are often evident both during the acute phase of COVID-19 infection and during long-COVID. In this study, we evaluated a population of patients with prior COVID-19 infection who showed signs and symptoms consistent with neurological long-COVID.

Methods: We prospectively collected demographic and acute phase course data from patients with prior COVID-19 infection who showed symptoms related to neurological involvement in the long-COVID phase. Firstly, we performed a multivariate logistic linear regression analysis to investigate the impact of demographic and clinical data, the severity of the acute COVID-19 infection and hospitalization course, on the post-COVID neurological symptoms at three months follow-up. Secondly, we performed a k-means clustering analysis to investigate whether there was evidence of different subtypes of neurological long COVID-19.

Results: Clustering analysis on the five most common neurological symptoms returned two well-separated and well-balanced clusters: long-COVID type 1 contains the subjects with memory disturbances, phycological impairment, headache, anosmia and ageusia, while long-COVID type 2 contains all the subjects with reported symptoms related to PNS involvement. The analysis of potential risk-factors among the demographic, clinical presentation, COVID 19 severity and hospitalization course variables showed that the number of comorbidities at onset, the BMI, the number of COVID-19 symptoms, the number of non-neurological complications and a more severe course of the acute infection were all, on average, higher for the cluster of subjects with reported symptoms related to PNS involvement.

Discussion: With reference to what is reported in the literature, we researched the potential pathogenetic mechanisms of the symptoms reported by the patients. Memory disturbances, phycological impairment, headache, anosmia and ageusia seem to be related to the presence of SARS-CoV-2 per se and to a direct mechanism of damage, while the involvement of the PNS seems to require an additional damage, either by immune-mediated or iatrogenic mechanism.

Conclusion: Neurological involvement during the acute phase of COVID-19 is frequent and multifaceted and can lead to disabling disorders that persist for many months, the so-called long-COVID. Some neurological complications result from the direct action of the virus, whereas in other cases complications are related to long hospitalization.

NEUROLOGICAL AND MENTAL HEALTH SYMPTOMS ASSOCIATED WITH POST-COVID-19 DISABILITY IN A SAMPLE OF PATIENTS DISCHARGED FROM A COVID-19 WARD: A SECONDARY ANALYSIS

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Aim: This study aims to address the impact of a set of new-onset neurological and mental health symptoms on post-COVID-19 disability.

Materials: A total of 83 COVID-19 survivors, without pre-morbid brain conditions, completed the following instruments approximately three months after hospital discharge: the 12-items WHO Disability Assessment Schedule (WHODAS-12), herein used as a primary outcome, the Hospital Anxiety and Depression Score, the Pittsburgh Sleep Quality Index, the Montreal Cognitive Assessment, a standardized medical and neurological symptoms checklist, and a neurological examination.

Method: Neurological and mental health symptoms, assessed through the questionnaires used in the protocol, were considered as variables of interest to address disability variation. The ability of each variable to explain WHODAS-12 score variation was tested in a univariate regression model and only significant variables were retained for a subsequent multivariate model. Specifically, the retained variables were analysed with a backward procedure.

Results: The most common symptoms at follow-up were sleep disturbances, cognitive dysfunctions, and fatigue. As for the impact of neurological and mental health symptoms on disability level, our results showed that cognitive dysfunction, anxiety, fatigue, and hyposmia/hypogeusia explained 28.8% of WHODAS-12 variation.

Discussion: A previous study [1] has shown that COVID-19 survivors, in addition to reporting long-term symptoms, described persistent functional limitations and reduced quality of life. In line with other studies, our results added evidence on post-COVID-19 brain-related symptoms as potential drivers factor of disability. It is therefore essential to provide early medical and neurorehabilitative interventions, necessary for the recovery of long-term improvement and functional independence of patients. Rehabilitation interventions for anxiety, fatigue, cognitive dysfunction, and hyposmia could affect about a third of the disability found in COVID-19 survivors. Hence the importance of promptly highlighting and treating such symptoms to limit the consequences on the functioning of the individual. For instance, cognitive dysfunctions such as memory deficit are associated with an increased risk of future cognitive deterioration [2], as well as anxiety has a strong impact on the disability level of the general population [3].

Conclusions: In summary, our study found that the high prevalence of long-term neurological and mental health symptoms affects the disability and functioning of COVID-19 survivors, predicting almost one-third of WHODAS-12 variation. These findings highlighted the need for longitudinal follow-up assessments in patients and an early comprehensive rehabilitation system, allowing the COVID-19 survivors to restore their level of health and functioning.

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NEURO-LONG-COVID: A PROPOSAL FOR THE MANAGEMENT OF MEMORY IMPAIRMENT AND COGNITIVE DEFICITS IN A NEUROLOGY AMBULATORY SERVICE

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Background: Brain fog, minor memory impairments and difficulty in focusing are frequent symptoms reported after an acute phase of COVID. This subjective cognitive impairment has been referred as quite disabling, therefore neurological visit requests are booming. A new challenge for physicians is to identify these patients and direct them to the correct diagnostic logarithm. Nevertheless, no guidelines or management protocol have yet been provided for post-COVID-19 cognitive impairment.

Objective: The aim of this paper is to evaluate the main differential diagnoses of the post-COVID neurocognitive deficits and to identify a list of diagnostic investigations for these patients.

Methods: For each patient we collected anamnestic data, performed a neurological physical examination and evaluated each patient by submitting a MoCA. We took blood samples to have a complete view over co-existing pathologies (i.e., hypothyroidism, vitamin deficits). For the patients with a cognitive deficit confirmed by a neurologist, we suggested a neuropsychological evaluation to better focus on the impaired cognitive domains. Additionally, each patient has been screened by a trained psychologist to evaluate co-existing psychological discomfort. A brain MRI and an EEG have been proposed to exclude brain tumor, acute ischemic, hemorrhagic or inflammatory lesions and also epileptic abnormalities. Those people performing a low MoCA (<26) and confirmed at the neuropsycological evaluation have been recommended to undergo a cerebral PET/CT scan with FDG. A follow-up neurological visit has been performed after 3 to 6 months.

Results: Since January 2021, 323 patients have been reported for Long-COVID symptoms to the neurology outpatient service of Trieste. Within 30 days, 323 patients have been evaluated by a dedicated neurologist and 83 patients have been assessed for cognitive deficits. All 83 subjects have been screened with blood samples, MoCA test and psychological screening interview. So far, 55 brain MRIs and 58 EEG have been performed demonstrating the absence of brain tumor, acute vascular or inflammatory lesions and epileptic abnormities. 70 patients have been evaluated by the neuropsychologist and a third of them have undergone 10 sessions of cognitive training. 11 patients with persisting severe cognitive discomfort or scoring a pathological neuropsycologial assessment have carried out cerebral PET/CT.

Conclusion: Our protocol allows to promptly take into account Long-COVID suffering neuro-cognitive symptoms as to exclude the most frequent differential diagnosis. A timely response to the suffering of these patients seems to relieve their psychological discomfort and could be cost-effective for the health care system.

TWO YEARS' EXPERIENCE OF A SHORT STAY DEDICATED NEUROLOGICAL EMERGENCY UNIT (OBI-NEURO)

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Introduction: Acute neurological symptoms are responsible for 5-15% of referral to the Emergency Department (ED). Since the COVID-19 outbreak, our stroke network shifted toward a mothership model with direct transport of stroke patients to the Comprehensive Stroke Center ("M. Bufalini" hospital, Cesena, Italy). On March 2020 the Neurology service opened a four-bed Short-Stay Neurological Observation Unit ("OBI Neuro") to handle the increase in referrals due to mothership model and guarantee a neurological fast-track in the setting of a covid overcrowded emergency department. The OBI Neuro started as a 24hour/7 days service with a dedicated nurse also involved in the management of the acute phase of stroke patients (stroke team).

Methods: Patients treated in OBI Neuro from 15 March 2020 to 15 March 2022 were collected and retrospectively analyzed in terms of

admissions, discharge destinations, diagnosis (admittance and discharge), mean length of stay, readmission within three months

Results: Almost 1200 patients were managed in the OBI Neuro. Mean age was 65 yo and 1:1 F/M ratio. 58.8% of patients were discharged at home while, 0.6% denied hospital admission and 40.6% were admitted to a neurological or non neurological department. The most common diagnosis was cerebrovascular disease (40%), seizure (24%), headache (6.4%), transient global amnesia (4.8%) and other than neurological diagnosis (14,6%). Mean length of stay in OBI Neuro was 19.3 h (SD 33.0). Admittance to the OBI Neuro was during day shifts (h8-20) for 69.2% of patients while 30.8% of patients were admitted during the night. Readmission at three months in ED occurred in 5.4% of cases, 25% of them was due to neurological symptoms. In one case we performed thrombolysis for a stroke occurred during the observation period. We also managed neurologic patients with asymptomatic COVID infection.

Conclusions: OBI Neuro has shown to be feasible and helpful to reduce the burden of neurological patients in ED setting during COVID-19 pandemic. Moreover it was strategic for the management of stroke referrals in the mothership model. Finally it contributed to ameliorate the performances of intra-hospital stroke pathway (data previously published).

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CAN COVID-19 INDUCE LONG-LASTING COGNITIVE IMPAIRMENT WITH BRAIN AMYLOID DEPOSITION? CASE REPORT

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Objective: To assess long term cognitive status, the brain metabolism and the presence of Aβ plaques after COVID-19

Methods: A 65-year-old man, who had been hospitalized for COVID-19 and showed neuropsychological deficits after 12 months from hospital discharge, was recruited.

Material: Patient received neuropsychological assessments 5 (T1) months and 12 (T2) months from hospital discharge using the Brief Repeatable Battery of Neuropsychological Tests (BRB-NT) and Montreal Cognitive Assessment (MoCA). We assessed also the presence of depressive symptoms with the Beck's Depressive Inventory-II (BDI-II). Demographic and clinical data were collected to characterize patient and describe his clinical course. Since clinical assessment suggested a progressive neurocognitive impairment, the patient was referred to the Nuclear Medicine Unit to assess the status of brain glucose metabolism, using 18F-FDG PET/CT and 18F-amyloid PET/CT order to assess the presence of Aβ plaques.

Results: After discharge, cognitive assessment revealed a MoCA test of 26.11/30 at T1 and 23.11/30 at T2. Neuropsychological assessment at T1 revealed deficit in Spatial Recall Test (SPART) (10.62), Symbol-Digit Modalities (SDMT) (29.53), Spatial Recall Test – Delayed recall (SPART-D) (3.56) Serial Recall Test – Delayed recall (SRT-D) (4.88) and at T2 SDMT (37.53) SRT-D (4.88), showing that processing speed and verbal memory were still impaired after one years from hospital discharge. Also, patient showed a worsening in depression symptoms from mild to moderate (T1: BDI-II=11; T2 BDI-II=20). Scans showed a significant reduction of FDG uptake in the left mesial temporal cortex. 18F-flutemetamol PET/CT showed significant Aβ deposition in the superior and middle frontal cortex, in the posterior cingulate and, with lesser extent, in the rostral and caudal anterior cingulate.

Discussion: A growing body of evidence [1] suggested the potential SARS-CoV-2 neurological injury [2] that could lead to the development of neurodegenerative diseases, including Alzheimer's Disease (AD). Several studies have established a causal relationship between an inflammatory state and neurodegeneration. Though we cannot rule out the possibility of a pre-existing AD, our case rises the challenging question whether focal hypometabolism on FDG-PET arises from brain amyloid deposition triggered, or favoured by COVID19

Conclusion: Cognitive impairment is a long-term complication of COVID-19 [3]. It's possible correlation with amyloid-related cognitive impairment need to be carefully explored in the next years.

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SIMPLE REACTION TIME AFTER COVID-19

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Objectives: To investigate long term effect of COVID-19 on speed processing.

Materials: 308 volunteers (mean age: 38.75 ± 13.06 years, 235 women) recovered from COVID-19 answered an online psychological and cognitive test. We gathered demographic (biological sex, age, education), clinical data (date of COVID-19 diagnosis and severity, comorbidities, drug assumption), persisting symptoms after COVID-19 and Reaction Times (RTs).

Methods: An ad hoc simple RTs Task was designed for online completion. Furthermore, to evaluate self-perceived repercussions of persisting symptoms on activities of daily living, we administered a self-report scale comprise of 24

questions assessing: physical symptoms (headache, fatigue, vertigo/balance impairments, visual or hearing impairment, variation in appetite, sense of taste and/or smelling, nausea, fainting, muscular pain), psychological condition (concern, irritability, sleep quality, mood, anxiety), and neuropsychological condition (memory, attention, learning, concentration and linguistic competency). The severity of each symptom was assessed via a 5-point Likert-type scale (0 = None, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe). We tried to characterize a regression models able to account for participants' RTs performances.

Results: Patients reported symptoms such as fatigue (90%), headache (70%), photophobia (55%), pain (58%), memory issues (59%), difficulties in processing new information (50%), attention problems (60%), problem in all day live activities (51%), language problems (65%), low mood (65%), irritability (50%), concerns. Patients showed lower RTs in the months following recovery (RTs [mean ± SD] = 667 ms ± 652 ms), compared to data from studies on the general population [1]. A positive correlation was found between RTs and days elapsed between COVID-19 infection and the date of the test ($r = 0{,}161$, $p < 0{,}05$). ANCOVA found a significant effect of "Intensity of headache" on RTs $F(3, 303) = 6.55$, $p < 0.001$. Post-hoc testing with Bonferroni correction revealed that subjects with severe headache were significantly slower compared to those with none, mild and moderate ($p < 0.001$) headache. Pearson's Correlations revealed a small correlation between RTs performances and the level of "Concern" ($r = 0.11$, $p = 0.047$).

Discussion: To date it is known that headache can deteriorate the performance on RTs [1]. The pain caused by COVID-19 infections may be the cause of attention and speed processing deficits lasting for months after recovery [2] with repercussions on activities of daily living. Additionally, pain due to headache can play a strong role on RTs performance.

Conclusions: Here, we found that presence and intensity of headache, as physical symptom, is a significant predictors of speed processing abnormalities in subjects recovered from COVID-19. Decreased speed processing after recovery can interfere with work and daily activities.

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CHANGE IN ADMISSION INTO HOSPITAL OF NEUROLOGICAL DISEASES BEFORE AND AFTER PANDEMIC PERIOD IN LOMBARDIA

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Objectives: The aim of this work is to analyse the change in frequency of hospital admissions for different neurological diseases in relation to the COVID-19 pandemic in a region severely hit by it, Lombardia.

Materials and methods: We took advantage of the codes of discharge from hospital to compare the frequency of different diseases including cerebrovascular diseases (ischaemic and haemorrhagic stroke, TIA, sinus venous thrombosis) and autoimmune neurological diseases (myasthenia, poly and dermatomyositis, NMOSD, multiple sclerosis, myelitis, encephalitis, arteritis) before (from 2017 to 2/2020) and during the pandemic (3/2020-12/2021) in Lombardia region. A Chi-square analysis was performed to compare frequencies in the pre-pandemic versus pandemic period. OR and 95% CI are presented.

Results: Despite an overall decrease in hospital admittances which affected all non-COVID diseases over the investigated period, a statistically significant increase in admission into hospital for ischaemic stroke (OR: 1.11, 1.09-1.12), haemorrhagic stroke (OR: 1.23, 1.19-1.26) and thrombosis of cerebral veins (OR: 1.72, 1.42-2.08) was detected, while TIA were reduced in frequency (OR: 0.94, 0.91-0.98). As of neurological inflammatory disorders, a significant increase of encephalitis was found (OR: 1.19, 1.09-1.30), while Multiple Sclerosis (MS) (OR: 0.83, 0.79-0.86), NMOSD (OR: 0.69, 0.55-0.86), and myasthenia (OR: 0.89, 0.85-0.95) were reduced in frequency.

Discussion and conclusion: The effect of pandemic event resulted in a reduction in admissions into hospital of inflammatory neurological disorders like MS or myasthenia which were probably treated at home and of milder phenotypes like TIA which were under referred to hospital or directly discharged from the emergency departments. On the contrary, there was an increase of cerebrovascular disease admissions. Analysis of risk factors contributing to this increase suggests that COVID19 infections were associated to this increase. It is also plausible that the vaccination partially influenced this pattern.

DOES GENDER INFLUENCES OUTCOME OF STROKE IN COVID + AND COVID - PATIENTS: A LARGE COLLABORATIVE STUDY IN NORTHERN ITALY

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Objectives: The impact of the COVID19 pandemic during the first wave in Italy caused a decrease of hospital admissions, delays in reperfusion treatments and an overall worse outcome in COVID+ patients with stroke. However, few data are available on outcome of stroke stratified by gender.

Materials and methods: A multi-center observational study on neurological complications in COVID-19 patients was conducted in 19 Neurology Units by the Italian society of Hospital Neuroscience (SNO). Adult patients admitted to Neurological units between March-April 2020 with ischaemic stroke were recruited. Demographic, clinical, treatment and outcome data were compared in patients with (COVID19+) and without COVID19 (COVID19-), as well as in male and female patients.

Results: 812 patients with ischemic stroke were enrolled (682 COVID-, 129 COVID+); males were 54.1% and 52.7%. Intra-hospital mortality

was 31.9% in COVID+ patients (38.6% in male and 27.8% in female) and 7.2% in COVID- (8.4% in male and 6% in female patients). Male patients with COVID+ were more likely to have cPAP (30.9% vs 14.8%; p=0.03) or being intubated (14.9% vs 3.3%; p=0.02) than females. Reperfusion treatment was administered more frequently in women if COVID- (34.5% vs 29.8%), while less frequently if COVID + (11.5% vs 29.4%; p=0.01). COVID+ patients had a higher frequency of ESUS than COVID- (31.8% vs 22.3%; p=0.02), with a higher frequency in COVID+ females compared to males (36.1% vs 27.9%).

Discussion and Conclusions: Our study detected some differences due to gender in ischaemic stroke with and without COVID19 infection. Multivariate analyses is ongoing to define predictors of mortality across gender categories.

PERSISTENT COGNITIVE COMPLAINTS AFTER COVID19: A PROXY FOR A MALADAPTIVE RESPONSE TO AN APPLIED STRESSOR IN THE UNIQUE PANDEMIC ENVIRONMENT?

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COVID-19 pandemic has been an unprecedented challenge for our global society. The high symptomatic burden of acute infection is frequently followed by post-acute sequelae, often including cognitive and neuropsychiatric complaints. We aimed to describe persistent cognitive and/or neuropsychiatric symptoms reported after SARS-CoV-2 infection. 167 consecutive subjects, referred to the neurologist office by the infectious disease department for cognitive complaints. Each subject underwent cognitive screening with the Montreal Cognitive Assessment. A sample of enrolled patients also completed a detailed symptomatic questionnaire and testing of psychiatric comorbidities through validated self-administered scales (including the Impact of Event Scale revised, IES-r). As of March 31, 2022, 167 patients have been referred to our service, after an average of 11.9±5.4 months from acute infection. Mean cognitive symptoms duration was 14.7±5.4 months from positive nasopharyngeal swab. Among persistently reported symptoms, the most common were fatigue (92%), sleep problems (69.5%) and headache (52.4%). Severity of acute infection was low for most patients, with approximately 51% treated in outpatient settings and only 8.5% of cases requiring ICU admission. Most patients had infection early in the pandemic period (46% in the first wave, 40% in the second, 13% in the third). MoCA outlined cognitive deficits in at least one cognitive domain in 34% of patients, with commonly affected domains being memory and attention (alone, in 26% and 8% of cases, or combined in 11%). Among the 80 patients who completed the additional questionnaire, about 56.3% resulted affected at a clinical level by either depression, anxiety or post-traumatic stress disorder (42% anxiety, 42% depression, 43% stress). In linear regression models, MoCA scores and cognitive symptom duration were significantly correlated with single and aggregated scores on psychiatric scales (especially IES-r total scores, which reports on post-traumatic stress disorder) while no correlation was found between either variable and acute infection severity. In our cohort, cognitive complaints encompassed mainly memory and attention, confirmed by MoCA findings in a significant proportion of cases, and are often associated with mild acute infection syndromes and a high proportion of psychiatric comorbidities. Cognitive complaints and MoCA scores correlated significantly with psychopathological and post-traumatic stress burden, while no correlation was found with infection severity. We postulate that persistent cognitive complaints after COVID-19 might be the expression of a deeper overtly clinical or subclinical traumatic process, brought about by the experience of infection within the unique pandemic context.

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ALTERATION OF GABAB INHIBITION AND SPARING OF GABAA, CHOLINERGIC AND GLUTAMMATERGIC REGULATION IN NEURO-LONG-COVID BRAIN FOG

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Aim: By means of transcranial magnetic stimulation of the M1 cortex in Neuro-Long-Covid patients with sub-optimal performance in executive functions, we investigated the functional state of GABA, Glutammate and Acetylcholine regulation.

Materials: We enrolled 18 patients complaining of cognitive impairment who have been visited in our Neuro-Long-Covid outpatient service and 21 healthy controls (HC) among the hospital personnel. Inclusion criteria were: subjective cognitive impairment or a sub-optimal performance in executive-functions at the tests. Methods: we performed transcranial magnetic stimulation (TMS) of the motor (M1) cortex in all the patients and the HC, evaluating resting motor threshold (RMT), median amplitude of the motor evoked potential (MEP), short intra-cortical inhibition (SICI), intra-cortical facilitation (ICF) and long intra-cortical inhibition (LICI) and short-afferent inhibition (SAI) in the subjects.

Results: Eighty-three % of the patients (15/18) were found to perform sub-optimally either in the executive sub-items of the MoCA or in the neuropsychological assessment. The RMT and baseline MEPs of the patients and the HC were comparable. Compared to HC, the patients showed a reduced amount of inhibition in LICI (p=0,025). SICI, ICF and SAI were not found to be significantly different between the two groups.

Discussion: A recent study found LICI and SAI to be abnormal in Neuro-Long-Covid [1]. SAI reflects a cholinergic regulation and has been described to be altered in Alzheimer's disease and Lewy Body Dementia [2]. On the other hand, LICI is regulated by GABAb. Its alterations have been linked to Fronto-temporal Dementia [2]. Our findings confirm the alteration of GABAb inhibition and show cholinergic inhibition to be spared.

Conclusion: Our study suggest that GABAb inhibition, rather than GABAa, cholinergic or glutammatergic regulation, might functionally underlie Neuro-Long-COVID impairment in executive processing.

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SEX-DEPENDENT CHARACTERISTICS OF NEURO-LONG-COVID: DATA FROM A DEDICATED NEUROLOGY AMBULATORY SERVICE

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Aim: "Long-COVID" is a clinical entity that consists of persisting post-infectious symptoms that last for more than three months after the onset of the first acute COVID-19 symptoms. Among these, a cluster of neurological persisting symptoms defines Neuro-Long-COVID. Sex differences have been individuated for both the acute and the chronic stage of the infection.

Materials: Demographic and clinical data were collected in a specifically designed Neuro-Long-Covid outpatient service.

Methods: We conducted a retrospective study describing sex differences in a large sample of patients with Neuro-Long-COVID.

Results: Our sample included 213 patients: 151 were females and 62 were males; no significant differences was present between the demographic features across the two groups. Despite the prevalence of the specific chronic symptoms between male and females showed no significant differences, the total number of females accessing our service was higher than that of males, confirming the higher prevalence of Neuro-Long-COVID in female individuals. Conversely, a worse acute phase response in males rather than females was confirmed by a significant difference in the rates of acute respiratory symptoms (p=0,008), dispnea (0,018) and respiratory failure (0,010).

Discussion: The existence of a "female effect" in the pathogenesis of Long-COVID has been recently debated [1]. The fact that more women than males accessed our outpatient service could reveal higher awareness in females when it comes to one's own body and its alterations compared to males [1]. However, this is unlikely to be due solely to gender-related psychological factors [1]. The role of sex hormones in determining stronger immune responses has been described [2]. This is reflected by higher rates of autoimmune diseases in females as opposed to males [3].

Conclusion: Taken together, these findings offer a subgroup analysis based on sex-dependent characteristics, which can support a tailored-medicine approach.

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THE NEUROPSYCHOLOGICAL ASSESSMENT OF NEURO-LONG-COVID SHOWS A MULTI-DOMAIN INVOLVEMENT WITH A FRONTAL-DYSEXECUTIVE EPICENTRE

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Aim: "Long-COVID" is a clinical entity that consists of persisting post-infectious symptoms that last for more than three months after the onset of the first acute COVID-19 symptoms. Among these, a cluster of neurological persisting symptoms defines Neuro-Long-COVID. Low mood, anosmia and "brain fog", i.e. minor memory impairments and deficits in focusing, have been reported. We conducted a retrospective study describing the results of a full neuropsychological assessment in a large sample of Neuro-Long-COVID patients complaining of cognitive impairment.

Materials: Demographic and clinical data were collected in a specifically designed Neuro-Long-Covid outpatient service.

Methods: The patients complaining of cognitive impairment were subministered a MoCA test. In case no neurological or psychiatric comorbidity was detected, they underwent a full neuropsychological examination.

Results: Our sample included 74 patients. The mean MoCA corrected score was 23.41 (standard deviation 2,52). The mean score for none of the neuropsychological tests was pathological. In the executive functions domain, 48.14%, 62.96% and 88.88% of the patients totalized scores that were lower than those corresponding to the 5th, the 20th and the 50th percentile, respectively, of a healthy population according to the normative data. The nine percent, 26.38% and 44.44% of the patients in our sample totalized scores inferior to those corresponding to the same percentiles in the memory domain. Similar patterns were seen in the visuo-spatial (15.00%, 31.00%, 52.00%) and in the language domain (12.94%, 12.94%, 53.70%). These findings describe a global impairment of cognitive performances in the post-infective stage of COVID19 infection.

Discussion: A dysexecutive syndrome in the chronic post-COVID19 infection has been previously described [1]. We confirm that, despite affecting also memory and language, Long-Covid correlated cognitive impairment mainly involves executive functions. Key areas for executive processing are located in frontal lobes of the brain [2]. Covid19-correlated deficits in executive processing have been linked to functional alterations in frontal lobe metabolism in a early timeframe since the onset of the infection [3].

Conclusion: Our findings aligns to the emerging view that cognitive impairment in Long-Covid might be explained by a functional impairment of the frontal regions of the brain.

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DEFINITION OF PERSISTENT COGNITIVE IMPAIRMENT AFTER COVID-19: A SCOPING REVIEW

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Aim: A significant number of COVID-19 patients are reported to have persistent symptoms, including delayed-onset neurological and cognitive manifestations, for variable periods of time after clearance of infection by SARS-CoV-2. We aimed to review the literature about the various definitions employed to describe syndromes following COVID-19 acute illness, in terms of symptoms,

their timing of onset and duration, with a specific interest in cognitive symptomatology.

Materials: A scoping review of the medical literature was conducted on Pubmed on March 11, 2022. The following search string was devised and employed to find any published article that pertained chiefly to neurological or cognitive symptoms/syndromes started during or after COVID-19 infection: (neurocovid*[Title/Abstract]) OR (neuro-covid*[Title/Abstract]) OR (neuro*[Title/Abstract]) OR (neurocog*[Title/Abstract]) OR neuro covid*[Title/Abstract]) AND (COVID-19[MeSH Terms] OR covid 19[MeSH Terms]) AND (cogn*[Title/Abstract] OR neurocog*[Title/Abstract]).

Methods: Abstracts and full texts were assessed for relevance in a two-person cooperative review using Covidence systematic review software. Any conflict was discussed and resolved by consensus. Data were then extracted focusing particularly on specific terminology employed, type of symptoms displayed, timing of onset and duration.

Results: As far as terminology is concerned, the cognitive syndrome following COVID-19 infection has been variously termed: approximately 27% of the included studies used the terms "neuro-COVID", "long COVID" or "post-COVID syndrome/condition". In some studies, "post-acute COVID-19" was also used. In other studies, "long COVID" or "post-acute sequelae of SARS-CoV-2 infection (PASC)" are considered equivalent. As far as symptomatology is concerned, mostly reported symptoms include dyspnea, fatigue, brain fog/confusion, palpitations, cognitive deficits (memory complaints, difficulties in word finding or concentrating), and anosmia/hypogeusia. Symptomatology appears on average between 4 and 12 weeks after SARS-CoV-2 infection and has most frequently a duration of at least 12 weeks.

Discussion: All employed definitions refer to a variable, often vaguely defined, plethora of symptoms after initial infection primarily encompassing pulmonary, cardiac, gastrointestinal, and cognitive manifestations. Specifically, only the term "neuro-COVID" was used in reference chiefly to neurological or cognitive manifestations, but also in this case even symptoms with a vague neurological origin were often included in these descriptions.

Conclusion: There is no universal definition or label for the prolonged post-COVID syndrome, as this has not even been equivocally defined. Such definition is strictly necessary both to correctly classify and enroll patients in clinical studies that investigate post-COVID sequelae, and possibly to approach treatment strategy to alleviate their symptoms burden.

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NEURAL BASES OF FATIGUE IN LONG-COVID SYNDROME

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Objectives: Fatigue is a frequent and long-lasting symptom after Sars-Cov2 infection. Despite its clinical relevance, to date, however, its neural bases are poorly understood. In this study, we thus decided to use brain FDG-PET imaging to explore the relationship between perceived fatigue levels and brain metabolism in subjects with long-COVID syndrome.

Methods: 18 subjects (age: 67.0 +/- 8.3 years; 10 females), who presented with Sars-Cov2 without need for hospitalization, were assessed with a validated questionnaire for fatigue (i.e. the short modified fatigue impact scale-sMFIS[1]) and underwent a FDG-PET brain scan at least six months after the resolution of COVID infection. PET images were processed using the SPM12 pipeline to assess the correlation between MFIS scores and regional metabolism, after controlling for inter-individual differences in sex and age. Results surviving a p value of 0.001 uncorrected at the voxel level and of 0.05 FWE corrected at the voxel level, were considered significant.

Results: sMFIS score were 9.1 +/-3.2. The voxel-wise correlation of MFIS scores with brain metabolism revealed a single significant cluster in the left temporal pole, with subjects with a lower relative metabolism showing higher levels of perceived fatigue.

Discussion and conclusions: After Sars-Cov2 infection, perceived fatigue is associated with regional metabolism in the left temporal pole region. These data suggest that perceived levels of persistent fatigue after Sars-Cov2 infection are associated with functional changes in brain architecture.

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HEMODYNAMIC CHANGES IN PATIENTS WHO UNDERWENT SARS-COV-2 INFECTION: FROM A QUANTITATIVE TO A TREATMENT POINT OF VIEW USING PHOTOBIOMODULATION DEVICE

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Objective: SARS-CoV-2 infection determines an overall immune response leading to uncontrolled inflammations. The immune response is mediated by different cells and molecules such as cytokines and chemokines increasing hyperinflammation that also affect brain oxygenation. In more than 10 years of using Near-Infrared Spectroscopy as a functional analyzation technique to detect hemodynamic variation in brain areas, our group succeeded in obtaining 3 different hemodynamic states in patients who had COVID-19 disease and underwent neuromodulation treatment to alleviate Neuroinflammation symptoms.

Materials: Between 2015 and 2019, 22 subjects aged between 43 and 76, were recruited to assess their cerebrovascular function with Near-Infrared Spectroscopy (NIRS). The heterogeneous sample included 12 males and 10 females with different symptoms, evaluated for clinical purposes. Of the initial 22 subjects, 16 adhered to re-evaluation with NIRS 6-12 months after SARS-CoV-2 infection (between 2021 and 2022). Subsequently, they underwent rehabilitation protocols for Neuroinflammation with a non-invasive method of Photobiomodulation (PBM) device (10 sessions, twice a week). At the end of the treatment cycle, they were re-evaluated with NIRS. Data obtained from pre-COVID (T0), post-COVID (T1) and post-treatment (T2) NIRS evaluations were compared in terms of hemodynamic states variation.

Methods: The Near-Infrared Spectroscopy evaluation was assessed with NIRX Sport 8x8 Channel device with detectors and sources placed on Prefrontal-Auditory-Occipital Brain Areas. The hemodynamic states obtained in T0, T1 and T2 were analysed with NirsLab Software. Patients underwent transcranial Photobiomodulation treatment with Cerebro® NIR-Infrared device. Results were compared and statistically analysed using Microsoft Office Excel.

Results: Comparison of data obtained from hemodynamic assessment at T0, T1 and T2 showed a marked T2 improvement in patients with impaired T1 cerebral-vascular function. In particular, 3 out 16 subjects reported a total restoration of initial hemodynamic functioning following neuromodulation treatment. The remaining 13 presented an increase in T2 vascular exchange activity above initial T0. Even after the subdivision into symptomatology, age, and gender group the average values showed positive results.

Conclusions: The last two-year experience in clinical assessment and treatment in patients who underwent SARS-CoV-2 infection allowed us to use our experience with Near-Infrared Spectroscopy to determine the effective improvements of Neuroinflammatory symptoms after transcranial Photobiomodulation treatment sessions by quantitatively determine the hemodynamic variation rate in each patient in a three-time evaluation period. Photobiomodulation treatment continues to show its efficacy in alleviating SARS-CoV-2 infection symptoms and Long COVID Syndrome.

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POST COVID-19 BELLY DANCER'S DYSKINESIA

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Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the etiological pathogen of Coronavirus Disease 19 (COVID-19) pandemic. The post-COVID syndrome, initially referred to as "long COVID" and more recently as "post-acute sequelae of SARS-CoV-2 infection" (PASC), is characterized by symptoms related to inflammation, organ damage, worsening of a pre-existing health conditions and effects due to hospitalization or prolonged ventilation (post-intensive care syndrome). Neurological manifestations of PASC (neuro-PASC) include fatigue, muscle weakness, myalgia, chronic pain, headache, neurocognitive disorders (such as dementia, anxiety, psychotic disorder), sleep disorders, persistent smell and taste dysfunction and peripheral neuropathies. With this case report we aim to describe a novel and rare neurological hyperkinetic disorder in the context of a post-COVID syndrome.

Case description: A 30-year-old woman presented to our attention for evaluation of involuntary, continuous, rhythmical movements of the left abdominal wall. The abdominal movements were entrainable, variable during walking and absent during sleep; were causing respiratory distress, with hypophonia and tachypnea. In her history she had child-onset obesity, white coat hypertension and anxiety–depressive disorder. In October 2020 she had COVID-19 presenting with an upper respiratory syndrome, fatigue, anosmia and ageusia, followed in a few days by acute respiratory distress syndrome with lobular ground-glass opacities at chest-CT, needing respiratory support (noninvasive ventilation and high flow nasal cannulae). In June 2021 the patient was re-admitted for an episode of thoracic pain and dyspnea and need of respiratory support. She underwent echocardiography, right cardiac catheterization, EEG with polysomnography registration, laryngoscopy, without pathological evidence. Two weeks after discharge, an incoercible hiccup appeared with resolution within 10 days, and appearance of involuntary movements of the abdominal wall. Brain and spine MRI, phrenic nerve ENGs, CFS analysis and serum antibodies tests were all negative and total body contrast enhanced CT scan showed the absence of phrenic lesion. Chest fluoroscopy showed normal diaphragmatic movements. Surface EMG of external abdominal oblique (EAO) muscles with EEG registration evidenced synchronous muscular contraction of left EAO muscle, with duration of 300-400 ms and frequency of 1 Hz, increased to 0.5 Hz after Valsalva manoeuvre, without pathological correlation at EEG registration.

Conclusion: Belly dancer's dyskinesia is a rare movement disorder and it has never been described during COVID-19 or in its sequelae. We hypothesized that post-COVID respiratory symptoms may have been a trigger of this manifestation.

COGNITIVE IMPAIRMENT FOLLOWING COVID-19 INFECTION. CLINICAL CHARACTERISTICS AND BIOMARKERS LONGITUDINAL PROFILING

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Targets: Memory and attention complaints after Covid-19 have been reported in at least 1 third of patients1. The aim of this study was both to evaluate the prevalence of cognitive impairment after Covid-19 infection and to characterize its clinical and laboratory features.

Materials: We enrolled 47 survivors with moderate to severe Covid-19 infection and without neurological complications, nor a history of previous neurological diseases. We collected their clinical history, familiar background, and dementia risk factors. Patients were followed up with visit at 2 and 10 months (T1 and T2 respectively).

Method: Patients underwent clinical neurological evaluation and blood sampling at baseline and at follow-up visits. Follow-up visits included a comprehensive battery for cognitive assessment and the following clinical scales: MMSE, MoCA, HAM-A, BDI-II, IES-R, ESS, PSQI, SF-36. A prespecified protocol for blood tests included the longitudinal determination of serum levels of NfL, proADM, ICAM-1, VCAM-1, Lipocalin2, TREM-2, IL1b, IL6, IL8, IL2Ra, IL10, IP10, IFN-gamma, IgM and IgG against Covid-19.

Results: The mean age was 60,0 (IQR 51-68). Seventeen/47 (36.2%) required ICU management, while 30/47 (63.8%) were treated in medical wards. Seven patients/47 (14.9%) reported subjective cognitive impairment prior to Covid-19 infection. This proportion increased at T1 (29.8%) and T2 (43.2%); 62% of patients had at least 1 compromised cognitive function both at T1 and T2, but patients had a higher number of impaired functions at T2. Covid-19 severity was not correlated with cognitive symptoms at follow-up. The levels of all biomarkers of inflammation and neurofilaments light chain were higher in the acute phase except for IL2-Ra and IFN-gamma, whose levels were higher at the end of follow-up. Female sex and TREM-2 levels were significantly and positively correlated with cognitive impairment after multivariate analysis.

Discussion: We found a cognitive impairment in more than 60% of patients after Covid-19 infection. There was no correlation in the univariate and multivariate analysis between the number of cognitive impaired functions and the scores at scales evaluating anxiety and depressive symptoms, sleep quality and post-traumatic stress disorder. The patterns of inflammatory response in these patients suggest an endothelial and microglial activation in acute phase. These patterns, along with the neuronal damage seen in acute phase, have been already described in Alzheimer's disease and other neurodegenerative diseases.

Conclusions: Patients after Covid-19 infection showed high prevalence of cognitive impairment. The common pathogenetic pathways with Alzheimer's disease shed new light on the link between neurodegeneration and neuroinflammation.

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BRAIN NEURONAL AND GLIAL DAMAGE DURING ACUTE COVID INFECTION IN ABSENCE OF CLINICAL NEUROLOGICAL MANIFESTATIONS

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Aims: Growing evidence indicates that neurological manifestations become evident and may persist over a long time in patients with COVID-19. A number of studies have provided a detailed characterization of the clinical neurological involvement occurring during SARS-Cov-2 infection. While this bulk of data are definitely in favour of a particular tropism of SARS-Cov-2 for the central and peripheral nervous system leading to overt clinical manifestations, it is interesting to know, however, whether the SARS-Cov 2 infection may damage the nervous system, specifically neurons and glia cells, even without signs of clear clinical involvement.

Materials and methods: To provide consistent evidence whether SARS-Cov 2 infection can cause damage of nervous system even when signs of clear clinical involvement are absent, we studied the serum levels of neurofilament light chain (sNfL) and glial fibrillary acidic protein (sGFAp) in 149 hospitalized COVID-19 patients without clinical neurological manifestations and compared them to a group of 108 healthy controls (HCs) and to a group of 53 patients with interstitial lung diseases (ILD) different from COVID-19.

Results: sNfL levels where higher in COVID-19 patients (median log10 sNfL 1,40; IQR 1,04-1,82) than ILDs (median log10 sNfL 1,18; IQR 0,98-1,38; $p < .001$) and HCs (median log10 sNfL 0,89; IQR 0,72-1,14; $p < .001$) (Fig. 1A). sGFAP levels where higher in COVID-19 patients (median log10 sGFAP 2,25; IQR 2,02-2,52) in comparison to ILDs (median log10 sGFAP 2,15; IQR 1,94-2,30; $p < .001$) and HCs (median log10 sGFAP 1,87; IQR 0,64-2,09; $p < .001$) (Fig. 1B). No significant difference was found comparing HCs and ILD patients ($p= .388$ for sNfL and $p= .251$ for sGFAp). Interestingly, there was no significant difference in sNfL and sGFAP levels between COVID-19 patients when they were grouped accordingly with disease severity (median log10 sNfL 1,39; IQR 1,11-1,70 in moderate and median log10 sNfL 1,42; IQR 1,10-1,98 in severe COVID-19 patients; p = ,191).

Discussion and conclusions: The results of our study suggest neuronal and glial degeneration occur in COVID-19 patients regardless of clinical neurological manifestations. The long term consequences of the subclinical neuronal and glial damage revealed by the elevation of these biomarkers in COVID-19 patients is currently unknown and warrants further investigations.

IMPACT OF COVID-19 VACCINATIONS ON HOSPITAL ADMISSIONS FOR ISCHEAMIC STROKE, TIAS, CEREBRAL HAEMORRHAGE AND CEREBRAL VENOUS THROMBOSIS IN THE LOMBARDIA OVER-12 POPULATION. PRELIMINARY DATA FROM A SELF-CONTROLLED CASE SERIES ANALYSIS

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Introduction: The influence of COVID19 vaccination of the risk of different neurological diseases has been subject of intense investigation; large population-based analyses [1] have shown an increase in relative risk of various neurological diseases in the 28 days following vaccination, but this risk was in most cases lower than the risk induced by COVID19 infection and by far outweighted by the benefits of vaccination. No large scale results have been published so far in the population of Lombardy.

Methods: By using the adapted SCCS method for event dependent exposures, we estimated the relative incidence of transient ischemic attack/ischemic stroke/cerebral hemorrhage/ cerebral venous thrombosis following pre-specified windows at risk after vaccination in the over-12 population of Lombardia, in a within-person comparison of different time-periods. The method allows for the control of all time-independent characteristics of subjects. Follow-up time before vaccination (Pre-Vax period) was compared with follow-up time 0-28 days (high-risk period) from the day of vaccination for the first, second and third doses. The SCCS model was fitted using a conditional Poisson regression model to estimate the Relative Incidences (RI) and their 95% Confidence Intervals (CI). We carried out subgroup analyses by age group (12-39, 40-50, 60+ years) and gender. We conducted the analyzes over a period of one year, starting on 27 December 2020 (start of the vaccination campaign in Italy) and ending on 31 December 2021. Analyses on the frequency of multiple sclerosis, encephalitis, and myasthenia gravis and on the risk conferred by Sars-CoV2 infection per se are ongoing.

Results and discussion: Over the study period, 10472 cases of ischeamic stroke, 2564 cases of cerebral heamorrhage, 1710 TIAs and 70 CVT were hospitalize. The rate of vaccinated individuals was 87 percent. The 28-day post-vaccination period was associated with a slight increase in the occurrence of ischemic stroke, cerebral haemorrhage, TIAs (IRR 1.54, 1.36 and 1.97, respectively) and to a moderate increase in CVT (IRR 2.86). When the risk conferred by COVID19 infection was assessed in the same cohort, IRR were of similar magnitude, but confidence intervals included 1, with the exception of CVT. The large study in the UK reported an increase in IRR in haemorrhagic stroke (only for BNT162b2 vaccine), whereas it did not investigate CVT nor ischemic stroke nor TIAs. Our data add to the existing evidence on this point and suggest that increased risk of non-inflammatory CNS disorders following COVID-19 vaccination is negligible, with the possible exception of CVT.

Further analyses are ongoing considering the different vaccines utilized in Italy and inflammatory neurological diseases.

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NEURO-COVAX: AN ITALIAN POPULATION-BASED STUDY OF NEUROLOGICAL COMPLICATIONS AFTER COVID-19 VACCINES

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Objective: Little is until known about adverse events following COVID-19 vaccination. This sounded like an urgent call for researchers to independently assess vaccines safety profile in different populations. In this Italian population-based study, we aimed to evaluate neurological complications after first and/or second dose of COVID-19 vaccines and factors potentially associated with adverse effects.

Methods: This observational study included adults aged 18 years and older, who received two vaccine doses in vaccination Hub Novegro

(Lombardy) between July 7-16 2021. NEURO-COVAX questionnaire has been developed to capture neurological events, clinical onset and duration. Data digitized centrally by Lombardy Region were used to match demographic/clinical characteristics and identify a vulnerable clinical profile. Associations between vaccine lines and development of neurological complications were assessed.

Results: NEURO-COVAX cohort included 19.108 vaccinated people: 15.368 mRNA BNT162b2, 2077 INN Covid 19 mRNA, 1651 ChAdOx1nCov-19 and 12 Ad26.COV2, subsequently excluded. About 31.3% of sample developed post-vaccination neurological complications, particularly ChAdOx1nCov-19. Vulnerable clinical profile emerged, since over 40% of symptomatic people showed comorbidities in clinical history. Defining neurological risk profile, we found an increased risk ChAdOx1nCov-19 of tremor (OR:5.12, 95% CI:3.51-7.48), insomnia (OR:1.87, 95% CI:1.02-3.39); muscle spasms (OR:1.62, 95% CI:1.08-2.46) and headache (OR:1.49, 95% CI:0.96-1.57); following INN-Covid 19 mRNA an increased risk of parethesias (OR:2.37, 95% CI:1.48-3.79), vertigo (OR:1.68, 95% CI:1.20-2.35), diplopia (OR:1.55, 95% CI:0.67-3.57), excessive daytime sleepiness (OR:1.28, 95% CI:0.98-1.67).

Discussion and Conclusions: This study estimates prevalence and risk of neurological complications associated to COVID-19 vaccines, thus improving vaccination guidelines and loading in future to a personalized preventive medicine.

IMPACT OF COVID-19 IN A POPULATION OF MYASTHENIC PATIENTS BEFORE AND AFTER VACCINATION

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Objectives: To find predictive factors in the past and present myasthenic course related to a different COVID-19 outcome and assess if vaccination for SARS-CoV-2 is protective for patients affected by Miasthenia Gravis (MG).

Materials: We evaluated 13 patients affected by Myasthenia Gravis who had COVID-19 before vaccination and other 8 myasthenic patients who contracted infection of SARS-CoV-2 after the vaccination.

Methods: We used Student's t test and Spearman test to perform statistical examinations and compare the previous stability of myasthenic disease (graded by the MGFA scale) and the severity of SARS-CoV-2 infection (based on the classification proposed by M. Jakubikovà) between the two groups.

Results: The two groups were comparable in severity of previous Myasthenia Gravis course (mean maximum MGFA=3) and at the moment of the infection (mean MGFA at COVID-19=2). In the first group of non-vaccinated patients, the hospitalization rate was 61.5% and the mortality reached 30%. In the second group of vaccinated patients, the hospitalization rate was 12.5% and the same for the mortality rate; infact only one vaccinated patient suffered from respiratory failure and deceased and it is interesting to note that he was previously treated with Rituximab.

Discussion: While in the group of non-vaccinated patients was demonstrated a statistically significant difference that correlates a previous myasthenia instability with a more severe course of infection (p=0.032), this association was not found in the second group (p=0.29). Similarly, the duration of neuromuscular disease in the first group correlated with a more severe course of infection (p=0.03, Spearman r 0.59) but in the second group it was not confirmed (p=0.09, Spearman r 0.09).

Conclusions: Based on our data we can assume that the vaccination may have played a protective role for myasthenic patients, who are a fragile and at risk category for severe course of SARS-CoV-2 infection. Independent risk factors remain the age of the subjects and their comorbidities. Interestingly, the therapy with anti-CD20 may be associated with a poor immune response to vaccines resulting in lower protection against the SARS-CoV-2.

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LONG-TERM OUTCOME IN COVID-19 RELATED CRITICAL ILLNESS POLYNEUROPATHY

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Aim: Numerous neurological complications following SARS-COV-2 disease were reported (encephalitis, cerebrovascular disease, acute inflammatory demyelinating polyneuropathy). Few studies described critical illness neuropathy or myopathy (CIP/CIM), related to hospitalization in intensive care units (ICU). Little is known regarding the long-term outcome in SARS-COV-2 related CIP/CIM and if there are differences as compared to the picture typically occurring in non-Covid-19 patients.

Materials and methods: We evaluated 16 patients (4 females and 12 males). Inclusion criteria: SARS-Cov-2 infection with respiratory failure, hospitalization in ICU with the need for mechanical ventilation, clinical picture suggesting CIP/CIM. We collected personal and clinical history data, and all subjects underwent clinical-functional evaluation. Conduction velocities and needle EMG were carried out by testing both proximal and distal muscles. All patients were assessed by MRC and INCAT Disability Scale to upper and lower limbs (UL/LL), at discharge from the ICU (T0), the intensive rehabilitation care (T1) and at the follow-up (FU) visits (T2: 6 months). ANOVA test was used to compare MRC and INCAT.

Results: Mean age is 64.5 ± 7.8, with an ICU stay >30 days and mechanical ventilation >15 days. Two patients required reintubation. Mean time of admission to rehabilitation was 30 days. All the subjects presented a picture of muscular wasting and weakness, both proximal and distal with hyporeflexia and mild sensory changes mainly distal. The neurophysiological study showed a marked reduction in the amplitudes of cMAP in all patients, with conduction velocities at the lower limits of the norm, suggesting a predominantly motor, axonal polyneuropathy. Upon discharge from the intensive rehabilitation care (T1), all patients showed a significant improvement in INCAT scores at UL and LL and MRC (T0 UL 2.93 ± 1.16, T0 LL 4.4 ± 0.73; T1 UL 1.29 ± 0.83, T1 LL 2.29 ± 1.14, T0 MRC 39.8 ± 7.1; T1 MRC 52.1 ± 3.7; p<0,0001). On average, a further significant improvement was found at the T2 visits (T2 UL 0.4 ± 0.6, T2 LL 0.6± 0.9, T2 MRC 58.9±1.8 p<0,0001).

Discussion and Conclusions: CIP/CIM in patients SARS-COV-2 infection has clinical and neurophysiological features similar to non-covid cases. Unexpectedly, the long-term clinical course is more benign, with a recovery in a shorter time than previously described in non-covid patients. We also demonstrate the central role of early rehabilitation, to optimize clinical-functional recovery and prevent functional disability.

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DUAL TASK COST IN SUBJECTS WITH MILD-TO-MODERATE COVID-19: A PROSPECTIVE LONGITUDINAL CASE-CONTROLLED STUDY

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Aim: The aim of the study is the evaluation of Cognitive-Motor-Interference (CMI) in patients with mild-to-moderate Coronavirus disease (COVID-19) since first hospitalization and after 6 months from discharge, in comparison with healthy controls (HC).

Materials: COVID-19 subjects and HC were evaluated with a motor task (2-minute walking test – 2MWT) and a cognitive task (counting backwards by two), performed in single-task (ST) and dual-task (DT). Dual-task-cost (DTC) was calculated. Depression and anxiety symptoms were screened with HAM-D and HAM-A, respectively.

Method: Patients included with mild-to-moderate COVID-19, admitted to a COVID-19 Unit (North of Italy), had positive antigenic swab, COVID-19-related pneumonia, no need of oxygen and/or mechanical ventilation, were independent at home and were not affected with pre-existing neurological and/or cognitive alterations before COVID-19. HC recruited were independent at home, were not affected with COVID-19, had no pre-existing neurological and/or cognitive alterations and no history of COVID-19. The first cohort was examined during hospitalization (T0) and after 6 months (T1). HC were examined once at T0.

Results: 100 patients with mild-to-moderate COVID-19 [mean age 67.32(12.08) years (53M/47F)], after 13.94(9.71 days) from the first positive nasopharyngeal swab and 39 HC [mean age 63.11(9.90) years (20M/19F)] were recruited. T0: the groups differed for motor-ST [190.81(33.54)/98.55(33.59) m; p=0.0002) and cognitive-ST [87.35(29.91)/57.58(24.92) correct numbers; p=0.0001], motor-DT [170.08(27.15)/80.05(34.71) m; p=0.0001] and cognitive-DT [85.30(30.68)/47.38(23.66); p=0.0002], cognitive-DTC [-9(17.30)/-19.99(14.12); p=0.0003] and motor-DTC [-1.52(19.38)/-16.73(30.59); p=0.006], lower in HC. T1: 41 COVID-19 patients were evaluated [mean age 64.85(10.85) years (22M/19F); mean follow-up 174.63(52.11) days]. The groups differed for motor-ST [190.81(33.54)/156.27(38.26) m; p=0.0001] and cognitive-ST [87.35(29.91)/67.76(35.81) numbers; p=0.011], motor-DT [170.08(27.15)/137.76(38.86) m; p=0.0002] and cognitive-DT [85.30(30.68)/64.56(34.67) numbers; p=0.007], with better performances in HC. Cognitive-DTC [-9(17.30)/-11.69 (13.27) %; p=0.442] and motor-DTC [-1.52(19.38)/0.5 (25.25) %; p=0.696] were comparable.

Discussion: Amongst COVID-19 complications, cognitive alterations have been reported, with a possible negative influence on every-day life activities. The conduction of these activities requires the integration of cognitive and motor tasks, two types of tasks influencing each other. Since hospitalization, COVID-19 patients experienced a rise in DTC and the reduction of both motor and cognitive performances in ST and DT when compared with HC. DTC increased at T1, with comparable values in the two groups, but with a persistent reduction of ST and DT motor and cognitive performances in respect of HC.

Conclusion: In patients with mild-to-moderate COVID-19, CMI and DTCs are altered since admission to hospital, possibly determining a lower performance in every-day life.

PREVALENCE OF DYSPHAGIA IN ELDERLY INPATIENTS WITH MILD-TO-MODERATE COVID-19: A CROSS-SECTIONAL STUDY

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Aim: The aim of the study is the evaluation of the prevalence of dysphagia in elderly affected with mild-to-moderate Coronavirus disease (COVID-19).

Materials: Patients being ≥65 years underwent water swallowing test (WST). Those failing it underwent a specific deglutition examination administered by a trained speech and language therapist (SLT) scored using ASHA-NOMS. Method: All patients having mild-to-moderate COVID-19, being ≥65 years admitted to a COVID-19 Unit, were enrolled if not having need or history of mechanical ventilation.

Results: Out of 195 patients with mild-COVID-19, 73 subjects with ASHA-NOMS≤5 [mean age 85.04(5.52) years (M/F); length of stay 23.63(14.6) days; mean ASHA-NOMS 3.64(0.99)]. The prevalence of dysphagia in the whole population was 37.43% [13 patients with ASHA-NOMS 5 (17.8%), 32 with 4 (43.8%), 20 with 3 (27.4%), 5 with ASHA-NOMS 2 (6.8%), 3 having ASHA-NOMS 1 (4.1%)]. Thereafter, on the basis of the presence of neurologic diseases, patients were divided in Non-Neurological Disease Group (NNDG – 38 subjects) and Neurological Disease Group (NDG 35 - subjects). NNDG and NDG differed for age [mean age 86.31(5.27)/83.66(5.53) years; p=0.039], ASHA-NOMS [3.86(0.99/3.4(0.95); p=0.043] and heart rate [77.30(12.73)/70.17(12.18); p=0.027]. They were similar for SpO2, blood cell count, D-dimer, total protein and albumin, Lactate dehydrogenase and C-reactive protein.

Discussion: During COVID-19 the risk of dysphagia has been reported, with high frequencies in those who underwent intubation and mechanical ventilation. In the studied population the global prevalence of dysphagia was 37.43%. Although the presence of known neurological disease represents a recognized risk factor for dysphagia, ASHA-NOMS was pathological also in NNDG. Ostensibly, neurological diseases are not the exclusive risk factor for dysphagia in older patients with mild-to-moderate COVID-19. Thus, the precocious identification of dysphagia should be considered a matter of fundamental importance, in order to reduce the risk of malnutrition and aspiration pneumonia. WST might be a useful and practical screening tool, for its easy administration. If failing the WST, a proper detailed deglutition examination by a LST should be implemented.

Conclusion: Older patients with mild-to-moderate COVID-19 are at risk of dysphagia and the evaluation of these subjects is necessary.

IMPAIRMENT OF TRIGEMINAL FUNCTION IN PATIENTS WITH COVID-19 AND SMELL DISTURBANCES. AN ELECTROPHYSIOLOGICAL STUDY

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Objective: Cranial nerves are frequently affected in patients with COVID-19, indeed smell and taste disturbances are some of the most frequent self-reported neurological symptoms. Previous studies suggested a concomitant impairment of the trigeminal nerve in patients with olfactory disturbances, however it has never been confirmed with objective measurements techniques. The aim of this study was to assess the trigeminal function with electrophysiological tests and its correlation with clinical data.

Materials: The study involved 16 patients with mild course COVID-19 infection and smell disturbances and 14 healthy controls (HCs). Olfactory and gustatory symptoms were assessed with self-reported questionnaires, whereas the trigeminal impairment was assessed by electrophysiological tests.

Methods: At the time of enrollment (T0), all participants underwent a baseline interview, assessing general demographic and clinical variables, a neurological and ear-nose-throat physical examination. A clinical follow-up was performed after one month (T1) in all patients and after 20 months (T2) in a subgroup of seven patients. Electrophysiological evaluations of Masseter Inhibitory Reflex (MIR) and Blink Reflex (BR) were assessed at T0 and at T2 in a subgroup of seven patients.

Results: At T0 MIR revealed a significant increase in the latency of the ipsilateral and contralateral early Silent Period (SP1) compared to HCs. Differences in SP1 and SP2 duration between patients and HCs were not significant; however, a subgroup of patients showed an increase of SP1 duration compared to HCs. The analysis of BR revealed a significant increase of R1 amplitude compared to HCs. At T2 the number of alterations at MIR examination was reduced and the amplitude of R1 normalized at follow-up in most of the patients.

Discussion: The increase in the latency of ipsilateral and contralateral SP1 in the patients' group suggests a peripheral involvement of the mandibular branch rather than the ophthalmic division of the trigeminal nerve. The increased amplitude of R1 at BR examination and the prolonged SP1 duration at MIR might be explained as a compensatory upregulation of trigeminal function as consequence of the olfactory damage.

Conclusions: Patients with COVID-19 and smell impairment show a subclinical trigeminal nerve impairment. Trigeminal alterations seem to mainly involve the oligosynaptic pathway, as result of either direct viral damage or secondary neuroinflammation of the peripheral trigeminal fibers, whereas the polysynaptic ponto-medullary circuits seem to be spared.

SERUM NEUROFILAMENT LIGHT CHAIN LEVELS IN COVID-19 PATIENTS WITHOUT MAJOR NEUROLOGICAL MANIFESTATIONS

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Objectives: To investigate whether serum neurofilament light chain (sNFL) levels: 1) are elevated in Covid-19; 2) are influenced by disease severity; 3) are associated with alterations of respiratory and routine blood parameters; 4) change longitudinally during the in-hospital disease course.

Materials: 57 hospitalized Covid-19 patients without major neurological manifestations and 30 neurologically healthy controls.

Methods: sNFL levels were measured with single molecule array (Simoa) technology. Patients were evaluated for PaO2/FiO2 ratio on arterial blood gas, Brescia Respiratory Covid Severity Scale (BRCSS), white blood cell counts, serum C-reactive protein (CRP), plasma D-dimer, and plasma fibrinogen at admission. Patients were stratified in 3 classes of Covid-19 severity (mild, moderate, severe). In 20 patients, NFL was also measured on serum samples obtained at a later timepoint during the hospital stay.

Results: Covid-19 patients had significantly higher sNFL levels compared to controls. Although no significant differences were observed between the three categories of Covid-19 severity, patients who died during the hospital stay had significantly higher baseline sNFL levels. sNFL did not correlate with BRCSS nor with PaO2/FiO2 ratio, but correlated positively with serum CRP and plasma D-dimer in patients with mild Covid-19 and negatively with blood lymphocyte count in the same patients and in the whole Covid-19 cohort. There was a strong correlation between baseline and longitudinal sNFL levels of individual patients. Among the 20 longitudinally sampled patients, the median follow-up sNFL level was nominally, but not significantly, higher than the baseline one. While longitudinal sNFL levels did not correlate with BRCSS score or PaO2/FiO2 ratio at admission, both serum CRP and plasma D-dimer at admission positively correlated with longitudinal sNFL. Longitudinal sNFL variation did not correlate with PaO2/FiO2 at admission but positively correlated with BRCSS score, serum CRP, and plasma D-dimer at admission.

Discussion: We provide neurochemical evidence of subclinical neuroaxonal damage in Covid-19 also in the absence of major neurological manifestations. This is apparently not fully explained by hypoxic injury; rather, systemic inflammation might promote this damage. However, a direct neurotoxic effect of SARS-CoV-2 cannot be excluded.

Conclusions: The mechanisms and significance of subclinical neuroaxonal damage in Covid-19 deserve further investigation. Future work should examine the relationships of NFL with neuroimaging and neurophysiological features, the association of NFL levels with long-term neurological complaints, the possible changes of NFL levels as a result of antiviral treatments, and the dynamics of other neurochemical biomarkers during and after infection with SARS-CoV-2.

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NEUROEPIDEMIOLOGY

RECURRENCE OF TRANSIENT GLOBAL AMNESIA: A RETROSPECTIVE OBSERVATIONAL STUDY

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Objective: To evaluate whether age, gender, and results of specific investigations could predict the risk of recurrence of transient global amnesia (TGA).

Methods: This study is a double-center retrospective observational study, conducted at the emergency department and neurology departments of the hospitals in Merano and Lodi. In each hospital, a group of medical neurologists manually and independently re-evaluated all records to ascertain the diagnosis of TGA. Data were collected on demographics, results of diagnostic investigations, and TGA recurrence.

Results: During the study period, we identified 342 patients with TGA. The median age of the patients was 65 years (IQR: 61-71) and 60.5% (207/

342) were female. 6.7% of patients (23/342) experienced a recurrence during the follow-up period (median follow-up time: 77 months (IQR: 37-122). No differences were found in routine blood investigations between patients with and without TGA recurrence. An abnormal CT scan was found in 18.8% (60/319) of patients without TGA recurrence and in 8.7% (2/23) of those with recurrent TGA episodes (p = 0.397). MRI examination was performed in 31.3% (107/342) of patients. A MRI abnormality was found in 37.5% (36/96) of patients without subsequent recurrence versus 45.5% (5/11) of patients with recurrent TGA episodes (p = 0.745). No difference was found in the type of abnormality (chronic vascular encephalopathy; cortical/subcortical atrophy or other) found in head CT or brain MRI between the two groups. The EEG was performed in 79.2% (271/342) of patients. EEG abnormalities (slowings) were found in 8.3% (21/252) of patients without TGA recurrence versus 10.5% (2/19) of those with recurrent episodes (p = 0.669); no epileptiform abnormalities were found. Finally, 47.4% (162/342) performed a duplex sonography of the neck vessels; 29.9% (43/144) of patients without recurrence had abnormal findings compared to 40% (4/10) of patients with a TGA recurrence (p = 0.495).

Discussion: In our study, no differences were found in the proportion of patients with abnormalities in blood tests, neuroimaging, EEG and duplex sonography of the neck vessels between the two groups. This result suggests that additional investigations, besides having an extremely limited role in the diagnosis of TGA, are probably irrelevant in the prediction of TGA recurrence.

Conclusion: Further population-based prospective studies are required to identify risk factors for TGA recurrence. Additional blood tests, neuroimaging investigations and EEG are probably irrelevant in the prediction of TGA recurrence.

VALIDITY OF THE MANCHESTER TRIAGE SYSTEM IN THE PRIORITISATION OF PATIENTS WITH TRANSIENT GLOBAL AMNESIA IN THE EMERGENCY DEPARTMENT

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Objectives: The Manchester Triage System is one of the most widely used and studied triage systems in Emergency Departments (ED). MTS does not have a specific presentational flow chart for patients with transient global amnesia (TGA). The goal of this study was to determine the adequacy of priority code assignment for patients with TGA presenting at the ED and triaged using the MTS. In addition, the correct application of MTS by triage nurses was assessed through the audit method.

Methods: This is a single-center observational retrospective study from 1 January 2013 to 31 June 2020. All patients with a medical diagnosis of TGA were considered. An audit was conducted on these triages to assess the correct application of MTS by the triage nurses. Correct triage was considered as a patient classified as yellow.

Results: During the study period, 216 patients with a diagnosis of TGA were considered. Of these 49.5% were classified as yellow, 13.0% were undertriaged and classified as green or blue and 37.5% were overtriaged and classified as orange or red. The audit demonstrated that 98.8% of overtriaged patients were triaged incorrectly and 57.1% of undertriaged patients were triaged incorrectly. In addition, in 38 patients the triage nurse confused TGA with an acute neurological deficit suggestive of Stroke or transient ischaemic attack.

Conclusion: The present study demonstrates an inability of MTS to correctly stratify patients with TGA. The results of the present study indicate the need for a specific flow chart for patients with neurological problems to improve the performance of MTS.

NEUROLOGICAL SYNDROMES FOLLOWING SARS-COV-2 VACCINATION: ARE MEDICAL UNEXPLAINED SYMPTOMS THE KEY PLAYERS?

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Abstract: Background: SARS-CoV-2 vaccination has been associated with rare neurological syndromes. The aim of this study is to evaluate the risk of association between specific neurological symptoms and syndromes and SARS-CoV-2 vaccination.

Methods: In this prospective single center cohort study, we included all adult inpatients consecutively admitted to a tertiary Neurological Centre from January 2021 to February 2022. Vaccinated cases were subgrouped according to the onset of neurological manifestation in the first 30 days (V<30d), 30-60 days (V30-60d) and more than 60 days (V>60d) following SARS-CoV-2 vaccination. The incidence and characteristics of neurological syndromes were compared between unvaccinated and vaccinated cases (including subgroups) adjusting for the effect of age, sex and premorbid conditions in linear regression analyses.

Results: 830 subjects entered the study, namely 398 unvaccinated (UVC) and 432 vaccinated cases; these groups were comparable for demographic characteristics and clinical diagnosis distribution and. Compared to UVC, V<30d exhibited higher prevalence of Medical unexplained symptoms (MUS, 24.5% vs 10.6%), primary headache (10.9% vs 5%) and lower number of cerebrovascular diseases (30.7% vs 41.9%). V30-60d cases exhibited higher number of primary headache (13% vs 5%) compared to UVC, whereas V>60d showed similar diagnosis distribution with UVC.

Conclusions: Unexplained transient neurological symptoms and primary headache appeared to be the most common neurological conditions following SARS-CoV-2 vaccination. The findings confirmed the safety of SARS-CoV-2 vaccination and argued against a prominent role in the pathogenesis of either cerebrovascular or inflammatory-mediated neurological disorders, exception made for rare CVT cases.

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TRACE ELEMENTS IN HIGH INCIDENCE AREAS OF MULTIPLE SCLEROSIS: A ROLE OF VOLCANOGENIC ASHES?

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Objective: To study the blood levels of selected trace elements (TE) in

Multiple Sclerosis (MS) patients living in high-incidence cluster areas in the Etna volcano region.

Methods: MS patients living in the province of Catania have been retrospectively enrolled among those followed by the Neurologic Clinic of the AOU Policlinico "G. Rodolico-San Marco" who had the disease onset between 2005 and 2020. A serum sample was used for the determination of TE levels (As, Cd, Cr, Cu, Fe, Mg, Mn, Ni, Se, Zn). All the analyses have been conducted with an ICP-MS with the standard addition technique, previous digestion of the samples with nitric acid. MS patients living the high incidence clusters were frequency matched with MS patients living outside the clusters. Comparisons of TE across the groups were conducted using the Mann-Whitney test.

Results: A total of 86 (48 women; 55.8%) MS patients was recruited, with a mean age of 41.6±13.1 years, a mean disease duration of 2.0±2.6 years and a mean Expanded Disability Status Scale of 2.3±1.7. Of these patients, 40 belonged to high incidence clusters and 46 were outside the clusters. No differences were found in demographic characteristics between the groups. Concerning TE, we found a significant higher concentration of Mn in in-cluster patients (6.7±16.6 μg/L vs 2.5±5.9 μg/L).

Discussion: Several environmental factors may modulate the pathogenesis of the disease, and among them TE play an important role. Our findings suggest that Manganese, which has several toxic effects, might contribute to the higher incidence of MS previously observed in a cluster of communalities in the south-eastern flank of the Etna volcano, where volcanic ashes rich in TE usually fall due to the prevailing winds.

Conclusions: Exposition to high levels of Mn could be a cofactor in the pathogenesis of MS.

GUILLAIN-BARRÉ SYNDROME IN PATIENTS DYING WITH COVID-19 IN ITALY: A RETROSPECTIVE STUDY

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Objectives: To describe four cases of COVID-19 deaths occurring in patients with the spectrum of Guillain-Barré syndrome (GBS) between February 2020 and January 2022 in Italy.

Materials: All cases, ranged between 48 and 73 years, showed classical clinical onset of GBS - limb weakness, sensory deficits, hypoareflexia - and progressed to respiratory failure: 3 of them were admitted in intensive care unit for ventilator support. They were extracted from 8,436 medical charts, reviewed from a cohort of 138.099 COVID-19 related deaths in Italy.

Methods: Data were obtained from the Italian National Institute of Health (ISS, Istituto Superiore di Sanità) Integrated Surveillance System. Our cases were demonstrated by RT-PCR or nasopharyngeal swab. Diagnostic assessment included: cerebrospinal fluid (CSF), nerve studies, chest (RX) X-rays or (CT)computed tomography scan.

Results: The cerebrospinal fluid showing albumin-cytological dissociation was performed in 2 cases. Nerve conduction studies in all cases revealed increase distal motor latencies, slow conduction velocities and prolonged F wave latencies. Interstitial pneumonia was documented like ground glass opacities by chest RX or CT in all cases. All of them were treated with intravenous immunoglobulin (IVIG) and with drugs used for COVID-19 infection: hydroxychloroquine, antiretroviral (lopinavir and ritonavir) alone or in combination, azithromycin alone or in combination with hydroxychloroquine, steroids or tocilizumab. None of them was vaccinated for SARS-CoV-2 infection.

Discussion: Few data about characteristics of fatal COVID-related GBS cases have been reported until now. The most frequently causes of death in GBS are respiratory failure, pneumonia, cardiac arrest, and autonomic dysfunction. As reported, we also observed in all four our cases pneumonia and respiratory failure. Considering neurophysiological features, 2 patients had a mixed form, demyelinating and axonal, the other 2 only demyelinating. All our patients were treated with intravenous immunoglobulin, but without effect.

Conclusions: GBS is considered a post-infectious neuropathy, developing 2–4 weeks after an acute infection, rather than a parainfectious one. Our case group, differently from other study, does not comprise only a pandemic peak, but a large COVID-GBS population, identified in the entire pandemic. Although the mechanism of GBS onset is still unclear in COVID-19, fatal cases may be more frequent than other virus-related GBS. Clinician should be aware to promptly diagnose and treat this condition to understand if strictly monitoring in patients with an high risk profile could dramatically decrease the mortality of GBS.

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REDUCTION OF IN-HOSPITAL INFECTIONS ASSOCIATED WITH RESTRICTIONS DUE TO COVID-19 PANDEMIC

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Objective: The Covid-19 pandemic imposed measures to contain the infection which included use of personal protective devices and limitations in visits to hospitalized patients. Those measures could have contributed to reduced the risk not only of Covid-19, but also of other infections. We aimed to assess the rates of infection in patient hospitalized for stroke before and during the Covid-19 pandemic in the district of L'Aquila, central Italy.

Materials and methods: We performed a retrospective multicenter analysis involving all inpatients with a diagnosis of ischemic or hemorrhagic stroke admitted to 4 hospitals located in the district of L'Aquila. We compared two study periods, i.e., March 2020 to February 2021 (study period), and March 2019 to February 2020 (control period). Data were retrospectively retrieved from administrative codes. Extracted data were checked with medical records to verify the accuracy of the diagnostic code. Our primary outcome was the difference in the infection rate (overall infection, pulmonary infection, gentitourinary infection) in patients hospitalized for stroke in the study period as compared with the control period. We also performed quarterly comparisons to assess the relationship between the change in infection rates and seasonality.

Results: In the study period, 520 patients were hospitalized, as compared with 667 patients in the control period. Mean age, sex distribution, stroke type distribution were similar between the two periods. Regarding infections, we observed a reduction in the rate of infections overall infection in the study period (n=24, 4.6%) vs the control period (n=77, 11.5%; $p<0.01$) and in pulmonary infections (n=13, 2.5% vs n=46, 6.9% respectively; p=0.01). There were no differences in genitourinary infections between the two periods

(n=9, 1.7% vs n= 23, 3.4%; p=0.07). By making an analysis stratified by seasonality, we observed that the differences between the study period and the control period in overall and pulmonary infections persisted both in June-August and in December-February.

Discussion and Conclusions: In accordance with previous studies [1], during the Covid-19 pandemic we noticed a decrease in hospital infections including non-Covid-19 pneumonia in patients admitted for stroke compared with the previous period. A possible explanation was that preventive measures reduced the rate of non-Covid-19 infections together with Covid-19 [2]. Notably, the decrease in the rate of infections did not affect GTIs which are not airborne like Covid-19. For these reasons, we can conclude that it could be useful to maintain such preventive measures even after the end of the pandemic to limit the spread of nosocomial pneumonia.

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ISOLATED ACUTE OCULAR MONONEUROPATHY IN NEUROLOGICAL URGENCY SETTING: AN EPIDEMIOLOGIC RETROSPECTIVE STUDY

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Objectives: The study aims to describe the demographic and clinical characteristics of all patients admitted to urgent neurological outpatient visits with an ocular motility impairment, due to an isolated acute ocular mononeuropathy (IAOM) of either the oculomotor, trochlear or abducens nerve.

Materials and methods: We retrospectively reviewed the demographic, clinical, imaging and treatment data of 31 patients with IAOM admitted to urgent neurological outpatient visits at "Maggiore della Carità" Hospital, Novara, Italy, between January 2018 and April 2022.

Results: Among our cohort of 31 patients, 19 (61.3%) had an abducens nerve palsy, 10 (32.3%) a trochlear nerve palsy, and only 2 (6.4%) an oculomotor nerve palsy. The left side was more frequently involved, with a left to the right ratio of 2:1. The mean age was 68.4 years (SD ± 12.2). Males were more affected than females, respectively, 20 (64.5%) vs 11 (35.5%). The main risk factor for IAOM was an altered glucose metabolism, since 11 (35.5%) patients were affected by diabetes or impaired fasting glucose. Only 2 (6.4%) IAOMs were post-traumatic. Even though the diagnosis was made by a neurologist based on a clinical examination in each case, it was frequently confirmed by an orthoptic evaluation (24/31 - 77.4%). All the radiologic assessments (CT scan in 32.2% of the patients and MRI in 58.1 were unremarkable. Only two (6.4%) received prednisone, while nine (29.0%) received food and vitamin supplements.

Discussion: IAOM is a common disease that affects older people, often involving the abducens nerve. In the great majority of the cases, it is not possible to define a direct cause, but the most reported risk factor was impaired glucose metabolism. Since radiologic imaging is frequently unremarkable, an accurate clinical and anamnestic assessment, aimed to exclude neurological findings other than the ocular mononeuropathy, is helpful for a correct diagnosis.

Conclusions: At our knowledge, this is the first retrospective study designed to process the epidemiological characteristics of acute ocular mononeuropathies. However, larger studies are needed to better define the clinical and etiologic features of IAOM and, only by then, the most accurate clinical interventions in an emergency setting.

INCIDENCE OF GUILLAIN BARRÉ SYNDROME IN LAZIO REGION DURING SARS-COV2 PANDEMIC PERIOD

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The relationship between the SARS-COV2 infection and the Guillain Barré Syndrome is not entirely clear. Two studies, one based on a cohort of patients from northern Italy and one based on data collected from emergency departments in Spain, suggested an increased incidence of GBS during SARS-COV2 pandemic and supported a pathogenic link between the virus and GBS [1-2]. By contrast, an epidemiological and cohort study on the UK population showed a reduction of GBS during pandemic which may be related to the reduction of the transmission of other pathogens during the lockdown phase [3]. Finally, despite an association between vaccine and GBS has not been proven, the GBS is reported as a rare complication in every summary of medical product of vaccines.

However, given the incidence of GBS and the large amounts of people involved in vaccination programs, it is inevitable that many sporadic cases of GBS caused by other factors will appear temporally associated with COVID-19 vaccination. Data from health information systems (HIS) represent a great opportunity to clarify the role of SARS-COV2 infection and vaccine on GBS and reduce public concern. We obtained data from HIS (Sistema Informativo Ospedaliero (SIO), piattaforma "Emergenza CoronaVirus" (ECV) della Regione Lazio, SIES, Anagrafe Tributaria) by the use of specific algorithms. The cases of GBS were identified using the ICD-9-CM diagnosis code at discharge (357.0) from any department. In the Lazio Region as of 31.12.21 80% of the population received two doses of the vaccine. About 20% of the population has contracted the virus. In our study, patients admitted more than once with a code for the same pathology were excluded. In the period January 2015-December 2021 we obtained 1160 patients diagnosed with GBS in the Lazio Region. The data available to us has shown a downward trend over the past 7 years. Our study did not demonstrate an increase of GBS incidence during the SARS COV2 pandemic or during the first phase of vaccination in Lazio region. A lower diffusion of SARS-COV2 in Lazio region and the reduction of the other infections, due to prevention measures, could explain the apparent discrepancy with data from Northern Italy. We suggest that a national epidemiological study could give great information to better evaluate the impact of SarsCOV2 on GBS in Italy. Finally the stable incidence of GBS during vaccination period seems a reassuring data on vaccine safety.

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LIFE AND DEATH IN MULTIPLE SCLEROSIS: 20 YEARS-LATER REAPPRAISAL OF A COHORT OF PATIENTS RESIDING IN VERONA, ITALY

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Introduction: Multiple sclerosis (MS) is one of the most disabling diseases affecting young adults. Earlier age at death and increased excess mortality in people with MS (pwMS) have been previously demonstrated, although more recently it has been postulated a rise in survival occurring in the last 20 years.

Objectives: To assess survival in a cohort of pwMS residing in the town of Verona, Italy, over 20 years.

Methods: We evaluated a cohort of pwMS comprising all the prevalent cases residing in Verona at 31/12/2001. We retrospectively investigated the survival state of each pwMS at 31/12/2021 through the consultation of medical records of the Neurology Units of the two Verona Hospitals – referral centers for MS – to assess if patients were still on follow-up; for those with no records at 31/12/2021, we surveyed the death certificates from Verona municipality to verify death notification and date. We evaluated mean age to death of MS patients compared to the general population of Verona province and mean time from disease onset to death by age and disease course.

Results: Among 270 MS prevalent cases (158 females, F) at 31/12/2001, on 31/12/2021 59 (36F) patients had died, while 155 pwMS (119F) were currently undergoing clinical follow-up; 137 of them were still residing in Verona. 10 cases (4F) had been lost at follow-up while for 46 of them the investigation is still ongoing. Mean age at disease onset was 32±11 years for both F and M; mean age at prevalence day was 47±14 years for F and 47±12 years for M, Mean age at death was 68±13 years (67±12 in M and 68±14 in F), as compared with a mean of 81±1 years of the general population of Verona province between 31/12/2001 and 31/12/2021; mean time from disease onset to death was 31±13 years (36±13 M and 28±13 F, $p<0.001$; mean age at MS onset for the dead group: 39±11 for F and 31±13 for M); it was significantly lower in patients with primary progressive MS (27±13 years) than in those with relapsing-remitting or secondary progressive MS (34±13 years, $p<0.001$).

Conclusions: Mean age at death is lower in pwMS compared to the general population; we surprisingly observed a lower time from disease onset to death in females than in males: further investigation is needed to clarify if the result is attributable only to the different age at onset in the two groups or to other factors.

A MULTI-SOURCE POPULATION-BASED STUDY ON INCIDENCE AND PREVALENCE VARIATION IN AGE AT ONSET OF MULTIPLE SCLEROSIS IN THE PROVINCE OF PALERMO, SICILY

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Objective: Recent studies on the Incidence and prevalence of Multiple Sclerosis (MS) indicate increasing trends of disease frequency, partly explained by changes in diagnostic criteria but updated large population-based studies in Sicily are lacking. The present study was aimed at investigating patterns of MS age at onset by means of a population-based study in Sicily.

Methods: MS incidence had been previously investigated in several Sicilian municipalities by multi-source methodology. In the present study, we investigated MS frequency in the Province of Palermo on June 30th 2018 (prevalence day) in a population of 1,252,588 inhabitants. Incidence rates were calculated for the period 2000-2018 (18,875,588 person/years). We obtained clinical and demographical data for each patient from MS clinics and centres in the study area, Hospital and Neurological Departments, and general practitioners. We calculated age and sex specific onset adjusted prevalence and incidence rates with 95% confidence intervals.

Results: Crude onset adjusted prevalence was 169,9/ 100,000 inhabitants (95% CI 161.7-177.1), it was 114.5 in men and 221.8 in women (W:M ratio 1.94), with a peak of nearly 300/100,000 in the age classes between 35 and 45 years of age. Mean annual incidence rates were 6.3/100.000 inhabitants (95% CI 6.0-6.7) for the whole population, with a peak of 13.8/100,000 in the age class between 25 and 29 years of age. Incidence was 4.1/100,000 in men (95% CI 3.7-4.5) and 8.5/100,000 (95% CI 8.0-9.1) in women.

Discussion and Conclusion: This is the largest population-based study performed in Sicily. The present study revealed Prevalence and incidence rates considerably higher compared to all previous studies performed in the same area, and among the highest among other studies performed in the Mediterranean area. The present study confirms that age MS onset tends to increase over time.

AGE AT MIGRATION AND PHENOTYPE DIFFERENCES IN MULTIPLE SCLEROSIS: A MULTICENTER STUDY IN ITALY

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Introduction/Objectives: Previous studies considering migrant individuals affected by Multiple Sclerosis (MS) indicate that phenotype differences across Countries may be driven by genetic and cross-cultural characteristics. The present study investigated if age at migration could contribute to phenotype differences between individuals with MS living in Italy but born abroad.

Methods: The MigIt study included 1360 individuals affected by MS (458 foreign-born and 902 age- and sex-matched native-born Italian patients). Age disease onset, symptoms at onset and MRI parameters at diagnosis were analyzed by comparing people migrating to Italy within or after 15 years of age. Logistic regression models were built. All analyses were two-sided with an alpha level set at 0.05.

Results: Fifty, out of the 458 individuals with MS born aboard migrated to Italy within the age of 15. Italian individuals had less frequently a progressive onset (OR 0.73; CI 0.54-0.98; $p <= 0.03$) and higher disability (OR. 0.46; CI 0.29-0.73; $p=0.001$). A complete diagnostic workup was performed more frequently among patients migrating before age 15 compared to the others (OR 1.55; CI 0.83-2.90; $p=0.1$). Patients who migrated earlier showed an

inverse association with higher age at disease onset (above or not 28 years old) (OR 0.50; CI 0.27-0.94; p= 0.027), a progressive disease course since onset (OR 0.34; CI 0.12-0.98; p= 0.036).

Discussion/Conclusion: The present study confirms how age at migration in people with MS can represent a disease modifying factor of phenotype characteristics. This observation strengthens the need to consider the effects of the population as well as cross-cultural differences, in the management of individuals with MS belonging to different geographical areas.

INCIDENCE, SURVIVAL AND GEOEPIDEMIOLOGICAL ANALYSIS OF SCHWANNOMAS IN THE PROVINCE OF CATANIA, ITALY, DURING THE 2003–2016 PERIOD

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Objectives: Nerve sheath tumors (NSTs) are the third most common Primary Brain Tumors (PBTs), accounting for the 8.6% of all CNS tumors, with an incidence of 2.0/100,000person-years [1]. The most common subtype of NST is schwannoma, accounting for 89% of all cases [2]. Schwannomas can involve brain and spinal-cord and the most common schwannoma is vestibular schwannoma [1-3]. Despite their benign behaviour, schwannomas and, especially, vestibular schwannomas, could significantly impact on quality-of-life, leading to hearing loss, dizziness and disequilibrium [2]. No previous studies investigated epidemiology of schwannomas in Italy. We performed the first study evaluating epidemiology of not only overall schwannomas but also of each anatomical subtype, including spinal and cerebral schwannomas. Moreover, considering cerebral schwannomas, we evaluated epidemiology of both parenchymal and intracranial subtype, and, within the latter group, of both vestibular and non-vestibular schwannomas. Furthermore, we analysed the distribution of schwannomas incident-cases in the province of Catania using a geoepidemiological analysis, to identify possible spatial- and temporal-cluster. Indeed, although the physiopathology of these tumors is still debated, a possible role of different environmental factors has been hypothesized. Understanding geographical distribution of brain tumors might be useful to shed light on environmental risk factors and on their possible contribution to cancer occurrence. Up to date, no previous geoepidemiological studies were performed on schwannomas.

Materials and Methods: From local cancer-registry, subjects with schwannomas diagnosed during 2003-2016 in the province of Catania were collected. Incidence rate (IR) was assessed for overall, spinal and cerebral schwannomas (vestibular and non-vestibular). Incidence trend was assessed using Joinpoint-regression-analysis, survival-analysis using Kaplan-Meier method and cluster analysis using Kulldorff's-spatial-scan-statistic.

Results: Overall, 214 cases of schwannomas were identified, with an IR of 1.4/100,000person-years(95%CI 1.2-1.6).Cerebral schwannomas represented the 90.7% of overall schwannomas, with an IR of 1.3/100,000person-years(95%CI 1.1-1.5),while vestibular schwannomas were the 75.8% of cerebral schwannomas, with an IR of 1.0/100,000person-years(95%CI 0.8-1.1).Overall, cerebral and vestibular schwannomas had a significant female predominance, a peak of incidence in 55-64 years-old-group and a stable incidence throughout the study period. Non-vestibular and spinal schwannomas represented only the 17% and 9.3%, respectively [IR=0.2/100,000 person-years (95%CI 0.1-0.3) and 0.1/100,000 person-years (95%CI 0.1-0.2), respectively]. Mean survivals for cerebral, vestibular and non-vestibular schwannomas were 13.4, 13.6 and 12.0 years, respectively, with age as independent risk factor for death. No deaths occurred among spinal schwannomas. Neither spatial nor temporal clusters of schwannomas were found. A significant low-incidence space-time cluster was detected in the south-western side of the province(p-value=0.02).

Discussion and conclusion: Epidemiology of schwannomas in the province of Catania is close to that reported worldwide. Space-time cluster of low-incidence of schwannomas was found in the south-western side of Catania. Further risks factor studies are necessary.

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EMERGENCY STROKE MANAGEMENT DURING COVID-19 PANDEMIC: EXPERIENCE FROM TRIVENETO AREA

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Background and aims: COVID-19 pandemic is a major problem for global healthcare. There are many challenges for stroke emergency chain to maintain high medical care levels: many European Countries showed changes in neurological admissions and treatments. Our aim was to investigate the amount of admissions and treatment of stroke patients Friuli-Venezia-Giulia, Veneto and Trentino-Alto-Adige during the first wave of COVID-19.

Materials: We retrospectively collected patients admitted to most Triveneto Stroke Units, eventually treated with thrombolysis or thrombectomy, from January to May 2020 (the first Italian pandemic wave).

Methods: Primary endpoint was the number of patients arriving to these Stroke Units; secondary endpoints were number of thrombolysis and/or thrombectomies. Chi-square analysis was used on all patients; furthermore patients were divided into two cohorts (pre-lockdown and lockdown) and Kruskal-Wallis test was used.

Results: 2536 patients were admitted in 22 centres. There was a significant decrease (p=0.016) of admissions in April (464) compared to January (570); significant decrease (p=0.032) of thrombectomies in April (32) compared to January (64); thrombolysis rate was unaffected. Analysing non-COVID-19 period - January and February - and COVID-19 period - March and April - there was a significant decrease of admissions (11%) with a collapse of thrombectomies (42%), while thrombolysis rate remained unchanged.

Discussion and Conclusions: We found a decrease of stroke patients admissions in North-East-Italy during first wave period, with no impact on thrombolysis rate, confirming a great response of emergency care system to pandemic; instead the significant decrease in thrombectomy rate addresses some considerations on Triveneto stroke networks organization.

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AMYOTROPHIC LATERAL SCLEROSIS IN TWO ITALIAN REGIONS: OCCURRENCE BASED ON HEALTH ADMINISTRATIVE DATABASES AND VALIDATION THROUGH A DISEASE REGISTRY

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Objectives: Several epidemiological studies on Amyotrophic lateral sclerosis (ALS) report heterogeneous estimates of prevalence and incidence [1,2]. Administrative healthcare data may represent a key source for exploring the epidemiological data associated with a disease. This study aimed: 1) to estimate prevalence and incidence of ALS in Latium and Tuscany regions during the period 2014-2019, using regional administrative healthcare data; 2) to validate the algorithm for the identification of ALS cases from administrative healthcare data, using a disease registry available in the Latium region.

Materials: We employed different administrative databases, namely: the Healthcare Assistance File, the Hospital Information System, the Healthcare Emergency Information System, the Co-payment Exemptions Register, and for validation, the Latium ALS registry.

Methods: Patients were identified as ALS cases if they met any of the following criteria in the years 2014-2019: 1) hospital discharge with a primary diagnosis, or with a secondary diagnosis of ALS in combination with a discharge from a neurological hospital ward; 2) emergency department discharge with a primary diagnosis of ALS; 3) disease specific co-payment exemption for ALS. All databases were linked through an anonymous unique patient identifier. Patients not alive, not resident in the study areas or younger than 18 years were excluded. Yearly incidence was estimated from 2014 to 2019. Standardized prevalence was stratified by sex and 5-year age groups, using the Italian adult population for reference. The algorithm for the identification of patients affected by ALS was validated in terms of sensitivity and specificity.

Results: On 31/12/2019, 546 and 375 alive patients with a diagnosis of ALS were identified in Latium and Tuscany, respectively. Standardized prevalence ranged from 11.52/100,000 (95%CI: 10.59-12.53) in Latium to 12.31/100,000 (95%CI: 11.17-13.56) in Tuscany, with higher rates in men and in the population aged 65-79 years. Incidence rates in 2019 were: 1.99/100,000 (95%CI: 1.63-2.44) in Latium and 4.26/100,000 (95%CI: 3.61-5.02) in Tuscany. Validation confirmed a good performance of the algorithm in identifying cases of ALS (sensitivity 84.84%; specificity 99.98%).

Discussion: The use of administrative data provided prevalence and incidence rates in two Italian regions and the validation study demonstrated a good performance of the algorithm used.

Conclusions: Administrative healthcare data represent an efficacious source to estimate epidemiological data for diseases like ALS and can be useful for assessing patient needs and planning targeted social assistance interventions. The study was funded by the Italian Medicines Agency (call 2012 13 14).

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PERIPHERAL FACIAL NERVE PALSY: EPIDEMIOLOGY, DIAGNOSIS AND TREATMENT IN AN URGENT NEUROLOGY AMBULATORY SETTING

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Objectives: In the present study, we evaluated the incidence of outpatients' visits for peripheral facial nerve palsy (PFNP) in our urgent ambulatory setting. Furthermore, we analyzed the patients' demographic features and the diagnostic and therapeutic approach.

Materials and Methods: We reviewed records of patients referred for PFNP as urgent outpatient visits at our Department of Neurology from October 2018 to April 2022. We considered patients with evidence of weakness of the upper and lower portions of the face on physical examination and excluded patients with hemifacial spasm or with extra-cranial involvement. Information related to age, sex, diagnostic tools, and treatment approach were collected.

Results: We collected data from 66 patients. The mean age at presentation was 52 years (SD ±15,7). Females were 34 (51.5%), and among these one was pregnant. Sixty-two patients (94%) presented an idiopathic PFNP, two cases (3%) had vesicles in the external auditory canal, one patient (1.5%) had a parotid tumor-infiltrating the VII nerve, and only one underwent SARS-CoV2 vaccine close to the onset of symptoms (1.5%). Four patients presented with recurrent PFNP on the same side as the previous episode (6%), and 25 patients (38%) were already evaluated at the Emergency Department at the symptom's onset. The diagnoses were primarily made by history taking and physical examination. Moreover, twenty-seven patients (41%) underwent a radiological brain investigation (10 CT, 17 MRI). Management included mainly medical (95,5% of patients were treated with prednisone, medium dose of 47,7 mg) and physical therapy.

Discussion: PFNP is the most common acute-onset cranial mononeuropathy. It recognized many causes; however, most of the cases are idiopathic. Therefore, patients with PFNP often seek evaluation in an emergency setting. The clinicians must distinguish patients who need further investigations and specific therapy based on history and physical examination.

Conclusion: Notwithstanding, PFNP is frequent in the emergency areas, but there are no recent epidemiological studies with large case series in the literature. This is the first study that retrospectively analyzed the epidemiological characteristics of patients and the diagnostic and therapeutic approach in an acute setting.

EPIDEMIOLOGY OF SEROPOSITIVE MYASTHENIA GRAVIS IN NORTH-WESTERN SARDINIA

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Objective: To determine the incidence and prevalence of myasthenia gravis (MG) associated with acetylcholine receptor (AchR)-IgG and muscle tyrosine kinase (MuSK)-IgG in North-Western Sardinia (Italy).

Material and Methods: Patients were retrospectively identified from the registry of the Neurochemistry Laboratory of the University-Hospital of Sassari (reference laboratory for AchR-IgG and MuSK-IgG testing for the upper-mid Sardinia) based on the following criteria: 1) serum positivity for AchR-IgG (titer ≥0.5 nmol/L) and/or MuSK-IgG (titer ≥100 pg/ml) detected between 1998-2022; 2) medical records available; 3) clinical phenotype compatible with MG; and 4) residence in North-Western Sardinia (former Province of Sassari) during the study period. Incidence (January 1, 2010-December 31, 2019) and prevalence (on January 1, 2020; population 325,288) were calculated. Antibody positivity was assessed by radioimmunoprecipitation assay.

Results: Out of 517 seropositive patients identified since 1998, 183 were included in the study (incident, 97; prevalent, 165). We excluded 334 patients due to missing clinical information (n=65); residence outside the province of Sassari (n=168); death before 2010, MG onset before 2010 and death before 2020, or MG onset after 2019 (n=56); and clinical phenotype not consistent with MG (n=45; median AchR-IgG titer, 0.7 [range, 0.5-5.5]). The crude prevalence of MG on January 1 2020 was 50.7 per 100,000 (95% CI, 43.4-58.9), whereas the incidence was 29.8 per 1,000,000 person-years (95% CI, 24.3-36.2). Antibody specificities were AchR in 170 (92.9%) and MuSK in 13 (7.1%) patients; median antibody titers (highest in case of multiple tests available) were 5.7 (range, 0.5-22) nmol/L and 1,255 (range, 136-1730) pg/ml, respectively. Overall, the median age at MG onset was 57 (range, 8-90; IQR, 39-71) years; 94 (51.4%) patients were female; and 9 (5%) had onset before 18 years of age (median 15, range 8-17). Among incidence cases, age at disease onset was distributed as: pediatric, <18 years (n=2; 2%); early onset, 18-50 years (n=14; 14.4%); late onset, 51-65 years (n=25; 25.8%); and very late onset, >65 years (n=56; 57.7%). In 45 (46.4%) incident cases, MG was initially restricted to ocular muscles (ocular MG).

Discussion and Conclusions: The global mean incidence and prevalence of MG have been assessed at ≈15 (range, 4-29) per million person-years and 20 (range, 2-37) per 100,000, respectively. Sardinia is an area at higher risk of MG, similar to what previously reported for other immune-mediated disorders (e.g., multiple sclerosis, type-1 diabetes). The environmental and genetic determinants of MG risk in the Sardinian population need to be investigated.

NEUROGENETICS

PHENOTYPIC HETEROGENEITY AMONG ABCA7 MUTATIONS CARRIERS IN ALZHEIMER PATIENTS: A SINGLE-CENTER STUDY

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Objective: Variants in the ABCA7 (ATP Binding Cassette Subfamily A Member 7) gene have long been associated with an increased risk of both early-onset and late-onset Alzheimer's Disease (AD), while only a few families have been reported segregating loss-of-function mutations. However, to date, the phenotypic characteristics of these mutations' carriers remain largely unknown. We aim to contribute to the phenotypic characterization of these patients by retrospectively reviewing the cases identified in our center's AD cohort.

Materials and methods: For this purpose, we screened 177 AD patients for the presence of ABCA7 loss-of-function or pathogenic missense mutations. The diagnosis of AD and related clinical variants was made according to the 2014 IWG-2 criteria. Then, we analyzed the medical records of ABCA7 mutation carriers for in-depth evaluation of clinical histories, CSF analysis results, and neuroimaging data. Results: Of the 15 patients identified as mutation carriers, 8 had a 'typical' memory-disordered presentation. The others showed alternative phenotypes, including 2 "frontal", 2 "logopenic" and 3 "posterior" variants. Some patients additionally exhibited atypical characteristics, including REM sleep behavior disorder (RBD) (n=1), parkinsonism (n=2), and recurrent visual hallucinations (n=1). The mean age of onset of cognitive symptoms was 62.9 ± 8.3 years, with 10 patients presenting an early-onset cognitive decline. Only 5 subjects reported a family history of cognitive impairment. Depression was present in 10 patients at the time of diagnosis.

Discussion and conclusions: Our study expands the case series of AD patients carrying ABCA7 mutations described in the literature. Remarkably, 47% (n=7) of mutation carriers had an 'atypical' clinical presentation, compared with an expected 6-14% in the AD general population. Heterogeneity in presentation and age of onset also suggests the existence of phenotype modifying factors, which are currently unknown. In line with a previous study, the high rate of depression observed in our cohort compared to what is expected in the AD general population (20-30%), suggests a possible role of ABCA7 mutations as a risk factor also for this condition. The presence of patients with atypical features such as parkinsonism and RBD could indicate a possible overlap with Lewy body disease, in which the role of ABCA7 should be better investigated. Further studies, in larger case series, and possibly including neuropathology, should improve genotype-phenotype correlation and characterize the genetic and/or environmental factors responsible for clinical heterogeneity in these patients.

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ALEXANDER DISEASE IN ADULTS: CHARACTERIZATION OF A LARGE ITALIAN COHORT

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Background and Aims: Alexander disease (ALXDRD, OMIM #203450) is a rare astrocytic leukodystrophy caused by autosomal dominant, mostly de novo GFAP pathogenic variants, and can be classified into two forms: type I, with onset by age 4, and type II, with onset after age 4. Our work is aimed at describing the clinical features and evolution of an Italian cohort of adult subjects with ALXDRD to further expand the disease knowledge [1].
Materials and Methods: We recruited the ALXDRD patients from the Carlo Besta Adult Leukodystrophy Database from the date of its creation (January 2004) to April 2022.

Results: We identified 40 genetically-diagnosed ALXDRD patients (all type II with 23 different pathogenic variants). 13 cases were subsequently excluded for insufficient data. Among the remaining 27 (21 probands and six related family members), we identified 21 symptomatic and six asymptomatic cases. Among the symptomatic patients, 19 had age at onset ranging from 13 to 66 years, and typically presented with ataxic-spastic gait. Two had late-childhood onset with vomit and growth retardation. The disease course was unevenly progressive, with varying degrees of dysarthria, dysphagia, and urge-incontinence after median follow-up of six years. Pain and dysesthesias, mild-to-moderate cognitive impairment, obstructive sleep apnoea, scoliosis, and subclinical dysautonomia were often observed. Palatal myoclonus was rarely found. In two patients, we observed rapid worsening after head trauma. Four patients died. The six asymptomatic patients were identified at mean age of 55 years (three incidentally and three because of affected relatives), and five of them had the same pathogenic variant (p.Arg376Leu). MRI constantly showed bulbar and cervical spinal cord atrophy with signal abnormalities.

Discussion: In adults, MRI bulbospinal abnormalities are the ALXDRD hallmark, as they were present in all subjects, including the asymptomatic ones. A consequence of this is that, in adults, we should be cautious in considering GFAP variants as pathogenic, when those MRI abnormalities are lacking. Pain and dysesthesias (likely related to spinothalamic tract involvement or small fiber neuropathy) are common overlooked complaints. A link between head trauma and rapid progression was noted, suggesting clinicians should inform ALXDRD patients to minimize the head-injury risk [2]. Disease progression was highly variable among patients. This observation highlights the need to develop disease-specific clinical assessment tools for ALXDRD in adults and should be considered in the interpretation of the results of clinical trials with potential disease-modifying drugs in the late-onset forms.
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THAP1 GENE MUTATION: POSSIBLE GENETIC RISK FACTOR FOR PARKINSON'S DISEASE?

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Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder, affecting 3% of the population older than 75 years of age. Several studies have confirmed that genetic factors contribute for approximately 25% to the risk of developing PD. We report the case of a 61-year-old woman with a previous history of diabetes mellitus, obesity and autoimmune hypothyroidism, who developed since 2017 a resting tremor in the right lower limb with secondary extension to the ipsilateral arm. Her father and paternal aunt had postural tremor with onset after the age of 80 and 50 year, respectively. At the first neurological evaluation in 2019 an extrapyramidal syndrome with a tremoric phenotype prevalent in the right hemisome was detected. No non-motor symptoms were discovered, except for hyposmia since childhood. The neuro-imaging investigations performed, like brain MRI without gadolinium and SPECT-DATscan were compatible with an idiopathic PD. Levodopa therapy prescribed to the patient improved the neurological symptoms. In 2020 the patient was enrolled in the multicentric ROPAD study with the aim of identifying the main genetic mutations involved in PD.

Materials and methods: Gene panel testing was performed on DNA extracting from a blood sample after informed consent. ROPAD panel include the analysis of 71 genes involved in PD and related phenotypes. Confirmation of the result has been performed by a diagnostic laboratory in Italy by Sanger sequencing.

Results: The genetic study showed a heterozygous variant of the THAP1 gene (c.70-71+8del) causing a deletion of 10 nucleotides in the acceptor splicing site of the first exon of the gene. THAP1 (THAP domain-containing apoptosis-associated protein 1) is the causative gene of dystonia type 6 (DYT6), a form of autosomal dominant dystonia with incomplete penetrance. Discussion: DYT6 is an adolescent-onset segmental or multifocal dystonia characterized by an early involvement of craniofacial and laryngeal muscles and upper limbs. It has been associated with dystonic tremor or myoclonus, but no correlation with parkinsonism has yet been described in literature.

Conclusion: We suggest that the THAP1 gene variants may represent a new genetic risk factor for Parkinson's disease, although it cannot be ruled out that the reported patient represents a case of incomplete penetrance without dystonic phenotype with a superimposed idiopathic PD. Futher genetic studies will be needed to determine the possible causal link between THAP1 mutation and PD.
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INCOMPLETE PENETRANCE OF SOD1 SPLICE VARIANT INDUCED AMYOTROPHIC LATERAL SCLEROSIS: A CASE REPORT

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Aim: We present a case in which in-depth genetic analysis of patient and his asymptomatic relatives led the identification of c.358-10T>G SOD1 variant causes an alteration of splice site that inducing Amyotrophic Lateral Sclerosis (ALS) disease.

Method: A 48 years-old man presented with a 15-month history of cramps and progressive weakness in lower extremities leading to difficulty in ambulation. Previously an inflammatory neuropathy was diagnosed and he was treated with intravenous immunoglobulin, with a slight worsening. Our neurological examination detected the presence of asymmetrical hypotrophy and weakness in lower limbs. Nerve conduction study showed reduced CMAP amplitude of peroneal nerve, while Needle electromyography revealed widespread spontaneous activity in distal muscles of lower limbs and in paravertebral thoracic muscles. We diagnosed a flail leg variant of ALS, with

a mild disability equal to 41/48 at ALS Functional-Rate-revised (ALSFR-R) scale. Genetic analysis of core ALS gene (SOD1, FUS, TARDBP, VCP, OPTN, SQSTM1, TUBA4A, PFN1, UBQLN2 and C9orf72) revealed the presence of the heterozygous c.358-10T>G variant in intron 4 of SOD1 gene. In-silico analysis predicted that this variant could affect splicing reducing the score of the constitutive acceptor site and creating a new one. Proband family history was unremarkable: his parents, in their 80s', and his sister were in good health with normal neurological examination. The segregation analysis revealed the presence of this variant in the patient's mother and sister. mRNA analysis of proband's lymphocyte demonstrated that the T>G substitution creates an alternative acceptor site that resulted in an aberrant transcript containing nine additional nucleotides between exons 4 and 5 (r.357_358ins358-9_358-1;). This results in an in-frame insertion of three amino acids (p.Val119_Val120insPheLeuGln) to the SOD1 protein. The same effect on mRNA splicing was observed in lymphocytes from the unaffected mother raising question about the underlying mechanism of incomplete penetrance. One year later the ALS diagnosis, the patient beneficiated of intrathecal administration of Tofersen, an antisense oligonucleotide that mediates the degradation of SOD1 mRNA. Three years after the onset disease, the ALSFRS-R score of patient is 39/48 and the progression disease is limited at lower limbs.

Conclusion: We reported that the c.358-10T>G SOD1 variant causes an alteration of splice site inducing ALS disease with incomplete penetrance. These data underline the importance of mRNA analysis to evaluate the pathogenic role of all intronic variant in SOD1 gene allowing diagnosis of early or unusual ALS, which is particularly important for access to new gene therapies.

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TWO VARIANTS OF UNCERTAIN SIGNIFICANCE IN NPC1 GENE IN A FAMILY WITH ATYPICAL PRESENTATIONS OF NIEMANN-PICK DISEASE TYPE C

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Objective: Niemann-Pick disease type C (NPC) is a rare autosomal recessive disease caused by mutations in NPC1 and NPC2 genes and characterized by lipids accumulation in several organs. We present two siblings carrying two variants of unknown significance (VUS) on NPC1 gene.

Materials: Medical records, blood samples and skin biopsies of the patient attending our Centre, his sister and his parents.

Methods: Review of the subjects' clinical history.

Results: A 52 year-old man presented with a slowly progressive change in his voice, difficulty in swallowing and, a few months later, troubles in looking downward. He has suffered from bilateral progressive sensorineural hearing loss since he was adolescent, as did his sister. His family history was otherwise negative for neurological diseases. During examination, we detected dysphonia, dysphagia, supranuclear vertical gaze paralysis, upper limb asymmetric dysmetria and diffuse hyporeflexia. These findings were accompanied by splenomegaly at abdomen ultrasonography and mild disexecutive cognitive dysfunction at the neuropsychological evaluation. After excluding genetic causes of deafness, we investigated NPC disease. The oxysterols levels resulted markedly higher than normal values and two heterozygous VUS, c.481C>T (p.Arg161Trp), not previously reported, and c.1070C>T (p.Ser357Leu), were found in the NPC1 gene. The Filipin staining test resulted positive. Each parent, who exhibited normal blood oxysterol levels and did not complain of neurological symptoms, carried one of the two VUS found in their son. We proposed the diagnostic process to the sister to investigate whether her hearing loss could be explained by an incomplete phenotype of NPC; firstly, we examined her to exclude the presence of subclinical neurological signs, finding a supranuclear gaze paralysis. We, then, obtained her blood and skin biopsy samples, demonstrating the same biochemical and genetic alterations found in her brother, except for a lower, but still pathological, level of oxysterols.

Discussion: Adult-onset atypical phenotypes of the two siblings could be related to the NPC1 variants, both likely pathogenic considering the confirmation of the classic biochemical alterations of NPC both in blood and fibroblasts culture. Based on the presence of Miglustat, the only approved therapy for NPC in Europe, the diagnostic work-up for NPC should be considered also in patients with mild phenotypes or even isolated sensorineural deafness, after a careful neurological evaluation looking for subclinical findings.

Conclusion: Both p.Arg161Trp, that, to the best of our knowledge, was not previously reported in literature, and p.Ser357Leu substitutions could be considered pathogenic for NPC.

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A NOVEL DNM2 MUTATION IN A CASE WITH AN HEREDITARY PURE SENSORY AXONAL POLYNEUROPATHY

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Aims: Dynamin 2, encoded by DNM2 gene, belongs to a family of pleiotropic GTPases. DNM2 gene mutations have been associated with several neuromuscular disorders, such as intermediate and axonal forms of Charcot-Marie-Tooth (CMT) disease. In this report, we describe clinical, instrumental and genetic aspects of a 59-year-oid male patient carrying a novel DNM2 mutation and exhibiting a distinct phenotype of pure sensory axonal polyneuropathy.

Materials: We describe a case of a 59-year-old male with familial history positive for gait disorders. He presented an insidious onset of numbness and burning pain in the lower limbs. In addition, he had been suffering from ostinate constipation with intestinal obstruction. Neurological examination

showed a "stomping" gait, reduced patellar reflexes, lower limbs global hypoestesia with slocking distribution.

Methods: The patient underwent an ENoG examination, whereas nerve conduction study revealed an axonal damage. Considering the overall clinical picture and the positive familial history, we performed a comprehensive molecular analysis of the genes responsible for hereditary neuropathies.

Results: The molecular analysis of the genes responsible for hereditary neuropathies, by means of Next Generation Sequencing approach, showed a novel p.Hys128Arg-DNM2 heterozygous mutation.

Discussion: We described clinical, instrumental and genetic aspects in a patient affected by pure sensory axonal polyneuropathy and carrying the novel p.Hys128Arg-DNM2 heterozygous mutation.

Conclusions: This mutation and its clinical presentation, further expands the spectrum of DNM2 mutations and related phenotypes. Another interesting feature we observed is subtle constipation, possible expression of gastrointestinal autonomic dysfunction.

TARGETED NEXT-GENERATION SEQUENCING REVEALED A NEW MUTATION IN GLRA1 GENE IN A FAMILY WITH HEREDITARY HYPEREKPLEXIA

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Introduction: Hereditary Hyperekplexia (HPX) is a genetic neurodevelopmental disorder defined by the triad of neonatal hypertonia, excessive startle reflexes, and generalized stiffness following the startle. Defects in GLRA1 are the most common cause of HPX, inherited both in an autosomal dominant and autosomal recessive manner. To date, the pathogenetic mechanism of the disease is still not fully understood and a clear genotype-phenotype correlation has not emerged yet. Here we report two siblings with a typical HPX phenotype, linked to a novel GLRA1 mutation, inherited with a recessive pattern.

Objective: The aim of this study was to assess the genetic background of a familial case of two siblings affected by HPX, using a targeted Next Generation Sequencing (NGS) panel comprising known HPX-causative genes.

Materials and Methods: After DNA extraction by standard methods and quantization using the Qubit instrument (ThermoFisher Scientific, high coverage targeted NGS data were generated by an amplicon-based approach. We used a custom-made panel comprising HPX-related genes (GRLA1, GLRB, SLC6A5, GPHN and ARHGEF9). The enriched libraries were sequenced on the Ion Torrent Personal Genome Machine (PGM) system from ThermoFisher Scientific. The alignment and the variant caller was carried out using Ion Torrent Suite 5.10. Annotation and filtering/priorization of single-nucleotide variations (SNVs) and copy number variations (CNVs) discovered was made by Annovar.

Results: In the present study, the genetic investigation of a familial case of HPX using an amplicon based NGS approach revealed a novel homozygous nonsense variant c.G1509T (p.E403X) in the exon 9 of GLRA1 in both sibling, validated by direct sequencing. No mutations were found in other genes known to cause familial hyperekplexia. The parents, who were first cousins of Pakistani origin, were heterozygous for the p.E403X mutation. The p.E403X variation is a G-to-T substitution at the nucleotide position 1509 in exon 9, replacing glutamate to a premature stop codon at codon 403.

Discussions: We described the case of two siblings with HPX and a novel nonsense mutation c.G1509T (p.E403X) in GLRA1. Localized precisely in loop 3, between the TM3 and TM4 transmembrane domains, the variant causes the deletion of a protein portion, resulting in a truncated protein causing a loss of function, although the delineation of its mechanism requires further investigation.

Conclusion: In conclusion, NGS genetic testing of glycinergic neurotransmission-associated genes including GLRA1, is a readily available tool to confirm clinical suspicion, provide an appropriate diagnosis of HPX and for family screening.

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SORL1 GENE MUTATION AND OCTAPEPTIDE REPEAT INSERTION IN PRNP GENE IN A CASE PRESENTING WITH RAPIDLY PROGRESSIVE DEMENTIA AND CEREBRAL AMYLOID ANGIOPATHY

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Background and aims: Cerebral amyloid angiopathy (CAA), a major cause of spontaneous intracerebral haemorrhage and cognitive decline, has been associated with a variety of neurodegenerative disorders, included Alzheimer's Disease (AD) and Prion diseases (PrDs). Pathophysiology of CAA is still largely unknown. We report the case of an 80-year-old man with a rapidly progressive dementia and neuroimaging features consistent with CAA carrying two genetic defects in the prion protein (PRNP) and sortilin related receptor 1 (SORL1) genes.

Materials and Methods: Neurological examination, Brain Magnetic Resonance Imaging (MRI), electroencephalogram-electromyography (EEG-EMG) polygraphy and analysis of 14–3–3 and tau proteins, amyloid β40 (Aβ40) and amyloid β42 (Aβ42) in the cerebrospinal fluid (CSF) were performed. The patient underwent a detailed genetic study by next generation sequencing analysis including a panel of causal and risk genes known to be associated with dementia.

Results: The patient presented with progressive cognitive dysfunction, generalized myoclonus and ataxia. About 9 months after symptoms onset, he was bed-bound, almost mute and akinetic and died 23 months after the onset of the initial symptoms. Brain MRI was consistent with CAA. CSF analysis showed high levels of total tau (t-tau) and phosphorylated tau (p-tau), decreased Aβ42, decreased Aβ42/Aβ40 ratio, while was negative for 14-3-3 protein and for identification of misfolded prion protein via RT-QuIC assay. Genetic tests revealed the presence of the E270K variant in the SORL1 gene and the presence of a single octapeptide repeat insertion (OPRI) (24-base pair insertion) in the coding region of the PRNP gene.

Discussion: Clinical and laboratory findings supported the diagnosis of rapidly progressive AD, while the hypotheses of PrDs was less probable. The E270K mutation in SORL1 was reported to increase the risk of developing late onset AD, while the insertional mutation of one OPRI in the PRNP gene is considered of questionable pathogenicity. Both the genetic defects have never been associated with CAA, however literature data make plausible the

hypothesis of a causal association. CAA has the potential to link cerebrovascular and neurodegenerative pathways in the ageing brain.

Conclusions: The specific pathogenic contribution of the two DNA variations is certain difficult to determine in the absence of post-mortem studies. Vascular and degenerative pathways actually interact in a synergistic way, and genetic studies may lead to more insight into pathophysiological mechanisms.
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HEREDITARY SPASTIC PARAPARESIS TYPE 46 (SPG46): AN ITALIAN CASE SERIES AND REVIEW OF THE LITERATURE

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Objective: Spastic paraplegia type 46 (SPG46) is a rare autosomal recessive (AR) disorder caused by homozygous or compound heterozygous mutations in the GBA2 gene (locus 9p13.3) [1,2], which encodes for the non-lysosomal glucosylceramidase β2 (GBA2) protein. About twenty families have been described worldwide [3]. Clinically, SPG46 presents with an early onset spastic paraparesis, variably associated with cerebellar dysfunction, abnormal ocular movements, peripheral neuropathy, distal amyotrophy, extrapyramidal disorders, cognitive impairment, scoliosis, cataracts. Brain MRI may display white matter alterations (WMA), thin corpus callosum (TCC), brainstem and cerebellum atrophy. Herein, we report five SPG46 patients, the largest series so far described in Italy.

Materials and methods: Five patients were enrolled in five Italian centres and underwent neurological examination, clinical cognitive assessment, column RX for scoliosis assessment, ophthalmologic examination, brain MRI, GBA2 enzyme activity in peripheral blood cells (normal values in 2.5 – 5.3 nmol/mg range) and genetic testing.

Results: All subjects showed a rather uniform phenotype including spastic paraparesis with mild spasticity also in upper limbs (5/5), and cerebellar syndrome (5/5), impaired saccades (4/5), mild impairment of vibration sense (5/5), cognitive impairment (4/5) and distal atrophy (3/5). None of them but one showed extrapyramidal features. Extraneurological manifestations included scoliosis (2/5), and cataracts (4/5). Brain MRI showed WMA in 4 of 5, and TCC in 2 of 5. Four patients showed different homozygous but one compound heterozygous GBA2 mutations with no founder effect. Consanguinity was obvious in one patient, not ascertained in others. GBA2 activity was available for 2 of 5 and showed markedly reduced enzymatic activity (0.01 and 0.28 nmol/mg – n.v. 2.5 to 5.3 nmol/mg) in affected patients and from 50 to 70% reduction in two healthy carriers.

Discussion and conclusion: This is the largest series of SPG46 patients reported in Italy. It is indeed a very rare complex form of AR SPG, with a remarkably homogeneous clinical presentation including spastic paraparesis, cerebellar involvement, mild cognitive impairment and such extraneurological features as scoliosis and cataract, early onset and slow progression.
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SPINOCEREBELLAR ATAXIA TYPE 40: FIRST DESCRIPTION OF ITALIAN CASES, LITERATURE REVIEW AND JNK PATHWAY IMPLICATIONS

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Objective: Spinocerebellar Ataxias (SCAs) represent a clinically and genetic diverse group of autosomal dominant cerebellar diseases, with an estimated prevalence of about 2.7 per 105 [1]. More than 50 genes have been shown to cause SCAs, and their number is still growing. One of the rarest is SCA40, caused by CCDC88C mutations [2]. We launched a systematic search of such rare forms as SCA40 though next generation sequencing (NGS) in our series of patients with a clinical presentation of degenerative ataxic syndrome without genetic diagnosis for the most frequent (and tested) SCAs (1, 2, 3, 6, 7, 8, 10, 17).

Materials and methods: So far, four cases have been described worldwide (three families and an isolated case). Herein, we report three new SCA40 cases, associated with c.1878G>C (p.K626N), c.4283C>T (p.S1428F), and c.821C>T (p.T274I) variants in the HOOK domain of CCDC88C [2]. All subjects were evaluated in our centre, and underwent neurological examination, clinical cognitive assessment, ophthalmologic examination, brain MRI, and genetic testing.

Results: Genetic testing showed three new variants, thus far unreported in literature. All subjects showed cerebellar syndrome (gait ataxia, limb dysmetria, nystagmus and dysarthria) with spasticity in lower limbs. They also presented with postural and intentional tremor, head tethering and trunk instability, and moderate parkinsonism (particularly in upper limbs). One of them showed mild cognitive impairment and mild cervical dystonia. Extraneurological manifestations consisted in decreased nerve conduction velocity conduction in optic nerve. Brain MRI showed cerebellar and brainstem atrophy.

Discussion: The value of NGS as a potent diagnostic tool is shown by our findings. Indeed, a large number of undiagnosed degenerative cerebellar ataxias can be categorized, and hence the true prevalence of each type can be determined. We can also identify a shared phenotype, comparing our data with SCA40 patients described worldwide. The mutations of CCDC88C have been shown to cause activation the c-Jun N-terminal kinase (JNK) pathway, thus inducing caspase 3 cleavage, which triggers apoptosis.

Conclusions: This is the largest SCA40 case series ever described. Considering the major role of HOOK proteins in various cellular functions, especially in cerebellum and basal ganglia [3], we hypothesize a causative role in cerebellar and extrapyramidal dysfunction in SCA40.
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A NOVEL ATP2B4 MUTATION IN AN APPARENTLY SPORADIC CASE OF SPASTIC PARAPLEGIA

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Objective: We describe a patient with slowly progressive spastic paraplegia associated with a novel mutation of ATP2B4 gene.
Materials: Medical reports of outpatient visit, neuropsychological and instrumental examinations and neurogenetic analysis.

Methods: Review of the patient's medical history and literature analysis of hereditary spastic paraplegias specific related genes.

Results: An Italian 76-year-old woman presented a 20-year history of slowly progressive paraparetic-spastic gait disorder. Over the years, multiple falls had occurred. Neurological examination revealed a paraparetic gait and lower limbs bilateral pyramidal signs, including spasticity, brisk reflexes, Babinski sign and ankle clonus. Motor evoked potentials showed an increased central conduction time at lower limbs. Further investigations for differential diagnosis, including extensive blood tests, electromyography and brain and spinal cord MRI, were not significant. Although her family history was negative for similar disorders, a Next-Generation Sequencing (NGS) panel for hereditary spastic paraplegias (HSP)-related genes was performed. The DNA analysis identified three heterozygous variants of uncertain significance (VUS), not yet described in the literature as pathogenic: the non-sense mutation c.3451G>T (p.E1151*) in the ATP2B4 gene, the c.99C>G variant (p.H33Q) in the DYNC1H1 gene, and the c.3656_3658del variant (p.E1219del) in the LYST gene.

Discussion: Since LYST gene related diseases have an autosomal recessive inheritance, the LYST VUS was not considered as disease causing. DYNC1H1 related diseases are autosomal dominant, but usually have a phenotype different from our patient's clinical manifestations (i.e. axonal Charcot-Marie-Tooth disease, intellectual disorder, spinal muscular atrophy, and juvenile complicated HSP).[1] On the other hand, a mutation in the ATP2B4 gene has already been reported in a Chinese family with slowly progressive autosomal dominant HSP, a phenotype similar to our case. [2] Considering the mutation's predicted effect (non-sense mutation leading to a stop codon), with a likely pathogenic impact on protein function, and our patient's phenotype, we hypothesized the ATP2B4 gene mutation as the most likely cause of our patient's clinical manifestations. To our knowledge, this is the first description of a case of ATP2B4-related spastic paraplegia in Europe. Similarly to other HSP-associated genes (such as SPG7 and SPG20), [3] the protein encoded by ATP2B4 plays a role in calcium homeostasis, supporting the hypothesis that calcium dysregulation may be involved in HSP pathogenesis.

Conclusion: The reported case underlines the role of neurogenetic investigation, even in apparently sporadic cases of spastic paraplegia.
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A PUZZLING CASE OF TREATABLE ADULT-ONSET LEUKODYSTROPHY

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A 44-year-old male with a mild intellectual delay presented with a subacute onset of spastic paraparesis, rapidly progressing in a few months, along with episodes of urinary incontinence and erectile dysfunction. Current neurological examination showed a bilateral lower limbs weakness associated with marked spasticity. Tone and strength were normal at upper limbs. Deep tendon reflexes were brisk at both upper and lower limbs, and Hoffman and Babinski sign were present bilaterally. Cranial nerves and sensory examination were normal. The patient underwent spinal cord MRI, which was normal, and brain MRI, that showed an extensive T2 hyperintensity, involving bilaterally and symmetrically the white matter of the centrum semiovale and corona radiata, mainly of the posterior lobes, with corresponding T1 isointense signal. LMNB1 duplication and a targeted resequencing gene panel for leukodystrophies resulted negative. DNA of the patient was then sent for Next-generation clinical exome sequencing. Genetic testing showed compound heterozygosity for c.842 C>T and c.143 T>C of PAH gene mutations, prompting dosage of plasma phenylalanine (Phe), which was 10 times above the upper reference limit. Phenylketonuria (PKU) is an autosomal recessive inborn error of Phe metabolism, causing excessive Phe levels interfering with brain growth, myelination, and neurotransmitter synthesis. The Italian National newborn screening programme, including PKU, was commenced only in 1992, after the birth of our patient. However, as this is one the rare treatable causes of intellectual and motor disability, PKU should always be excluded in patients presenting with leukodystrophy and cognitive and motor impairment.

A NOVEL CCDC88C MUTATION ASSOCIATED WITH SPINOCEREBELLAR ATAXIA TYPE-40: A CASE REPORT

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Objectives: To describe a novel CCDC88C mutation associated with spinocerebellar ataxia type-40.
Materials: Medical records of in-clinic visits, neuropsychological assessment and instrumental examinations.

Methods: Review of the patient's and her family's medical history.

Results: We report the case of a 49-year-old woman who presented at the age of 48 with a 3-year history of disequilibrium and fluctuating gait disturbances. Neurological examination showed prominent cerebellar signs, such as ataxic gait, slurred speech, nystagmus, ocular and limb dysmetria, dysdiadochokinesis, hypotonia and hyporeflexia. In addition, she also displayed hypoesthesia and hypopallesthesia on left distal upper limb and right

lower limb. Interestingly, our patient experienced episodes of involuntary limb movements associated with a mild confusional state without loss of consciousness. Our patient had a positive family history for spinocerebellar ataxia (SCA), i.e. maternal aunt. Blood tests and instrumental examinations ruled out the main acquired causes of cerebellar ataxia, but MRI of the spine revealed a cervical spondylotic myelopathy; moreover, a diagnosis of inflammatory rheumatism with positivity of cyclic citrullinated peptide antibodies was formulated. The disease course was progressive. A preliminary genetic analysis for the most common SCAs (SCA 1-2-3-6-7-8) resulted negative. Therefore, we performed a next-generation sequencing (NGS) of SCA-related genes and we found a heterozygous variant of uncertain significance in the CCDC88C gene (c.1184A>G, p.His395Arg), which was absent in the Genome Aggregation Database (GnomAD) but reported to be damaging by in silico analysis.

Discussion: In literature, there are few reports of SCA40. Tsoi et al. first described a Chinese family in 2014. [1] Affected members displayed cerebellar degeneration with pyramidal involvement and carried a c.1391G>A mutation in the CCDC88C gene. In 2018 Leńska-Mieciek et al. found a c.127G>A mutation in the CCDC88C gene in a Polish family, [2] who exhibited cerebellar features along with extrapyramidal signs and dementia. Other variants in the CCDC88C gene associated with SCA40 have been discovered more recently in an Indian and another Chinese family. An autosomal dominant pattern of inheritance was observed in these cases, but clinical characteristics varied among different families. In agreement with this variability, our patient did not manifest any extrapyramidal signs, pyramidal signs or dementia. Notably, involuntary movements have been recognized as a possible manifestation of SCA40, in a Chinese patient with paroxysmal limb jitters. [3]

Conclusions: To our knowledge, this is the first description of SCA40 in Italy. NGS has assumed a fundamental role to disclose rare genetic causes for common disease phenotypes.

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CEREBELLAR ATAXIA, SENSORINEURAL DEAFNESS, AND HYPOGONADISM: CLUES TO A RARE DISEASE

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D-bifunctional protein (DBP) Deficiency is a disorder of peroxisomal fatty acid beta-oxidation. It was initially associated with a severe phenotype comprising encephalopathy, seizures, polyneuropathy and hearing loss generally fatal within the first 2 years of life. More recently new phenotypes with a milder course have been described with slowly progressive cerebellar ataxia, sensorineural deafness, and hypergonadotropic hypogonadism, overlapping with Perrault syndrome. We describe five subjects from two different families who presented with gait imbalance and hearing loss. One individual from one family developed gait disturbances at 18 years of age. He later developed dysarthria, sensory-motor neuropathy and hearing loss especially for high frequencies. Laboratory tests showed low testosterone levels with normal gonadotropin levels. He was wheelchair-bound by the age of 35. Four siblings from consanguineous parents developed gait disturbances between age 30 and 55. The older brother developed gait disturbances at age 35 years, he never had children and is now 70 years of age. Another sister developed hearing loss and gait imbalance at 45 years of age. Cognitive assessment showed mild attention deficits. The younger sister developed gait imbalance at age 55. She was diagnosed with primary ovarian insufficiency after two years of oligomenorrhea at 18 years of age. None of the siblings had neuropathy. All of the patients described had cerebellar atrophy mainly involving the vermis. The patients underwent an NGS panel for cerebellar ataxia. The proband with juvenile-onset DBP deficiency resulted compound heterozygous for the novel variants HSD17B4 c.2191C>T (p.Q731*) and c.727G>T (p.V243L). The siblings with adult-onset DBP Deficiency were found homozygous for the novel variant HSD17B4 c.632A>T (p.N2111). The variants were confirmed by Sanger sequencing. Our cases expand the phenotypic spectrum associated with DBP Deficiency. Of note, one of our adult-onset DBP deficiency patients had the latest onset of balance problems ever reported (55 years). Two of our male patients had infertility with normal secondary sexual characteristics confirming that reproductive problems can be found also in male patients, a finding reported only in three patients to date. We suggest that DBP Deficiency should be considered in the differential diagnosis in patients with cerebellar ataxia, hearing loss and hypergonadotropic hypogonadism.

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OCULOMOTOR FEATURES IN CANVAS

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Objective: CANVAS (Cerebellar Ataxia, Neuropathy and Vestibular Areflexia Syndrome) is a late-onset, slowly progressive, autosomal-recessive disorder due to a biallelic intronic expansion in the RFC1 gene. Vestibular areflexia caused by vestibular ganglia degeneration is considered as a distinctive feature. Objective of this exploratory study is the assessment of the oculomotor system in a cohort of CANVAS patients.

Materials: Seventeen genetically-confirmed CANVAS patients were assessed. The patients were six males and 11 females; mean age was 66.9 years (range: 52-85); mean disease duration was 11 years (range: 1-33).

Methods: Patients were assessed by bedside oculomotor examination, including a "reading test" (with slowly sinusoidal head movements), and by video-oculography (EyeSeeCam), to explore lateral vestibulo-ocular reflex, smooth pursuit, optokinetic nystagmus, gaze holding and saccadic system.

Results: The "reading test" was altered in 6/10 subjects (60%). The video-oculographic data were as follows: horizontal vestibulo-ocular reflex (VOR) impairment at video head-impulse test (vHIT) in 13/17 (77%), smooth pursuit impairment in 14/17 (82%); altered/absent optokinetic nystagmus (OKN) in 9/15 (60%); downbeat nystagmus (DBN) in 6/17 (35%), gaze-evoked nystagmus in 2/17 (12%), and mild-to-moderate saccadic dysmetria in 6/15 (40%). In 1 subject no clear oculomotor abnormality was found.

Discussion: In CANVAS, characteristic oculomotor abnormalities consist of a varying combination of vestibulo-ocular hypo-/a-reflexia, marked

reduction of smooth pursuit gain, reduction/lack of the optokinetic nystagmus, downbeat nystagmus.

Conclusions: Oculomotor features in CANVAS indicate a wider involvement of the vestibulocerebellum system, including flocculus and vestibular nuclei, beyond vestibular ganglia. The 'reading test' can be a simple test to identify vestibulo-ocular abnormalities at bedside.

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MULTIPLE SYSTEMIC LIPOMATOSIS (MSL) ASSOCIATED WITH 8344A>G TRNALYS MTDNA MUTATION IN A LARGE ITALIAN FAMILY: SEARCH FOR A THRESHOLD EFFECT

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Objectives: Myoclonic epilepsy with ragged red fibers (MERRF) is a rare mitochondrial DNA (mtDNA) disorder. The most common causative mutation, is 8344A>G (MT-TK codifying for tRNALys). Due to tissue-specific heteroplasmy and the threshold effect, it is characterized by high intrafamilial clinical variability. Myoclonic epilepsy, cerebellar ataxia, hearing loss, optic atrophy, cardiomyopathy, diabetes, and peripheral neuropathy can be variably present. Multiple systemic lipomatosis (MSL) has also been described, often as the only manifestation in carriers [1]. It has been suggested that MSL is the consequence of subtle mitochondrial dysfunction in vestigial brown fat, as confirmed by the anatomic location (midline) and the detection in lipomas of Uncoupling Protein 1 (UCP1) mRNA, a protein found only in brown fat [2,3]. The objective of this study was to quantify the 8344A>G mutation and establish a threshold of expression for MSL in a sample of MERRF-related family members.

Materials and methods: We evaluated a 28-year-old girl, for myoclonic epilepsy, cerebellar ataxia and peripheral neuropathy. We also noticed a large cervical lipoma suggesting a clinical diagnosis of MERRF, which was confirmed by the detection of the 8344A>G mutation. Thereafter we collected peripheral blood cells and urinary epithelial cells in 14 maternally related family members, who also reported variably extended cervical lipomas.

Results: We identified the 8344A>G in each family member. In subjects with isolated MSL (10 of 15, aged 14-84 years) mean mutation load was 48,2 ± 22 % in blood cells and 57,9 ± 22%, in urothelium, while in the proband we found 84,6% and 85,2%, respectively. In family members without MSL (5 of 15, aged 12-46 years), mean mutation load was 35,4 ± 23,5 % in blood cells and 51,9 ± 27,6 %, in urothelium.

Discussion and conclusion: We report a large family harboring the 8344A>G mutation. MSL was present in 66,6% of them, and in 40% as an isolated feature. Thus in families with maternal inheritance of MSL, a mtDNA related disorder should be suspected, specifically MERRF. Heteroplasmy explains tissue-to-tissue variability, herein showed by the difference of mutation load (11,7% higher in urine than blood). Different mutation load between symptomatic and asymptomatic patients (12,7% in blood, and 6% in urine) suggests a threshold effect for the development of MSL, even though to the small size of sample, proper statistical analysis could not be obtained. Further studies could confirm this hypothesis.

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HEREDITARY ATAXIAS: DIAGNOSTIC YIELD WITH NEXT-GENERATION SEQUENCING - EXPERIENCE FROM UNIVERSITY OF PISA NEUROLOGICAL INSTITUTE

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Hereditary ataxias (HAs) are a group of progressive monogenic rare neurodegenerative disorders characterized by a wide spectrum of ataxia-dominated phenotypes. They can be caused by disruption of cerebellar nuclei or fibres, its connection with the brainstem, or spinal and peripheral lesions leading to proprioceptive loss. Despite the identification of a large number of causative genes, up to 50% of HAs cases still remain without molecular diagnosis, mainly due to their vast clinical and genetic heterogeneity. However, massive parallel next-generation sequencing (NGS) analysis broadened our knowledge of HAs genetic aetiology and, consequently, stimulate the trend towards genetically-specific therapies. In this study the aim was to assess the diagnostic yield of NGS panel and exome analysis in the clinical practice of our setting. A cohort of 100 patients (average age 59.5 years) with a clinical diagnosis of HA but no molecular confirmation was studied. NGS panel (26 genes) and/or clinical exome sequencing (CES) were performed in the case of inconclusive first-line genetic tests for spinocerebellar ataxias (SCA1-3, 6-8,12,17), DRPLA, Friedreich's ataxia (FRDA) or phenotype-guided specific single gene sequencing. By means these traditional genetic tests a molecular diagnosis was achieved in 35% of patients; coherently with epidemiological data, FRDA (10%) and SCA2 (7%) were the most common. Of 65 patients with HAs of indeterminate genetic origin, 37 underwent new molecular evaluations: in 1 of 37 (2,7%) and in 8 of 25 (32%) known pathogenic mutations or putative pathogenic variants were found, using NGS panel and CES, respectively. Furthermore, in 54% of patients (20/37) one or more variants of unknown significance were detected. Overall, we present daily practice evidence that for one third of the patients with a clinical diagnosis of HA, but no molecular diagnosis on routine genetic testing, a definitive diagnosis can be reached with NGS approach.

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HATTR-RELATED POLYNEUROPATHY: A SINGLE-CENTER EXPERIENCE

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Hereditary transthyretin-mediated amyloidosis (hATTR) with polyneuropathy is a rare, life-threatening, multisystemic disease caused by mutations in the gene encoding transthyretin (TTR), transmitted as an autosomal dominant trait. In this study we aim to describe the characteristics of the patients followed at the Neurological Clinic of San Martino Polyclinic Hospital in Genoa. We retrospectively analyzed the demographic and clinical features of 12 patients treated in our center and we described how pre-symptomatic carriers are monitored. The routine biannual work-up includes modified Body Mass Index (mBMI), neurological examination, Neuropathy Impairment Score (NIS-244) and Neuropathy Impairment Score-Lower Limbs (NIS-LL-88), Karnofsky Performance Status (0-100), Compound Autonomic Dysfunction Test (CADT, 0-20), Norfolk Quality of Life (QoL), Sudoscan, and blood tests. Patients also annually undergo electroneurography (ENG) and cardiological examination with electrocardiogram and echocardiography. The patients referring to our Clinic over the last 10 years were 12 (2 of whom died). The genetic features were: 5 (36%) Phe64Leu, 4 (29%) Val30Met, 1 (7%) Ile68Leu, 1 (7%) Tyr98Phe, 1 (7%) Arg125Cys, 1 (7%) Val122Ile and 1 (7%) Ala120Thr. According to the Polyneuropathy Disability (PND) scoring system, 2 patients score 0, 4 score I, 3 score II, 1 score IIIa, 2 score IIIb and none have a score of IV. Five of our patients are currently on tafamidis therapy, 1 is on inotersen therapy and 4 patients are being treated with patisiran. Two patients switched from tafamidis to patisiran, 1 from diflunisal to patisiran and another 1 from tafamidis to inotersen due to clinical and neurophysiological worsening. A patient switched from inotersen to patisiran due to persistent thrombocytopenia. In our center, several presymptomatic tests were performed and we found a mutation of the TTR gene in two relatives of patients with hATTR. We start monitoring presymptomatic carriers 10 years before the predicted age of disease onset (PADO) based on mutation type and penetrance. We use a clinical questionnaire including sensory and dysautonomic symptoms, neurological examination with complete sensitivity examination, Sudoscan, mBMI and ENG. With the introduction of disease-modifying treatments, early diagnosis of hATTR amyloidosis with polyneuropathy is even more important. It is also essential to monitor presymptomatic carriers over time to assess the need for therapy. Drug choice should be oriented according to severity of disease, comorbidities and features of individual patients.

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TWNK IN PARKINSON'S DISEASE: A MOVEMENT DISORDER AND MITOCHONDRIAL DISEASE CENTER PERSPECTIVE STUDY

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Background: Parkinsonian features have been described in patients harboring variants in nuclear genes encoding for proteins involved in mtDNA maintenance, such as TWNK.

Objectives: To screen for TWNK variants in an Italian cohort of Parkinson's disease (PD) patients. To assess the occurrence of parkinsonism in patients presenting with TWNK-related autosomal dominant progressive external ophthalmoplegia (TWNK-adPEO).

Methods: Genomic DNA of 263 consecutively collected PD patients who underwent diagnostic genetic testing was analyzed with a targeted custom gene panel including TWNK, as well as genes causative of monogenic PD. Genetic and clinical data of 18 TWNK-adPEO patients with parkinsonism were retrospectively analyzed.

Results: Six of 263 PD patients (2%), presenting either with isolated PD (n=4) or in combination with bilateral ptosis (n=2), carried TWNK likely pathogenic variants. Among 18 TWNK-adPEO patients, five (28%) had parkinsonism.

Conclusions: We show candidate TWNK variants occurring in PD without PEO. This finding will require further confirmatory studies.

HTRA1 ACCUMULATION IN SMALL ARTERIES OF CADASIL PATIENTS

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Introduction: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited systemic vascular disease with main neurological manifestations. CADASIL is due to NOTCH3 gene mutations and is characterized by the abnormal deposition of mutated Notch3 protein in the artery walls as granular osmiophilic materials (GOMs), which were associated with smooth muscle cell (SMC) degeneration. How NOTCH3 gene mutations lead to SMC degeneration is still uncertain. A toxic effect of mutated Notch3 was proposed. An alternative mechanism is based on a loss of function in a negative dominant model. A third hypothesis concerns the possible sequestration of matrix components into the GOMs leading to their loss of function. Interestingly, Htra1 is a serine protease of the artery matrix and is involved in a phenocopy disease, named CADASIL2, and in another inherited vascular disease, named CARASIL. In these diseases a loss of function of Htra1 was demonstrated.

Aim of the study: To investigate the possible accumulation of Htra1 in artery walls of CADASIL patients.

Materials and Methods: These were analysed two series of skin biopsies, one from CADASIL patients and the other from control ones. For each biopsy a corresponding blood sample was available for the genetic study. CADASIL diagnosis was verified by NOTCH3 gene sequencing and GOM identification at ultrastructural study. Also HTRA1 gene was sequenced in all cases to exclude CADASIL2 or CARASIL. Then, vessel Htra1 enrichment was searched by immunohistochemical study and a grading of Htra1 immunodecoration was determined. Also GOM density was measured in

artery walls to investigate the correlation between GOM burden and Htra1 accumulation.

Results: Multifocal Htra1 immunopositive deposits were observed in skin arteries of CADASIL patients, while control samples were negative. Differences in number and dimensions of Htra1 immunodecorated deposits were observed within CADASIL cases. A positive correlation was observed between GOM burden and Htra1 deposits.

Discussion: Our study demonstrated the accumulation of Htra1 protein in skin arteries of CADASIL patients. The observation of a direct correlation between GOM burden and Htra1 deposits agrees with the hypothesis of the Htra1 sequestration. Non-significant correlations were observed between density of Htra1 deposits and severity of the disease. We observed only that stroke onset cases had higher Htra1 accumulation compared with those cases presented with subcortical dementia.

Conclusions: These data underline the importance of Htra1 in SMC maintenance and support the hypothesis of a relevant pathogenic role of Htra1 sequestration in CADASIL.

A MAN WITH RESPIRATORY INSUFFICENCY, HYPERCKEMIA AND INVOLUNTARY MOVEMENTS: THE FIRST CASE OF MCLEOD SYNDROME IN LAZIO REGION

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Objectives: Neuroacanthocytosis syndromes (NA) are a group of genetically defined diseases characterized by the association of red blood cell acanthocytosis, progressive degeneration of the basal ganglia and neuromuscular features. The main NA syndromes include autosomal recessive choreaacanthocytosis (ChAc) and X-linked McLeod syndrome (MLS). A recent italian case-series described three family members from Venice affected by McLeod syndrome. Here we describe the first MLS case in Lazio region with an atypical presentation.

Materials and Methods: During hospitalization for respiratory insufficiency, a 46-years old man showed truncal and limbs involuntary movements and abnormal gait. He underwent to neurologic examination, nerve conduction studies and electromyography, echocardiography, blood smear and evaluation of Kell antigen expression.

Results: Clinical examination documented the presence of choreiform movements of trunk and limbs, anserin gait, motor impersistence, mild dysarthria and abolished deep tendon reflexes; the patient reported only a history of hyperCKemia since adolescence, no family history of neurological disorders, while he did not remember when the involuntary movements had started but tended to scotomize them. Neurophysiological studies showed a mixed picture of axonal neuropathy and myopathy; brain MRI showed no changes; the echocardiogram documented features of dilatative cardiomyopathy; blood exams showed hyperCKemia, peripheral blood smear documented the presence of acanthocytes (10%) and Kell antigen expression was reduced. in the suspicion of neuroacanthocytosis and in particular of MLS, the search for mutations in the XK gene was performed and highlighted the presence of the variant c.856_860delCTCTA (p.Leu286Tyrfs * 16) in hemizygosis in the coding region of the XK gene.

Discussion and conclusions: McLeod Syndrome is a rare genetic disease characterized generally by a young adult-onset and very typical features of choreiform movements, mixed neuropathy-myopathy, hyperCKemia, acanthocytes and reduced Kell antigen expression that can direct the clinician to search for the correct genetic diagnosis. Here we presented the case of a 46-years old man who had never performed any medical investigations, hospitalized for respiratory reasons but showing a more complex clinical picture that resembled the MLS phenotype, later confirmed genetically. Of note, XK gene is contiguous to dystrophin gene on X chromosome and in certain cases large or deleterious deletions could result in a picture also characterized by Duchenne Syndrome features; therefore, even if myopathy is part of MLS phenotype, the respiratory insufficiency and anserin gait displayed by our patient could possibly be part of this contiguous syndrome.

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CLINICOPATHOLOGIC AND MOLECULAR SPECTRUM OF MGME1-RELATED MITOCHONDRIAL DISEASE IN A COHORT OF ADULT PATIENTS FROM THE ITALIAN NETWORK

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Objective: We present the clinical and laboratory findings in 7 novel patients with mutations in MGME1, encoding for a mitochondrial exonuclease [1] which has been recently implicated in human mitochondrial DNA (mtDNA) instability disorders [2].

Methods: We reviewed the clinical, histochemical, and molecular genetics analysis of 7 unreported patients from 6 families together with all previous cases described in the literature with MGME1 mutations. Patients were recruited at clinical institutions belonging to the Nation-wide Italian Collaborative Network of Mitochondrial Diseases.

Results: Ptosis and ophthalmoparesis were almost universal clinical features among this cohort, with 57% (4/7) having proximal muscle weakness, 42% (3/7) presenting respiratory failure and 29% (2/7) reporting fatigue. Patient's age ranges from 24 to 78 years, with presenting symptoms within the fourth decade in most of the cases. A mild to moderate increase of CK levels was observed in 6 of 7 patients. Clinical features consistent with CNS involvement were rarely described except for mental retardation and ataxia, observed in one patient. Cerebellar or cortical atrophy were observed in 4 subjects. Cardiac abnormalities were observed in two subjects. Progressive kidney disease leading to hemodialysis was reported in a patient. COX-negative fibers, with or without ragged-red fibers, were observed in all the muscle samples analyzed. Multiple mtDNA deletions were rarely detected while increased levels of 7S mtDNA (whose processing depends on MGME1, [1]) were observed. Impaired activity of respiratory chain Complex IV was documented in muscle or fibroblasts from 3 patients. Five different MGME1 mutations were observed, three of them unreported so far and classified as pathogenic or likely pathogenic. The c.707T>C (p.Leu236Pro) substitution was the most frequently observed variant in our cohort (5/12 pathological alleles).

Discussion: Until now, recessive MGME1 mutations had been observed in 5 subjects from two families [2] and in 4 sporadic patients, two of them with early onset severe presentations. In adults, main symptoms include external ophthalmoplegia, muscle weakness and a progressive respiratory impairment.

Our findings support the prominent muscle involvement in MGME1-mutated adult patients. However, multisystemic involvement (cardiac/kidney abnormalities, cerebellar atrophy) is also frequent.

Conclusion: This is the largest case series of MGME1-mutated patients so far reported. Our data confirm that MGME1 defects are a rare cause of mitochondrial disease and that the phenotypic spectrum in adults is relatively homogenous. MGME1 genetic analysis should be considered in all patients with mitochondrial myopathy, even in absence of canonical signs of muscle mtDNA instability.

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SOD1 VARIANTS CLASSIFICATION IN AMYOTROPHIC LATERAL SCLEROSIS PATIENTS FROM SOUTHERN ITALY

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Aims: Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a progressive neurodegenerative disease of adulthood. Superoxide dismutase Cu/Zn enzyme (SOD1) is the first gene associated with the autosomal dominant form of the disease [1]. This gene is characterized by a high rate of rare variants, making an appropriate classification necessary for a correct patient stratification. In this study, we performed an updated evaluation of SOD1 variants reported in in-house database [2] according to the ACMG-AMP criteria. In particular, we classified the mutations based on the modified weight of the PM1 and PS3 criteria adapted specifically for SOD1.

Materials and Methods: We considered 11 SOD1 (NM_000454.5; NP_000445.1) variants listed in our database. For the evaluation of the minor allelic frequency (MAF), gnomAD v2.1 was used. A MAF value less than 0.001 and the absence from all population databases allowed assigning a PM2 with a moderate level of pathogenicity evidence. The PS3_Strong was assigned as the results of in vivo functional tests showing toxic SOD1 function and cell damage. We attributed two different weights to the PM1 criterion based on the number of pathogenic variants discovered in hotspot regions: PM1_Strong (≥14 variants) and PM1_Moderate (at least 7 variants).

Results: In total, only one SOD1variant (c.59A>G, p.N20S) was classified as VUS, with insufficient or conflicting evidence regarding the role of molecular alteration in disease; c.68A>T (p.Q23L), c.184G>C (p.G62R), c.251A>T (p.D84V), c.272A>C (p.D91A), c.320T>C (p.L107C), c.346C>T (p.R116C), c.449T>C (p.I150T) and c.137T>G (p.F46C) variants were classified as likely pathogenic while c.281G>C (p.G94D) and c.435G>T (p.L145F) variants were classified as pathogenic.

Discussion: The only application of the guidelines for the interpretation of variants developed and refined so far cannot be considered sufficient in ALS to address various issues related to the implementation of new genetic analysis technologies in the diagnostic and clinical context. A tailored-gene reinterpretation of variants is essential to allow for more correct stratification of patients and targeted therapy development [3].

Conclusion: To date, the diagnosis of ALS remains based on clinical criteria. Improving existing variant classification systems could provide a better basis for using genetic findings as diagnostic criteria and phenotype-genotype correlations.

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NEURODEGENERATION WITH BRAIN IRON ACCUMULATION (NBIA): NEW CANDIDATE GENES

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Objectives: Neurodegeneration with brain iron accumulation (NBIA) comprises a group of brain iron deposition syndromes that lead to progressive neurological impairment with mixed pyramidal-extrapyramidal features and progressive dementia. To date ten genes have been identified as associated with different NBIA subtypes. The two core syndromes are the pantothenate kinase-associated neurodegeneration (PKAN) caused by mutation in the PANK2 gene and PLA2G6-associated neurodegeneration (PLAN) caused by mutation in the PLA2G6 gene, both with autosomal recessive transmission and a variable phenotype. Approximately half of the clinically relevant cases with iron deposits on brain MRI remain without any molecular deleterious alteration. To better understood the genotype-phenotype correlations of such disorders we performed clinical and genetic studies in 12 patients with NBIA. Moreover, in order to achieve a more efficient molecular diagnosis, we performed whole exome sequencing in those patients without molecular diagnosis with the aim to identify new candidate genes.

Materials and Methods: Our patients were subjected to extensive clinical investigations. Four of the 12 patients had a clinical phenotype compatible with PKAN, 1 patient presented with INAD, 2 with static encephalopathy of childhood with neurodegeneration in adulthood (SENDA) and 5 with an atypical phenotype. Mutation analysis of the 10 genes associated with NBIA was performed using targeted next generation sequencing in all patients. Finally, whole exome sequencing was performed in patients without molecular diagnosis.

Results: Genetic analysis showed homozygous or compound heterozygote mutations of PANK2 gene in the four patients with PKAN, a novel homozygous mutation (L596F) of PLA2G6 gene in the patient with INAD and two different heterozygous mutations of WDR45 gene in the two patients with SENDA. Whole-exome sequencing revealed the heterozygous de novo mutation c.920G>A (R307Q) in KIF1A gene and the novel homozygous mutation c.13433dupA (Y4478fs*0) in SACS gene, respectively, in a woman and in a boy with an atypical phenotype characterized by intellectual disability and progressive ataxia and spasticity.

Conclusions: Mutations in the SACS gene have been found to cause autosomal recessive spastic ataxia of Charlevoix-Saguena (ARSACS), while changes in the KIF1A gene can lead to three different disorders: the autosomal dominant condition nonsyndromic intellectual disability 9 (MRD9), and the

recessive conditions hereditary sensory neuropathy type IIC (HSNIIC) and hereditary spastic paraplegia 30 (SPG30). Our results enlarge genotype-phenotype correlations for these two genes and suggest that SACS and KIF1A represent new candidate genes that should be considered in the NBIA spectrum of disorders.

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A NOVEL MUTATION IN COA7 LEADING TO FRIEDRICH'S LIKE ATAXIA

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Objective: We aim to describe a clinical case of Friedrich's like ataxia due to a novel mutation of COA7 gene. Friedreich's ataxia is a condition caused by an expansion of a GAA trinucleotide repeat in intron 1 of FXN gene on chromosome 9 (98%) that leads to reduced levels of the protein, Frataxin. Strong evidences suggest that Friedreich ataxia is the result of accumulation of iron in mitochondria leading to excessive production of free radicals, which then result in cellular damage and death. Sometimes Friedrich's like ataxia is caused by other mutations involving other genes.

Materials: A 8 year-old child came to our attention for frequent falls and coordination difficulties in the previous years. Around the age of 3 he developed slowly progressive toe walking attitude with bilateral foot deformity and ease to tripping.

Method: We performed neurological examination, laboratory tests (including LDL colesterol, triglycerides, apolipoprotein B and vitamin E level), neurophysiological tests (Electroneurography and motor and sensory evoked potential), brain and spinal cord magnetic resonance imaging and genetic analysis.

Results: Familiar history, physiological and past pathologic history were unremarkable. Clinical examination showed: convex left S italic scoliosis, bilaterally cavus feet, stepping gait (left>right), bilateral legs' muscles hypotrophy, dorsiflexion weakness (left>right) with yarrow retraction, hypereflexia in the 4 limbs (more evident in legs), cerebellar signs (telekinetic tremor and bilaterally dysmetria during finger to nose test), hypopallesthesia of the 4 limbs. Laboratory test and MRI were unremarkable. Electroneurography showed length-dependent motor sensory axonal polyneuropathy. Genetic analysis showed no expansion of triplets GAA in intron 1 of chromosome 9, while NGS showed homozygosis mutation in the COA7 gene c.59T>C (p.M20T) both in the proband and in his parents, where the mutation was present in heterozygosis.

Discussion: COA7 have a role in assembling mitochondrial respiratory chain complexes that function in oxidative phosphorylation. COA7 mutations have been associated with both Charcot-Marie-Tooth disease and ataxia associated with hereditary peripheral neuropathy. We describe a clinical case of a Friedreich's like ataxia, caused by a novel mutation of COA7 gene.

Conclusions: We describe a clinical case of a Friedreich's like ataxia, caused by a novel mutation of COA7 gene. So, in cases where mutations in the classic genes have not been found, it is appropriate to search for mutations in this mitochondrial gene.

THE EXPANDING LANDSCAPE OF FIG4 MUTATIONS IN THE FTD-ALS SPECTRUM: DESCRIPTION OF NOVEL GENE VARIANTS IN THREE PATIENTS WITH DIFFERENT PHENOTYPES

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Background and Purpose: FIG4 gene encodes a phosphoinositide-5-phosphatase involved in the endosomal/lysosomal trafficking regulation. Mutations of FIG4 are associated with CMT4J, a rare and severe motor-sensory polyneuropathy. However, since 2009 some 30 heterozygous FIG4 variants have also been described in ALS/PLS. Here, we report on three ALS patients (two of them with concomitant FTD) carrying novel gene variants.

Methods: We routinely perform a genetic screening of all consecutive ALS/MND patients referred to our Center. This procedure led to the identification of three male patients carrying variants of FIG4 that have not been previously associated with the disease. The genetic analysis was performed with the AmpliSEQ Ion-ALS panel, and sequencing of the coding exons with the adjacent intronic portions (+/-10bp) was done with the NGS technique through the Ion Torrent PGM platform (regions with coverage>40x: 98.4%). Allele frequency was analyzed with gnomAD and referred to the European population; interpretation of variants was made according to ACGM guidelines.

Results: The first patient was 75-years-old at onset and was affected by spinal ALS/FTD with an apathetic-type cognitive impairment, severe spastic paraparesis, dysarthria and atrophy of the upper limbs (ΔFS=0.86). He died 38 months after onset. He carried a p.Lys278Asn variant (1/4300), with conflicting data on its pathogenicity (class II/III ACGM). The second patient is a 75-years-old man with an apathetic-type FTD and binge-eating associated with a slowly progressive pyramidal syndrome and spastic paraparesis (ΔFS=0.3). We diagnosed him as FTD/PLS. Genetic analysis showed two variants of FIG4: a rare c.1434+7A>C variant (1/57000) located in the 21 intron potentially affecting the splicing (class III ACGM); a c-132A>G (1/400) located in the non-coding region of exon I (class II ACMG). The last patient is a 78-years-old cognitively normal man with bulbar-onset ALS (ΔFS=0.86). He carries a rare FIG4 p.Gly445Asp variant (frequency 1/11400; class III ACGM).

Discussion: The variants described herein are novel in ALS and reinforce the putative role of FIG4 in the disease. At least two of them (c.1434+7A>C [patient 2] and p.Gly445Asp [patient 3]) might be damaging. On the contrary, it is unclear whether the variant described in the first patient (p.Lys278Asn9) would be dangerous.

Conclusions: In the absence of available functional data, all variants described are at present considered of uncertain significance. Nevertheless, by increasing the number of discovered gene variants of FIG4 associated with ALS, our report adds to the hypothesis of an involvement of this gene in the ALS-FTD spectrum.

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LATE-ONSET LEIGH SYNDROME WITH DYSTONIC-SPASTIC TETRAPARESIS CAUSED BY A NOVEL NDUFA10 VARIANT: A CASE REPORT.

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Aim: This study aims to identify the genetic cause of dystonic-spastic tetraparesis in an Italian young man widening the genotypic spectrum of mitochondrial movement disorders.

Materials and methods: A 43 years old male born to non-consanguineous parents from Southern Italy was evaluated by neurologists specialized in movement disorders. A blood sample was collected for Whole-Exome Sequencing (WES) and segregation analysis was performed by Sanger sequencing.

Results: The disease presented at 5 years with motor incoordination and frequent falls, progressively followed by psychomotor delay (PMD), painful dystonic-spastic tetraparesis, choreo-athetoid movements, and frequent depressive episodes. Magnetic resonance imaging demonstrated bilateral striatal necrosis with prevalent involvement of right putamen. A diagnosis of late-onset Leigh syndrome (LS) was then performed. Neurometabolic screening including blood and cerebrospinal fluid testing and brain magnetic resonance spectroscopy resulted normal except for p-OH-phenyl-lactate elevation and N-acetyl-aspartate peak reduction. Skeletal muscle biopsy suggested mitochondrial myopathy and demonstrated oxidative phosphorylation (OXPHOS) deficiency. By filtering WES results with a virtual gene panel for LS we identified two heterozygous variants in NDUFA10 (NM_004544.4), encoding a subunit of OXPHOS complex I. One variant (c.296G>A, p.Gly99Glu) was already associated with LS; the other one (c.233_235delCAG, p.Ala78del) is of novel association with the disease, extremely rare (gnomAD allele frequency 0.000004), affecting a strongly evolutionary-conserved amino acid, and predicted pathogenic by in silico tools.

Discussion: We report the fourth case of mitochondrial disease due to NDUFA10 mutations. All previously reported cases displayed LS with PMD, hypotonia, OXPHOS deficiency, lactates elevation, and striatal and brainstem lesions. Case 1 carried a very deleterious mutation (c1A>G, p.Met1?) combined with a missense mutation (c.425A>G, p.Gln142Arg) and had a severe phenotype, distinguished for hypertrophic cardiomyopathy and death at 23 months. Cases 2 and 3, both Italian, carried the homozygous c.296G>A missense variant and had a milder phenotype. Our proband's phenotype, with the prevalence of dystonia-spasticity and later onset, is the mildest. Hence, we hypothesize that the combination of two alleles encoding a partially conserved protein (i.e., p.Gly99Glu in homozygosis or in combination with p.Ala78del) is sufficient to ensure an adequate myocardial function, and that the presence of an even milder mutation (i.e., p.Ala78del) can prevent hypotonia, lactate elevation, and brainstem lesions, with great impact for diagnostic counselling and follow-up.

Conclusions: The identification of the genetic causes underlying these diseases is fundamental to comprehend pathologic mechanisms and provide patients and families with an optimal diagnosis and appropriate genetic counselling, assistance, and therapies.

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NEUROIMAGING

ALTERED FUNCTIONAL CONNECTIVITY OF THE SUBTHALAMIC NUCLEUS IN PARKINSON'S DISEASE: FOCUS ON CANDIDATES FOR DEEP BRAIN STIMULATION

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Objectives: To investigate the resting-state functional connectivity (RS-FC) of the subthalamic nucleus (STN), the most frequently used deep brain stimulation (DBS) target for Parkinson's disease (PD), in different PD phenotypes.

Materials: Clinical data and RS-functional MRI were acquired from 60 PD patients and 60 age- and sex-matched controls. PD patients were divided into two groups: 19 patients eligible for DBS (PD-DBS) and 41 not candidate for DBS (PD-noDBS).

Methods: A seed-based RS-FC analysis was run between the bilateral STN and the rest of the brain and compared between groups. T1-weighted images and resting-state functional MRI (RS-fMRI) were pre-processed. Our regions of interest (left and right STN) were subsequently identified according to standardized atlas focused on deep nuclei. Based on the time series of STN voxel, connectivity was calculated as the correlation of time series for all other voxels in the brain; the result of this analysis was a connectivity map showing Z-scores for each voxel of seed indicating how well its time series correlates with the time series of rest of the brain.

Results: PD-DBS showed a reduced connectivity between bilateral STN and bilateral sensorimotor areas relative to both controls and PD-noDBS patients. On the contrary, PD-DBS patients showed an increased connectivity between bilateral STN and globus pallidus, putamen and thalamus bilaterally compared to healthy controls. Similar patterns were found when PD-noDBS

patients were compared to controls (albeit with lower connectivity levels than PD-DBS patients).

Discussion: We hypothesize that candidates for DBS showed an increased connectivity between STN and globus pallidus/thalamus, which in turn may provide a decreased connectivity with sensorimotor areas relative to patients not eligible for DBS.

Conclusions: Our results suggest that functional connectivity of deep nuclei changes among PD phenotypes and confirm an important role of functional MRI as tool for selection of candidates for DBS. The idea that STN-DBS works by modulating and restoring functional connectivity between basal ganglia and sensorimotor areas is further corroborated.

Supported by. Ministry of Education, Science, and Technological Development of the Republic of Serbia [grant number #175090]; Italian Ministry of Health [grant number # RF-2018-12366746].

NORMALIZATION OF ABERRANT PRE-THERAPEUTIC RESTING-STATE FUNCTIONAL CONNECTIVITY INVOLVED IN PAIN PERCEPTION IN TRIGEMINAL NEURALGIA PATIENTS WHO UNDERWENT GAMMA KNIFE RADIOSURGERY

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Objective: Growing evidence supports the role of central nervous system (CNS) in the modulation of pain in trigeminal neuralgia (TN) patients. The aim of this study was to assess brain functional connectivity alterations in patients with TN before and after neurosurgical treatment of affected trigeminal nerve.

Materials: Sixteen patients with idiopathic or classic TN, who underwent Gamma Knife radiosurgery (GKRS), were followed up for at least 3 months within an ongoing longitudinal project. They performed clinical and resting-state functional MRI (RS-fMRI) evaluation before (baseline) and 3 months after treatment. Thirty-three age-and sex-matched healthy controls were also recruited.

Methods: RS-fMRI brain networks of interest were identified on an independent sample of 33 healthy individuals using an independent component analysis and then regressed at the single-subject level in both healthy controls and TN patients. FLAME models in FSL were used to explore RS-FC changes within each network of interest in healthy controls relative to TN patients. Analyses were controlled for age and sex. The same analysis was performed at the baseline and at 3 months after GKRS.

Results: Before treatment, TN patients relative to healthy controls showed an increased FC (i) of the precentral and postcentral gyrus within the sensorimotor network, (ii) of the right supramarginal gyrus, right postcentral gyrus and bilateral precuneus within the posterior salience network, and an increased FC (iii) of the right fronto-orbital cortex and caudate within the basal ganglia network. Furthermore, a decreased FC of the precuneus, posterior cingulate gyri and lateral occipital cortex within the posterior default mode network was found relative to healthy subjects. Three months after surgery, all patients experienced a significant improvement of facial pain. At postoperative fMRI assessment, no more significant FC increase was found in TN patients relative to controls. On the contrary, a decreased FC of the precuneus and lateral occipital cortex within the posterior default mode network relative to healthy subjects persisted.

Discussion: In patients with idiopathic or classic TN, pattern of increased FC may reflect the involvement of a system that receives chronic nociceptive stimuli. An effective neurosurgical treatment of the trigeminal nerve appears likewise to modulate and thus reshape abnormal pre-surgical brain circuitries. Conclusions: The study provides novel insights into functional brain alterations of TN patients, which might contribute to disease development and pain change after surgical treatment.

CONTROL OF CORE TEMPERATURE IN MAJOR ORTHOPEDIC SURGERY AND NEUROTRAMOTOLOGY USING LEVOBUPIVACAINE IN OLD PATIENTS WITH STROKE AND DELIRIUM

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In major orthopaedic surgery in geriatric patients (N=25) aged between 75±85 with intraoperative heating, the incidence of overall delirium is 15%; delirium with a single event in the controls during the stay 40%; severe delirium 5%;.In major orthopaedic surgery in geriatric patients (N=25) aged between 75±85 without intraoperative heating, the incidence of overall delirium is 32%; delirium with a single event of delirium in the controls during the stay 50%; severe delirium 12%. In major orthopaedic surgery in geriatric patients (N=25) aged between 75±85 with intraoperative heating, the incidence of stroke: is 8 %.(MRI brain 1,2). In major orthopaedic surgery in geriatric patients (N=25) aged between 75±85 without intraoperative heating, the incidence of stroke is 18% (MRI brain 3,4). Pharmacological treatment of delirium: with intraoperative heating donepezil 5 1 pill day, haloperidol 8 drops, valproic acid and sodium valproate 500 2 pills once/day; without intraoperative heating donepezil 10 1 pill once/day, valproic acid and sodium valproate 500 2 pills once/day and haloperidol 1dose i.m. In the 50 patients before the operation, the mini nutritional assessment is 23±24, on discharge in group with intraoperative heating the mini nutritional assessment is 21±20; in group without intraoperative heating, the mini nutritional assessment is 19±18. The incidence of delirium is 47% in the postoperative stage and the incidence of the stroke is 26%.

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- B. Amarisse, V.A. Peduto Control of core temperature in major orthopaedic surgery and neuro-traumatology using levobupivacaine for spinal anaesthesia in old patiens Neurological Sciences Volume 40-October 2019 Congress of the Italian Neurological Society ABSTRACT s 477 vol. 40 Congress of the Italian Neurological Society Oral Communication October 2019

CONTROL OF CORE TEMPERATURE IN MAJOR ORTHOPEDIC SURGERY AND TRAUMATOLOGY IN OLD PATINETS WITH DELIRIUM AND VALUTATION MINI MENTAL TEST

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In major orthopaedic surgery in geriatric patients (N=25) aged between 75Â ±85 with intraoperative heating, the incidence of overall delirium is 15%; delirium with a single event in the controls during the stay 40% (MRI brain 1,2). In major orthopaedic surgery in geriatric patients (N=25) aged between 75Â±85 without intraoperative heating, the incidence of overall delirium is 32%; delirium with a single event of delirium in the controls during the stay 50%(MRI brain 3.4). Pharmacological treatment of delirium: with intraoperative heating donepezil 5 1 pill day, haloperidol 8 drops; without intraoperative heating donepezil 10 1 pill once/day and haloperidol 1dose i.m. In the 50 patients before the operation, the mini nutritional assessment is 23±24, on discharge in group with intraoperative heating the mini nutritional assessment is 21±20; in group without intraoperative heating, the mini nutritional assessment is 19±18. Mini mental test preoperative score in geriatric patients (N=50 pt) undergoing major surgery is 18. Mini mental test postoperative score in geriatric patients group is 10. Mini mental test postoperative score in geriatric patients group is 5. 47% of patients manifest delirium in the postoperative stage; the incidence of: hyperkinetic delirium is 17% and severe delirium is 19%.

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AGING INFLUENCES REGIONAL WHITE-MATTER AXONAL DENSITY LOSS: A CONNECTOME-WIDE NETWORK STUDY USING PROBABILISTIC MULTISHELL, MULTITISSUE CONSTRAINED SPHERICAL DECONVOLUTION TRACKING

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Objective: To investigate alterations in structural brain networks during aging using connectome-analysis with advanced diffusion-weighted metrics.

Materials: Forty-eight young (YC), aged 20-31 years, and 65 older controls, aged 41-85 years, were enrolled and underwent multi-shell diffusion brain MRI. Older controls were divided using 60-years as cut-off in 21 middle-aged [MC] and 44 elderly [EC].

Methods: Fractional anisotropy (FA) maps were computed. Intra-cellular Volume Fraction (ICVF) and Orientation Dispersion Index (ODI) maps were estimated using the NODDI model, providing a direct quantification of neurite morphology and its integrity. Graph analysis and connectomics assessed global and local structural topological network properties and regional structural connectivity.

Results: EC subjects showed altered structural (FA, ICVF and ODI) global network properties than YC. ICVF and ODI measures, at lobar level, depicted a more focal damage relative to FA between YC and MC. Considering FA, ICVF and ODI, EC subjects showed an altered mean nodal strength and clustering coefficient in the frontal, basal ganglia (BG), and temporal areas relative to MC. Widespread structural connectivity changes were observed in both MC and EC relative to YC (decreased FA and increased ODI in the whole-brain). EC are characterized by decreased FA relative to MC mainly in the connections within frontal, sensorimotor, parietal and temporal areas and between (i) frontal and sensorimotor (precentral and postcentral gyri and supplementary motor area [SMA]), parietal (precuneus, supramarginal and angular gyri), temporal (parahippocampal gyri and temporal pole), insula and BG; (ii) parietal and sensorimotor (precentral, postcentral gyri and SMA), temporal (superior and middle temporal gyri) and occipital (superior and middle occipital gyri); (iii) temporal and occipital (calcarine and cuneus), putamen and insula; (iv) occipital and sensorimotor (SMA and precentral gyri). Considering ICVF, the damage between MC and EC was more focal than FA, involving only frontal, parietal and temporal regions; connections between BG area (specifically thalamus) and frontal, sensorimotor, parietal and temporal regions were more altered than FA measure.

Discussion: These findings suggest that conventional DT-measures might be sensitive enough to highlight connections vulnerable to aging (frontal, parietal and temporal areas). However, the benefits emerged in the differentiation between MC and EC. ICVF demonstrated to be a relevant biomarker more specific to the initial alteration of the aging process.

Conclusions: Connectome-analysis based on advanced diffusion-weighted models may be useful to evaluate structural disruptions with greater anatomical specificity compared to DT-derived measures during aging.

Supported-by. European Research Council (StG-2016_714388_NeuroTRACK); Foundation Research on Alzheimer Disease.

BRAIN FUNCTIONAL CONNECTIVITY CHANGES INDUCED BY NEUROSURGICAL THALAMOTOMY FOR TREMOR IN PD

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Objective: Neurosurgical thalamotomy has proved highly effective for treating medication-resistant tremor related to Parkinson's disease (PD) or essential tremor (ET) targeting the thalamic ventral intermediate nucleus (Vim) involved in the dentate-ponto-cerebello-thalamo-cortical pathway. The aim of this study was to test whether resting state functional connectivity (rs-FC) between Vim and the rest of the brain was postoperatively modulated by thalamotomy, and whether such changes correlated with individual clinical outcomes.

Materials: An observational clinical and resting-state magnetic resonance imaging (rs-fMRI) in a single subject with tremor-dominant PD who underwent Gamma knife radiosurgery (GKRS) Vim thalamotomy was carried out.

The patient was assessed by clinical, wearable motion sensors and rs-fMRI evaluation before treatment and over the follow-up period (at 3, 6 and 12 months after treatment). Ten age- and sex-matched controls were also enrolled.
Methods: Targeted left Vim was selected as region of interest and a seed-based rs-fMRI connectivity analysis was performed in PD patient and healthy controls at baseline and over time.

1-year trend of progression of brain network changes was evaluated in PD patient and then compared to controls. Furthermore, correlations among functional measures and both clinical and motion sensors data were tested at baseline and over time.

Results: A 76-year-old right-handed woman with a 13-year history of PD was deemed to be a candidate for GKRS left Vim thalamotomy for treatment of severe refractory tremor in the dominant hand. Seed-based analysis showed a significantly increased FC between left Vim and left visual areas relative to healthy controls before treatment. Over 1 year, PD patient showed a progressive decreased FC between left Vim and left visual cortex, mainly after 6 months from GKRS. At 12 months after treatment, a normalization of aberrant pre-therapeutic FC between left Vim and visual areas was obtained. These FC changes over the follow-up were positively related to progressive tremor improvement over time, assessed by both MDS-UPDRS III and motion sensors measurements.

Discussion: Interestingly, our findings converged towards parts of the extrastriate visual system as being involved in tremor generation and further arrest after thalamotomy. Furthermore, GKRS Vim thalamotomy seems to bring abnormal pre-therapeutic FC of the extrastriate visual cortex to levels comparable to those of healthy subjects.

Conclusions: The idea that the FC between visual areas and deep nuclei might play a prominent role in tremor generation is raising. Such a hypothesis should be validated in larger cohorts.

MRI INVESTIGATION OF CAUDATE NETWORKS IN THE NORMAL AGING

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Objective: Neurogenesis decline with aging may be associated with brain atrophy. Subventricular zone (SVZ) neuron precursor cells possibly modulate striatal neuronal activity via the release of soluble molecules. Neurogenesis decay in SVZ may result in structural alterations of brain regions connected to the caudate, particularly to its medial component. The aim of this study was to investigate how the functional organization of caudate networks relates to structural brain changes with aging.

Materials: 143 normal subjects were recruited: 50 "young" (20-35 years [young controls: YC]) and 93 "old" (36-85 years [old controls: OC]).
Methods: In YC, stepwise functional connectivity (SFC) was used to characterize regions that connect to medial and lateral caudate at different levels of link-step distances. Atrophy of medial- (MCR) and lateral- (LCR) caudate connected regions was estimated in OC using T1-weighted images.

Results: In YC, medial- and lateral-caudate showed direct FC to basal ganglia, superior and caudal middle frontal and inferior parietal gyri, cingulate cortex, precuneus, pericalcarine and insula. With subsequent steps, caudate parts were also connected to precentral and superior temporal gyri and cuneus. In YC, medial-caudate showed higher direct FC to basal ganglia, superior, middle and inferior frontal and inferior parietal gyri (MCR) relative to the lateral-caudate. Considering the opposite contrast, lateral-caudate showed a stronger FC to basal ganglia, orbitofrontal, rostral-anterior cingulate and insula cortices (LCR) compared to medial-caudate. In OC, MCR showed greater atrophy relative to LCR. Splitting OC into two groups, the analysis showed that atrophy differences are driven by OC older than 60-years of age.

Discussion: Brain regions linked to medial-caudate appear to be more vulnerable to aging than lateral-caudate connected areas. The adjacency to SVZ may, at least partially, explain these findings.

Conclusions: SFC analysis can be useful to evaluate the role of the SVZ in the network disruptions in age-related neurodegenerative disorders.

Supported by: European Research Council (StG-2016_714388_NeuroTRACK); Foundation Research on Alzheimer Disease.

AGE-RELATED VULNERABILITY OF THE HUMAN BRAIN CONNECTOME

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Objectives: The study aim was to investigate whether and how structural brain changes and functional connectome play a central role in the pattern of neuronal dysfunction due to aging.
Materials: The study cohort included 128 healthy individuals (young [yC] age range: 20-30 years and old [oC] age range: 41-84 years), who underwent an MRI scan.

Methods: We performed stepwise functional connectivity (SFC) analysis, aiming to characterize regions that connect to specific seed brain areas at different levels of link-step distances. Eight well-known hubs were selected as seeds: middle frontal gyrus, rostral anterior and posterior cingulate cortex, precuneus, inferior parietal, middle temporal (DMN hubs) and lingual gyri and pericalcarine cortex (occipital hubs). Per each seed region the functional brain network architecture in yC was evaluated to identify highly functionally connected regions with hubs. Subsequently, we estimated structural changes of brain regions across lifespan. Cortical thickness trajectories with advancing age were modelled using Gaussian Process Regression and the regional changes over time were evaluated. Finally, spatial similarity between functional pattern in yC and gray matter atrophy in oC was estimated for each hub.

Results: SFC findings in yC revealed that seeds known to be part of the DMN showed distributed intra-network direct connections (within DMN regions). On the other hand, occipital hubs showed only local connectivity distribution within occipital lobe and to sensorimotor areas. At indirect steps, a spatial overlap was observed in SFC maps of different hubs reaching a common pattern. Structurally, great cortical thinning was observed in the DMN hubs, while occipital hubs showed subtle atrophy changes across lifespan. Regions belonging to temporal, frontal parietal lobes and in the insular cortex showed cortical thinning with aging. Significant positive correlation was found between SFC pattern of middle frontal hub in yC and the cortical thinning in oC, while significant negative correlation emerged between the functional network organization of lingual and pericalcarine hubs and the cortical thinning in oC.

Discussion: We observed that regions functionally close to the DMN hubs but far from the occipital hubs became the more atrophic during aging.

Conclusions: Our findings revealed how functional network rearrangements of brain hubs and their structural change trajectories across lifespan influence the functional and structural trend of changes of the remaining brain regions.

Supported by: European Research Council (StG-2016_714388_NeuroTRACK); Foundation Research on Alzheimer Disease.

WHITE MATTER MICROSTRUCTURAL CHANGES IN HEALTHY AGING: A DTI AND NODDI STUDY

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Objective: The goal of this study was to assess white matter (WM) integrity changes during aging using different diffusion metrics in a cohort of young and older adults.

Materials: Forty-eight young (yC), aged 20-31 years, and 65 old controls, aged 41-85 years, were enrolled and underwent multi-shell diffusion brain MRI. Older controls were then divided into two groups considering 60-years as cut-off (21 middle-aged (mC) and 44 elderly (eC)).

Methods: The diffusion tensor was estimated using diffusion-tensor imaging fit provided by the FMRIB Diffusion Toolbox. Fractional anisotropy (FA) and mean diffusivity (MD) maps were computed. Furthermore, Intra-cellular Volume Fraction (ICVF), Orientation Dispersion Index (ODI) and Isotropic Volume Fraction (ISO) maps were estimated using the NODDI model, providing a direct quantification of neurite morphology and its integrity. To assess significant variability of the metrics between the three groups of participants, whole-brain Tract-Based Spatial Statistic (TBSS) analysis was performed ($p<0.05$, family-wise error corrected, 5000 permutations).

Results: TBSS analysis demonstrated microstructural differences between the three groups. A widespread age-related reduction of FA was detected in supratentorial regions in both mC and eC relative to yC, whereas a specific decrease of FA affected the fibers of superior longitudinal fasciculus in the eC compared to mC. On the other hand, a more focal reduction of ICVF was found in eC relative to yC in the main WM frontal fibers. Of note, eC showed a greater damage in terms of decreased ICVF specifically in the superior longitudinal fasciculus and the superior corona radiata relative to mC. When the MD, ODI and ISO maps were compared between the three groups, a widespread increase of these metrics was observed in mC and eC relative to yC, replicating the widespread WM alteration pattern obtained by FA results. Discussion: The widespread damage, identified by FA, MD, ISO and ODI suggests how these metrics resulted highly sensitive to structural changes during lifespan, involving frontal fibers, followed by the parietal and temporal fibers. Moreover, ICVF showed to be a specific marker able to identify the WM structural damage in the frontal fibers in the advanced phase of aging.

Conclusions: Multiple diffusion metrics may lead to better profile healthy aging structural changes, allowing to quantify the extent of WM architecture deterioration and to model damage spreading along the most important structural connections.

Supported by: European Research Council (StG-2016_714388_NeuroTRACK); Foundation Research on Alzheimer Disease.

INVESTIGATING GREY MATTER ATROPHY AND ITS RELATIONSHIP WITH WHITE MATTER LESIONS IN MS, MOGAD AND AQP4-NMOSD

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Background: Brain grey matter (GM) damage is well known in MS, was recently described in MOGAD, while is controversial in AQP4-NMOSD. A relationship between GM atrophy and white matter lesions (WML) has been reported in MS, but their interplay is unclear in MOGAD and AQP4-NMOSD. Aims: To characterize GM atrophy in MOGAD and AQP4-NMOSD and its relationship with spatial patterns of WML.

Methods: In this cross-sectional study, we collected brain MRI scans of patients with RRMS/MOGAD/AQP4-NMOSD far from a relapse and healthy controls (HC) from 16 MAGNIMS centres. WML were semi-automatically segmented and classified according to their location as periventricular, juxtacortical, deep WM, deep GM and infratentorial. Voxel-wise analyses were performed using permutation testing as implemented in FSL. Differences in GM volume between groups were assessed using design

matrices within general linear model with disease as variable of interest and age, sex and centres as covariates. Similar design, but with the number of lesions in each location as regressor, was used to assess the relationship between GM atrophy and WML. For the significant results ($p<0.05$, corrected for multiple comparison), the number of voxels (V) is reported.

Results: We studied 175 patients with RRMS (132F, 40y ±10, EDSS: 2 [0-8]), 135 with MOGAD (83F, mean age: 41y ±14, median EDSS: 2 [0-7.5]), 135 with AQP4-NMOSD (111F, 51y ±14, EDSS: 3.5 [0-9]), and 144 HC (87F, 37y ±11). Compared to HC, lower GM volumes were found in RRMS diffusely (V:32576), in MOGAD in the temporal lobe, deep GM, insula and cingulate cortex (V:9474), in AQP4-NMOSD in the occipital cortex (V:4104). Lower GM volume was found in the deep GM in RRMS vs MOGAD (V:3487) and vs AQP4-NMOSD (V:5880), in the temporal cortex in MOGAD vs RRMS (V:839), in the occipital cortex in AQP4-NMOSD vs RRMS (V:2478). In RRMS a higher number of periventricular lesions was associated with reduced volume in the frontal, parietal, temporal cortex, deep GM and insula (V:9567). In MOGAD a higher number of periventricular and juxtacortical lesions was associated with reduced volume in the temporal cortex, deep GM and insula (V:5021 and V:5666). No correlation was found between WML and GM volumes in AQP4-NMOSD.

Discussion and Conclusions: GM atrophy in the temporal and occipital cortex seems to be prominent in MOGAD and AQP4-NMOSD, respectively. A relationship between regional atrophy and WML patterns was seen in MOGAD and RRMS, suggesting that there may be a disruption of the WM bundles projecting into the GM in both diseases.

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RAPID SOFTWARE EFFECTIVENESS IN SELECTING PATIENTS WITH ACUTE ISCHEMIC STROKE ELIGIBLE FOR ENDOVASCULAR MECHANICAL THROMBECTOMY

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Objectives: The RAPID CTP (CT scan and Perfusion) (IschemaView, Menlo Park, CA, USA), an automated image-analysis system based on perfusion maps, has been validated in several clinical studies. Herein, we evaluated the effectiveness of RAPID in selecting patients with acute ischemic stroke (IS) eligible for mechanical thrombectomy, from 1 February 2021 to 31 March 2022.

Materials and Methods: We prospectively included 154 consecutive patients accessing the Emergency Department of the San Bassiano Hospital with possible acute IS. These patients received brain CT scan and perfusion analysis by means of the RAPID CTP. Each neuroimaging study was evaluated by a radiologist of our hospital and a neuroradiologist in the hub center (San Bortolo Hospital, Vicenza) by means of the RAPID mobile and web apps, allowing real-time data availability and instant, secure inter-team communication. All patients received neurological evaluation, in-person whenever possible, or alternatively by remote consulting system.

Results: Overall, we included 154 patients (74 women). Mean age of included patients was 66.4±17.05 years; age range 27-96 years. Median door-to-needle time was 84.5 minutes (IQR 59.5-112.5), whereas median door-to-groin puncture time was 136 minutes (IQR 81.3-182.5). Overall, 39 patients received a diagnosis of acute IS caused by large vessel occlusion with the RAPID software, including 11 false-negatives. Thirteen patients were centralized to the hub center. Of these, 4 received only cerebral angiography due to difficult vascular access, affecting the interventional treatment, whereas 9 underwent mechanical thrombectomy. The RAPID software showed 96% sensitivity and 98% specificity in identifying large vessel occlusion, and a 97% sensitivity and 95% specificity in identifying mismatch volume.

Conclusion: The RAPID software showed a good sensitivity and specificity, and contributed to an improved diagnostic accuracy of patients with acute IS caused by large vessel occlusion. To our best knowledge, this is the first report of an Italian experience of RAPID application between a hub and a spoke stroke center in clinical practice.

CORRESPONDENCE BETWEEN GRAY MATTER ATROPHY AND NEUROTRANSMITTER MAPS IS RELEVANT IN MULTIPLE SCLEROSIS

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Objectives: In multiple sclerosis (MS), clinically-relevant gray matter (GM) atrophy progresses in a non-random manner, possibly due to the preferential involvement of specific neurotransmitter networks, which has not been fully evaluated yet. To investigate the associations among regional GM atrophy, neurotransmitter distributions and clinical manifestations in a large group of patients with MS (PwMS).

Material and Methods: Brain 3.0 T MRI scans were acquired from 286 PwMS and 172 healthy controls (HC). Regional GM volume differences, cross-correlations between regional GM atrophy and nuclear imaging-derived neurotransmitter maps and their associations with disease duration (DD), clinical disability, cognitive impairment, fatigue and depression were investigated using voxel-based morphometry and Juspace toolbox.

Results: Compared to HC, PwMS showed a widespread cortico-subcortical GM atrophy being spatially correlated with serotonergic, dopaminergic, opioid, noradrenergic, cholinergic and glutamatergic maps (false discovery rate, [FDR]-$p\leq0.004$). PwMS with a DD ≥5 vs <5 years had a significant GM atrophy in several deep GM, cortical and cerebellar regions being spatially correlated with a higher distribution of serotoninergic and dopaminergic receptors (FDR-$p\leq0.03$). Compared to mildly-disabled PwMS, those with Expanded Disability Status Scale (EDSS)≥3.0 or ≥4.0 had significant cortical, subcortical and cerebellar atrophy, which was associated with serotonergic and dopaminergic maps (FDR-$p\leq0.04$). A significant spatial correspondence with opioid and cholinergic maps was also found for PwMS with EDSS≥4.0 vs <4.0 (FDR-$p\leq0.04$). Cognitively-impaired vs cognitively-preserved PwMS had a widespread GM atrophy being spatially correlated with serotonergic, dopaminergic, noradrenergic, cholinergic and glutamatergic maps (FDR-$p\leq0.04$). PwMS with vs without fatigue had significant cortical, subcortical and cerebellar atrophy, which were associated with serotonergic, dopaminergic, opioid and glutamatergic maps (FDR-$p\geq0.07$). No significant

GM atrophy and associations with neurotransmitter maps were found according to depression.

Discussion: The analysis of the spatial correlations between GM atrophy and neurotransmitter distribution maps suggested that the widespread GM atrophy found in PwMS compared to HC was spatially associated with the majority of neurotransmitters. More limited spatial correlations with selective neurotransmitter distribution maps were found when we explored specific clinical features of the disease.

Conclusions: GM atrophy in regions belonging to specific neurotransmitter systems may contribute to explain part of MS clinical manifestations, including locomotor disability, cognitive impairment and fatigue.

RELIABILITY OF BRAIN TISSUE VOLUMETRIC MEASUREMENTS AS OBTAINED BY NON-HUMAN AIDED MRI SEGMENTATION SOFTWARE

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Aims: Brain tissue changes over time are known to be an important marker of both healthy aging and neurological disease progression [1,2]. Therefore, it is pivotal to know whether these changes are significantly larger than measurement uncertainty. The aim of this study was to estimate the reliability of regional brain volumetrics as assessed by structural MRI images using a popular automated segmentation algorithm.

Materials: We enrolled 3 healthy subjects (1 female [F] aged 30 years, and 2 males [M1, M2] aged 25 and 36 years). Each participant underwent 3T MRI scanning, which was repeated twice, 7 days apart for F, 7 and 24 days apart for M1 and M2, respectively. In each MRI session a structural brain volume (3D-T1) was acquired two times, for a total of 12 images (3subjects*2T1-images/session*2sessions/subject). This experimental asset allowed the determination of test-retest reliability both in single session (intra-session) and across sessions (inter-session).

Method: T1 images were segmented using a custom-made analysis based on FSL 5.0.11 (fsl.fmrib.ox.ac.uk/fsl/fslwiki). From each T1 scan, binary masks and volumes were computed for the following brain tissues: cortical and subcortical grey matter (GM-cort, GM-subcort), white matter (WM), CSF, Thalamus, Caudate, Putamen, Pallidum, Hippocampus, Amygdala, nucleus Accumbens and Brainstem. Intra- and inter-session reliability for each brain tissue volume was assessed computing both the relative error (RE=absolute_error/mean_val=(max_val min_val)/(max_val+min_val)) and the coefficient of variation (CV=std_dev/mean_val).

Results: All intra-session RE values were less than 0.9% (Pallidum) except Amygdala (5.8%) and nucleus Accumbens (3.6%). All inter-session REs were less than 1.7% (GM-cort) except CSF (4.7%), Amygdala (6.9%) and nucleus Accumbens (4.1%). All intra-session CVs were less than 1.3% (Pallidum) except Amygdala (8.4%) and nucleus Accumbens (5.8%). All inter-session CVs were less than 1.9% (GM-cort) except CSF (4.7%), Amygdala (9.0%) and nucleus Accumbens (5.5%). CSF and GM-cort presented higher 'RE (inter)-RE(intra)' and 'CV(inter)-CV(intra)' differences, with both values equal about 4% for CSF and 1.1% for GM-cort. Amygdala showed instead the highest REs and CVs, but nearly null 'RE (inter)-RE(intra)' and 'CV(inter)-CV(intra)' differences.

Discussion & Conclusions: This study highlights how inter-session REs and CVs exceed, as expected, the intra-session values. While in almost all considered brain regions test-retest reliability is most likely reduced by measurement errors, in the CSF, which showed the greatest 'intra- vs inter-session' volume differences, we cannot exclude a real inter-day volume change [3]. RE and CV values we computed here might be usefully exploited for the assessment of sample and effect size in human brain studies using similar processing pipeline.

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THE KEY ROLE OF DEPRESSION AND SUPRAMARGINAL GYRUS IN FRAILTY AGING: A CROSS-SECTIONAL STUDY

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Aims: The decline in reserves and resistance to age-related stress factors is recognized as frailty, one of the greatest challenges in recent years [1]. Despite a well-known association of frailty with cognitive impairment, depression, and gray matter morphology, there is no clear data on the nature of this relationship. This study seeks to disentangle the role of the behavioral, neuropsychological, and neural components as predictors or moderators of frailty.

Methods: Ninety-six older adults (58 females, mean age=75.49±6.62) were consecutively enrolled at Fondazione Don Gnocchi (Milan). They underwent (1) a screening for the Frailty Fried's phenotype [2], based on the presence of 5 indicators (poor handgrip strength, slow gait speed, involuntary weight loss, exhaustion, and sedentary behavior; frailty score=0-5), to be classified as robust (absence of indicators), pre-frail (1-2 indicators) or frail (>2 indicators); (2) a behavioral evaluation to assess the level of physical activity (PASE score), global cognition (MoCA score), depression (CES-D), wellbeing (SF-12;EQ5D5L), autonomy in daily living (ADCS); and (3) an MRI examination (3T PRISMA) including T1-3D(MPRAGE) to investigate brain morphology in terms of cortical thickness and subcortical volumes (Desikan's and Fischl's atlas). Differences among frails, pre-frails, and robust in clinical patterns were tested by Chi-squared analysis. Partial correlation analyses (covariates: age, gender, total intracranial volume) were run to test the link between Frailty, neural and clinical patterns. Variables significantly associated with Frailty were inserted in a logistic regression model as potential predictors. Finally, mediation analysis was performed to test the nature of the relation between neural pattern, clinical component, and Frailty.

Results: Seventeen subjects were classified frail, 45 pre-frail, and 34 robust. Partial correlations showed Frailty score as associated with age (pcorr<0.001), CES-D (pcorr<0.001), SF-12 (pcorr<0.001), EQ5D5L (pcorr<0.001), and ADCS (pcorr=0.001), left supramarginal (pcorr=0.005), and right rostral middle frontal (pcorr=0.004) gyri. Multiple regression model revealed that CES-D, MoCA, and left supramarginal gyrus predict frailty condition. A full mediation of depression on the relationship between cortical thickness and frailty was registered, while the cognitive level reported no significant mediating role. In particular, the left supramarginal thickness was predictive of depression, which in turn had an impact on the occurrence of frailty. Furthermore, in the study's cohort, handgrip weakness was the key frailty indicator.

Conclusions: These data represent frailty as a complex clinical entity in which handgrip weakness is a key indicator while depression, and not cognitive level, fully explains the association of cortical thickness with frailty.

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ECCHORDOSIS PHYSALIPHORA PRESENTING WITH HYPNIC HEADACHE

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Objective: We report two cases of Ecchordosis Physaliphora presenting with hypnic headache. Ecchordosis Physaliphora(EP) is a rare benign congenital hamartomatous lesion originating from remnants of the notochord, and it is usually asymptomatic [1].

Methods and Materials: A 61-year-old woman and a 41-year-old man had been complaining of a dull headache that woke them up every night for many months. Their past medical history was unremarkable. Neurologic examination was normal in both patients. In both cases, indomethacin (100 mg) administered in the evening produced a marked reduction in nocturnal headache attacks. Causes of nocturnal headache such as chronic obstructive pulmonary disease, sleep apnea, and hypertension were ruled out [2]. Patients also had a brain MRI to rule out any structural brain lesions.

Results: In both cases an enlarged cystic lesion in the pre-pontine cistern, compatible with Ecchordosis Physaliphora was found on brain MRI. The diagnosis of EP can be made on the basis of imaging presentation. In fact, the presence of CSF attenuation on MRI, absence of contrast and bony destruction are the necessary features for the diagnosis of EP [3]. The patients' nocturnal headache characteristics met the diagnostic criteria for a secondary hypnic headache (HH). Hypnic headache is a rare form of sleep-associated nocturnal headache whose pathogenesis is not fully elucidated.

Discussion and Conclusion: Our cases highlight for the first time the association between a nocturnal headache and EP [1]. One possible explanation for the sleep-associated headache of our patients is that the enlarged cystic lesion exerts a direct mass effect on brainstem structures. Thus, it causes a dysfunction of the circuits involved in sleep and headache pain, more specifically an alteration of the connection between the suprachiasmatic nuclei and the periacqueductal gray and an impairment of melatonin secretion [2]. The latter theory could be the reason why this type of headache occurs only after a certain age and during night hours. Alternatively, the same genes involved in abnormal migration of notochordal residues could cause a predisposition to develop hypnic headache. The low prevalence of both conditions (EP and HH), and their association in two cases strongly favors a causal association between the two conditions. Although the number of cases is too small for any final conclusion, this observation broadens the spectrum of secondary causes of nocturnal headaches, describes a new clinical presentation of EP, and supports new hypotheses about the pathogenesis of nocturnal headaches.
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ZINC TOXICITY IN A WELDER: AN ANCIENT BUT STILL CURRENT CAUSE OF MYELOPATHY

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Objective: Myelopathy in smelter workers is reported in 19th century. In literature only clinical descriptions of cases are made, because MRI study was not available [1]. Here we report an MRI imaging study of a welder that developed progressive paraplegia after zinc toxic exposure.

Methods and Materials: A 51-year-old welder (non-smoker) developed subacute lower paresthesias and progressive spastic-ataxic paraplegia. Previous medical history was unremarkable. Symptoms appeared ten days after first zinc exposure on a yacht construction site (8-hours-day/40 days in confined space, face-shield was the only protection he had). Neurological Examination revealed loss of vibratory-sensation, spasticity, hyperreflexia, sensory ataxia.

Results: Laboratory tests (vitamin B12, E, folate, copper) and paraneoplastic screening on serum and CSF were unremarkable too. Brain MRI was unremarkable. Spinal MRI on axial sections at the level of D10 showed a bilateral symmetrical T2 hyperintense signal within the posterior and lateral columns of the spine, where the lateral aspects formed an “inverted V sign” creating a 3-point sign: a “pair of binoculars sign” or a “dot-sign” or “dumbbell” on the axial plane of dorsal spinal cord (Figure B, arrow). Sagittal MRI spine showed a longitudinally extended spinal cord lesion with T2 hyperintense signal in the dorsal columns, T2-weighted imaging showed hyperintensities extending from D2 to D10 (white arrows) (C, D). Medullary cone was not affected. There was no cord expansion or atrophy. On T1 weighted images no abnormalities were detected. No contrast enhancement was found. A diagnosis of zinc-related myelopathy was postulated on the basis of a strong correlation with toxic exposure. After recovery, patient was removed from the construction site.

Discussion and Conclusion: Although myelopathy in zinc smelter workers was reported in 19th century only [1], it was recently rediscovered in excessive zinc-intake/exposure [2]. Copper malabsorption secondary to upregulation of zinc-induced metallothionein is the presumed mechanism even if in our case copper level was normal [3]. MRI spinal study showed a pattern of combined degeneration that explained exactly the clinical manifestations of our patient. To the best of our knowledge, this is the first neuroimaging picture of zinc-related myelopathy.
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SOMA AND NEURITE DENSITY IMAGING (SANDI) TO TYPIFY MULTIPLE SCLEROSIS NEUROAXONAL DAMAGE IN VIVO

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Objectives: To assess white matter (WM) and gray matter (GM) microstructural abnormalities in MS through soma and neurite density imaging (SANDI) and evaluate associations between SANDI-derived measures, clinical disability and conventional MRI variables.

Materials: We applied SANDI to 3T brain MRI diffusion data to evaluate the fractions of neurite (fneurite) and soma (fsoma) in 23 MS patients (11 relapsing-remitting [RR], 12 progressive [P]) vs 20 healthy controls (HC).

Methods: SANDI maps were estimated using the AMICO toolbox. Brain T2-hyperintense WM lesions, normal-appearing (NA) WM and cortical masks were transformed onto the diffusion space. Fneurite, fsoma and fextra were then averaged within the investigated brain tissues.

Results: Fneurite was lower in MS NAWM vs HCs' WM ($p=0.009$), whereas MS WM lesions showed lower fneurite and fsoma compared to both MS NAWM and HCs' WM ($p<0.001$). Cortical fneurite and fsoma were lower in MS vs HC ($p\leq0.007$). Compared to RRMS, PMS patients had lower fneurite in NAWM and cortex ($p\leq0.031$) and lower cortical fsoma ($p=0.004$). Fneurite and fsoma in the different brain compartments correlated with disease duration, disability, brain T2-hyperintense WM lesion volumes, normalized brain, cortical and WM volumes (r from -0.761 to 0.821, $p\leq0.033$).

Discussion: Brain T2-hyperintense WM lesions showed significantly lower fneurite and fsoma compared to HCs' WM and MS NAWM. Our results are in line with histopathological studies showing that WM lesions are characterized by a lesion core with severe demyelination, axonal loss, and hypocellularity. Consistently with histopathological studies, compared to HCs' WM, a significantly lower fneurite was observed in MS NAWM. Conversely, no significant differences of fsoma values were observed. This may be explained by the presence of increased density of activated microglia and astrogliosis that may counterbalance oligodendrocyte loss. Lower cortical fneurite and fsoma were observed in MS compared to HC, especially in PMS. Accordingly, neuronal shrinkage and loss may be useful to discriminate PMS from RRMS. The significant correlations observed between EDSS with fneurite in brain T2-hyperintense WM lesions and NAWM and with fsoma in brain T2-hyperintense WM lesions and cortex suggest a progressive and clinically relevant accumulation of neurodegenerative processes in these tissues. The strong correlations with brain volumes support the relevance of fneurite and fsoma as surrogate measures of irreversible tissue loss.

Conclusions: SANDI may be a clinically feasible and relevant model to better characterize the complex pathological substrates of MS, including neuro-axonal loss and astrogliosis.

Funding. Marco Palombo is supported by UKRI Future Leaders Fellowship grant MR/T020296/2.

VOXEL-WISE MULTIMODAL MRI REVEALS SPECIFIC PATTERNS OF BRAIN DAMAGE IN THE MAIN MULTIPLE SCLEROSIS PHENOTYPES

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Objectives: In this study, we applied a multimodal MRI approach to investigate in vivo the heterogeneous pathological processes occurring in the gray matter (GM) and white matter (WM) of the main MS clinical phenotypes.

Materials: Fifty-seven MS patients (42 relapsing-remitting [RR], 15 secondary progressive [SP]) and 47 healthy controls (HC) underwent brain 3T MRI.

Methods: Voxel-wise differences of brain GM and WM atrophy, T1weighted (w)/T2w-ratio, quantitative susceptibility mapping (QSM), neurite density index (NDI) and magnetization transfer ratio (MTR) maps in the main study groups were investigated.

Results: Compared to HC, RRMS showed significantly lower MTR of posterior periventricular and infratentorial WM, deep GM and frontal cortex, widespread lower T1w/T2w-ratio, atrophy of deep GM, insular cortex and WM, widespread lower NDI in supratentorial WM and cerebellum, small GM/WM clusters with either significantly increased or decreased QSM ($p<0.001$). Compared to RRMS, SPMS patients showed significantly lower MTR of periventricular WM, deep GM and cerebellum, lower T1w/T2w-ratio of fronto-temporal regions, widespread cortical atrophy, widespread lower NDI of WM, increased QSM in the pallidum and striatum and increased T1w/T2w-ratio of the pallidum ($p<0.001$).

Discussion: Our study confirmed that irreversible GM and WM volume loss accumulates along disease course. The demonstration of a diffuse GM atrophy, following specific topographic and temporal patterns, involving first deep GM nuclei and then affecting the cortex is consistent with previous studies. The significantly reduction of MTR, T1w/T2w-ratio and NDI values observed in the WM of RRMS patients, that became more prominent in SPMS, further confirmed that WM is characterized by the progressive accumulation of microstructural abnormalities, such as inflammation, demyelination and neuro-axonal loss. Compared to RRMS, significantly higher T1w/T2w-ratio and QSM values were observed in the striatum and pallidum of SPMS patients, suggesting that these metrics may reflect ongoing neurodegenerative processes.

Conclusions: By combining advanced MRI techniques, we found that demyelination and irreversible neuro-axonal loss are already present in RRMS and become more severe and widespread in SPMS. Higher T1w/T2w-ratio and QSM in the pallidum and striatum, possibly reflecting iron accumulation and neurodegeneration, may represent relevant MRI markers able to discriminate SPMS from RRMS.

THE FUNCTIONAL ANATOMY OF ANTON'S SYNDROME AND ITS RELATIONSHIP WITH ANOSOGNOSIA FOR HEMIPLEGIA

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Objective: Anton syndrome (AS) [1], or anosognosia for cortical blindness, is an intriguing form of unawareness for a neurological impairment, traditionally associated with occipital lesions. However, it is known that focal lesions can induce structural and functional disconnection far beyond the locus of damage [2]. In this study we examined the anatomy of AS and compared it to that of lesions inducing visual field deficits without anosognosia (Hemianopic Controls). We hypothesized that AS would exhibit greater disconnection of occipital with association temporal and parietal cortices. A second aim was to compare the disconnection of AS with that previously described in the anosognosia for hemiplegia (AHP) [3].

Materials: Sixteen AS post-stroke cases were retrieved from the literature. Sixteen post-stroke hemianopic patients were selected and flipped to the contralateral hemisphere as controls from [2].

Methods: Brain lesions were used as seed to estimate lesion structural (SDC) and functional (FDC) disconnections. SDC computes the probability that a specific white matter tract passes through the lesion; FDC assesses cortical areas functionally connected with the lesion. Both approaches rely on the comparison with a normative connectome including a large sample (n>100). Lesion topology, SDC, and FDC maps were then compared between groups through a non-parametric approach with n=5000 permutations. The same approach was used to compare AS and AHP (n=28) patients, from our previous study [3].

Results: AS lesions involved primary and extra-striate visual cortex, while HC showed greater damage of the geniculo-calcarine tract and primary visual cortex. AS showed higher SDC of temporo-parietal white matter tracts, while HC exhibited greater disconnection of temporo-occipital tracts. The FDC analysis confirmed the involvement of the dorsal association cortex in AS that localized to parietal and frontal regions. Finally, the comparison between AS vs. AHP revealed convergent regions of disconnection in the inferior parietal/temporo-parietal cortex, as well as divergent FDC patterns in visual occipital (AS) vs. motor network (AHP).

Discussion: For the first time, we show that AS is not only due to bilateral occipital damage, but to a combination of extra-striate damage and temporo-parietal disconnection. In addition, in contrast to current theories of awareness emphasizing either separate modality specific mechanisms or a common locus for awareness in medial parietal cortex, our analysis highlights the importance of temporo-(inferior) parietal cortex as a critical site for awareness for anosognosia.

Conclusions: This study emphasizes the importance of temporo-(inferior) parietal cortex for awareness, and a possible locus of stimulation to improve awareness deficits.

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A LATENT DIMENSIONAL FRAMEWORK FOR BRAIN DIFFUSION PROPERTIES IN HEALTHY AND STROKE

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Objective: Different models aimed at investigating brain tissue structure are applied to the diffusion weighted imaging (DWI) signal. Diffusion Tensor Imaging (DTI) depicts white matter anisotropy. Neurite Orientation Dispersion and Density Imaging (NODDI) estimates dendrites and axons complexity. Although these metrics are usually assessed independently, an underlying structure can be inferred by the presence of latent diffusion variables capturing brain properties in normal and neurological disorders. Thus, the aim of this study is to characterize latent factors from different brain diffusion metrics.

Materials: We included i) DWI from two cohorts (n=50) of the human connectome project (HCP); ii) longitudinal data from 30 healthy controls (two sessions one month apart) and 51 stroke patients (acute, 3 months, and 1 year) from the Washington University cohort (WashU).

Methods: For each subject we computed DTI fractional anisotropy (FA), radial, axial, and mean diffusivity (AD, RD, and MD), and NODDI orientation dispersion index (ODI), intracellular volume fraction (ICVF), and isotropic volume fraction (IsoVF). Brain maps were spatially normalized and for each metric a mean map was computed. Averaged maps were concatenated into a matrix (v×n; v= voxels, n=DWI metrics) fed into a factor analysis. This procedure was repeated independently for each cohort. Latent factors explaining more than 90% of the variance were retained and plotted in the brain space. We then compared factorial maps between the discovery and replicative HCP cohorts and the longitudinal WashU dataset.

Results: We consistently reported three latent factors in both datasets. The first factor loaded on AD, RD, MD, and IsoVF (factor1). The second factor mainly loaded on FA and ODI (factor2), while the third factor loaded on ICVF (factor3). Healthy factor maps showed a peculiar and consistent brain topology, highly correlated between subjects (HCP between-subjects: factor1, r=0.928; factor2, r=0.967, factor3: r=0.960, p<0.00001), and time (WashU within-subjects: factor1: r=0.977; factor2: r=0.975; factor3: r=0.915, p<0.00001). These factors were reproduced in stroke, where correlations between loadings among different time-points were highly significant (r=0.85 between acute and 3 months; r=0.83 between acute and 1 year, p<0.0001).
Discussion: These results suggest that three latent factors can capture the main microstructural brain properties computed with different DWI models. These factors were reproduced in stroke.

Conclusions: We described a new dimensional space of the DWI signal which might pave the way to new biomarkers in neurological disorders. Further studies should investigate whether these factors highlight cognitive abilities and stroke deficits.

BASAL GANGLIA HYPERMETABOLISM AS A POSSIBLE FDG-PET SIGNATURE OF AUTOIMMUNE ENCEPHALITIS

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Aim: Autoimmune encephalitis (AE) is diagnosed according to criteria proposed by Graus[1], based on subacute onset of working memory deficits, altered mental status or psychiatric symptoms, plus at least one supporting feature among CSF pleocytosis, seizures, MRI abnormalities, new focal CNS findings. Although 18F-FDG-PET is not included, a recent meta-analysis showed that metabolic alterations are common in these disorders [2]. As clinical diagnosis remains challenging, we seek to identify a possible PET metabolic signature of AE in our case series and assess the impact of PET findings on clinical diagnostic confidence.

Materials and Methods: We retrospectively analyzed the metabolic patterns of patients with AE diagnosed at our Institution; the final sample

comprised 8 patients whose PET images were assessed by an experienced rater and then analyzed with SPM12, both at a group and single subject level, using a local database of 33 healthy subject as controls. All patients also underwent MRI and CSF analysis. Autoantibodies reactive with neuronal surface antigens were analyzed in blood and CSF of each patient with commercial cell-based assays. Both pre-scan and post-scan clinical confidence for AE diagnosis was assessed by a neurologist, using a 5-point diagnostic confidence ordinal scale.

Results: None of our patients exhibited typical MRI features of AE; only one had CSF pleocytosis. PET abnormalities were present in all of our patients on semiquantitative analysis, the most consistent finding being at least unilateral basal ganglia (BG) hypermetabolism in all patients, a pattern clearly identified at visual assessment only in 5/8 patients. Notably, BG hypermetabolism was the only significant finding of the group analysis, and at single subject level it was more significant and consistent in the subgroup (3 cases) with LGI-1 autoantibodies. A simulation including BG hypermetabolism among diagnostic criteria confirmed the diagnostic confidence for LGI-1 cases and resulted in a 1-point increase for 80% of other cases.

Discussion: Basal ganglia hypermetabolism is already known to be present in specific types of AE, such as LGI-1[3], GAD and NMDAR. Our data show that this finding may be extended to cases without identification of autoantibodies, and may be an additional biomarker of AE. Semiquantitative analysis was superior to visual assessment and it should be recommended.

Conclusion: BG hypermetabolism on semiquantitative analysis of FDG-PET images might be used as an additional biomarker and supportive feature for AE diagnosis, but further studies are needed to define its contribution.

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CORTICAL THICKNESS DISTINGUISHES IDIOPATHIC NORMAL-PRESSURE HYDROCEPHALUS FROM PROGRESSIVE SUPRANUCLEAR PALSY: A MACHINE LEARNING APPROACH

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Objective: Progressive supranuclear palsy (PSP) and idiopathic normal pressure hydrocephalus (iNPH) share several clinical and radiological features, making the differential diagnosis challenging. In this study, we aim to differentiate between these two diseases using a machine learning approach based on cortical thickness and volumetric data.

Methods: Twenty-three iNPH patients, 50 PSP patients and 55 control subjects were enrolled. All participants underwent a brain 3T-MRI, and cortical thickness and volumes were extracted using Freesurfer 6 on T1-weighted images and compared among groups. Finally, the performance of a machine learning approach with random forest using the extracted cortical features was investigated to differentiate between iNPH and PSP patients.

Results: iNPH patients showed cortical thinning and volume loss in the frontal lobe, temporal lobe and cingulate cortex, and thickening in the superior parietal gyrus in comparison with controls and PSP patients. PSP patients only showed mild thickness and volume reduction in the frontal lobe, compared to control subjects. Random Forest algorithm distinguished iNPH patients from controls with AUC of 0.96 and from PSP patients with AUC of 0.95, while a lower performance (AUC 0.76) was reached in distinguishing PSP from controls.

Conclusion: This study demonstrated a more severe and widespread cortical involvement in iNPH than in PSP, possibly due to the marked lateral ventricular enlargement which characterizes iNPH. A machine learning model using thickness and volumetric data led to accurate differentiation between iNPH and PSP patients, which may help clinicians in the differential diagnosis and in the selection of patients for shunt procedures.

INFLUENCE OF ANTI-SEIZURE MEDICATION ON CORTICAL AND SUBCORTICAL GREY MATTER IN PATIENTS WITH BENIGN MESIAL TEMPORAL LOBE EPILEPSY: A COMPARISON STUDY

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Aims: Although several studies reported an effect of some anti-seizure medications (ASMs) on brain volume [1,2], the influence of these widely used drugs on the grey matter is still uncertain. We assessed the cortical and subcortical changes between subjects affected by benign mesial temporal lobe epilepsy (bMTLE) [3] on current treatment with ASMs and those not taking any medication compared to a group of healthy controls (HC).

Material: Sixty-three patients with bMTLE and 77 age- and sex-matched HC underwent a 3-Tesla MRI. In the MTLE group, 24 of them (mean age:41 ±3) had not yet started any treatment because at their first medical observation, and 39/63 (mean age: 40±2) assumed one ASMs (comprehending lamotrigine, carbamazepine, levetiracetam, topiramate, valproate). None of them had a history of other previous antiepileptic treatment. The two bMTLE groups had the same seizure frequency, mostly viscerosensory or experiential auras3, but a significantly different disease duration (non-treated patients: 6.4±8.4; treated patients: 10.2 ±9.4).

Methods: MRI-based quantification of subcortical volumes and cortical thickness were performed using Free Surfer software in bMTLE patients and HC. A one-way Analysis of Covariance (ANCOVA) was used to compare the measurements among naïve and on-treatment bMTLE patients and HC, with gender, age, disease duration and intracranial volume as covariates-of-no-interest.

Results: No statistical measurement differences were found between naïve and on-treatment bMTLE subjects. All bMTLE patients showed a significant thickness reduction in right entorhinal cortex ($p<0.001$), right isthmus cingulate ($p<0.001$), left putamen ($p<0.001$) and bilateral medial orbitofrontal cortex ($p<0.001$), middle temporal cortex (<0.001), posterior cingulate ($p<0.001$), rostral anterior cingulate ($p<0.001$), frontal pole ($p=0.001$), globus pallidus ($p<0.001$), amygdala ($p<0.001$), caudal anterior cingulate ($p<0.001$), compared to HC. The bMTLE patients on monotherapy had a more pronounced thinning in left entorhinal cortex ($p=0.003$), isthmus cingulate ($p<0.001$), pars orbitalis ($p=0.004$), and right fusiform gyrus ($p=0.002$), inferior temporal cortex ($p=0.002$), middle temporal cortex ($p<0.001$), temporal pole ($p<0.001$), compared to HC. DISCUSSION: Our study demonstrated no significant difference in the grey matter between naïve and on-treatment bMTLE subjects. Compared to HC, all epileptic patients displayed an extensive lower thickness involving the limbic system, basal ganglia, frontal, and temporal lobes, regardless of the ASMs assumption. In detail, currently treated bMTLE subjects versus HC showed a predominantly temporal lobe thinning.

Conclusions: Our results contribute delineating the ASMs' influence on the brain. The demonstration of similar volume and thickness measurements in naïve and on-monotherapy bMTLE patients suggests a limited ASMs effect on cortical and subcortical grey matter.

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QUANTIFICATION OF THALAMIC VOLUME IN MULTIPLE SCLEROSIS: FROM THE MULTICENTER INNI DATASET TOWARDS THE CLINICAL APPLICATION

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Objectives: Thalamic atrophy has been found since the earliest phases of multiple sclerosis (MS) and is clinically relevant. However, this measure is still not included in clinical practice, due to the time-consuming manual segmentation and technical challenges. This study aimed to obtain a reliable segmentation of the thalamus in MS by comparing existing automatic methods.

Materials: 141 relapsing-remitting MS patients and 69 healthy controls (HC) with baseline and 1-year 3D T1-weighted, T2-weighted and diffusion weighted (DW) MRI acquisitions were collected from the Italian Neuroimaging Network Initiative repository.

Methods: From DWI, fractional anisotropy (FA) maps were derived to be used with T1-weighted MRI, as input for multimodal thalamic segmentation for the FSL-MIST. The other automatic approaches applied were FSL-FIRST v5.0.9 and Freesurfer v6.0, both at baseline and at follow-up. The agreement among the results of the pipelines and the effect sizes in differentiating between MS and HC were assessed. In patients, correlations with age, disease duration, EDSS and T2-hyperintense lesion volume (LV) were also evaluated.

Results: At baseline, FIRST and MIST (R=0.87, p<0.001) showed the highest significant agreement in the results of thalamic volume, with the highest effect size in differentiating MS and HC found for MIST (Cohen's d=1.11). At baseline, FIRST showed the highest significant correlations with age (-0.36, p<0.001), EDSS (R=-0.3, p<0.001, adjusted for age), T2-hyperintense LV (R=-0.4, p<0.001) and disease duration (R=-0.2, p=0.02). At follow-up, MIST showed the lowest variability in estimating thalamic volume changes (TVC) for HC (standard deviation=1.07%) in comparison to the other pipelines, and a better capability to significantly differentiate between MS and HC (Cohen's d=0.21). In MS patients, only MIST TVC showed a significant correlation (adjusted for age) with T2-hyperintense LV change (R=-0.22, p=0.01).

Discussion: We found that the inclusion of FA contrast increased robustness of the results and a better capability to detect small longitudinal variations of thalamic volumes, as shown by MIST results. The advantage of a multimodal approach is also shown by the results of correlations with LV changes at follow-up for MIST.

Conclusions: Due to the lack of data on accuracy and precision, when selecting the appropriate pipeline for automatic thalamic segmentation, it would be important to consider the application context in a balance between ease of use (FIRST) and better reproducibility (MIST).

Funding. Partially supported by Fondazione Italiana Sclerosi Multipla (research fellowship FISM 2019/BR/009 and research grant FISM2019/S/3), and financed or co-financed with the '5 per mille' public funding.

CLINICAL AND PROGNOSTIC RELEVANCE OF SINGLE-SUBJECT BRAIN METABOLISM PATTERNS IN AMYOTROPHIC LATERAL SCLEROSIS MUTATION CARRIERS

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Background and Objectives: The ALS diagnosis requires an integrative approach, combining the clinical examination and supporting tests. Nevertheless, in several cases, the diagnosis proves to be suboptimal, and for this reason, new diagnostic methods and novel biomarkers are catching on. The 18F-fluorodeoxyglucose (18F-FDG)-PET could be a helpful method, but it still requires additional research for sensitivity and specificity [1]. We performed an 18F-FDG-PET single-subject analysis in a sample of familial ALS patients carrying different gene mutations, investigating the genotype-phenotype correlations and exploring metabolism correlations with clinical and neuropsychological data.

Methods: We selected ten ALS patients with pathogenic gene mutation who underwent a complete clinical and neuropsychological evaluation and an 18F-FDG-PET scan at baseline. Patients were recruited between 2018 and 2022 at the ALS Tertiary Centre in Novara, Italy. Patients were selected based on the presence of ALS gene mutation (C9Orf72, SOD1, TBK1, and KIF5A). Following a validated voxel-based Statistical Parametric Mapping procedure, we obtained hypometabolism maps at single-subject level. Based on the specific functions, we obtained clusters of hypometabolism which were grouped into three meta-ROIs (motor, prefrontal association and limbic) [2,3]. Then, the corresponding 18F-FDG-PET regional hypometabolism was correlated with clinical and neuropsychological features.

Results: Classifying C9Orf72 patients based on the rate of disease progression, we observed two different patterns of brain hypometabolism: an extensive frontal and prefrontal hypometabolism in patients classified as fast-progressors, and a more limited brain hypometabolism in patients grouped as slow-progressors. SOD1 patients showed a hypometabolic pattern involving the motor cortex, and frontal associative cortex, namely the mesial frontal region and the anterior cingulate cortex, with a relative saving of the extra-motor areas. The TBK1 patient showed an extended hypometabolism, in limbic systems, along with typical motor involvement, while the hypometabolism in the KIF5A patient involved almost exclusively the motor regions, supporting the predominantly motor involvement linked to this gene mutation. Additionally, we observed strong correlations between the hypometabolism in

the motor, prefrontal association and limbic meta-ROI and the specific neuropsychological performances.

Conclusions: To our knowledge, this is the first study investigating the difference in brain hypometabolism at single-subject level in genetic ALS patients carrying different mutations, and the relation with the clinical features and neuropsychological performances. The different brain hypometabolism patterns are indicative of sign/symptoms' correlations with the mutational status and possibly with different prognosis.

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COGNITIVE PROFILE AND CORRELATION WITH STRUCTURAL AND DIFFUSION CHANGES OF THE THALAMUS AND ANTERIOR THALAMIC RADIATION: LONGITUDINAL PRELIMINARY MRI STUDY IN SUBJECTS WITH EARLY RR-MS

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Objective: Studies highlighted a correlation between thalamic atrophy and cognitive impairment in Relapsing-Remitting Multiple Sclerosis (RR-MS) [1]. There is a strong reciprocal connectivity of mediodorsal nucleus of thalamus (MDT) with prefrontal cortex (PFC) via anterior thalamic radiation (ATR) [2]. This MDT-PFC network has been associated with cognitive functions [3]. We evaluated longitudinal changes of thalamus and ATR between RR-MS patients and healthy controls (HCs) in relation to clinical and cognitive profile.

Materials and Methods: We enrolled 18 RR-MS and 15 HCs. All 15 HCs underwent brain MRI. All RR-MS patients underwent evaluation with Expanded Disability Status Scale (EDSS), brain MRI at <6 months from diagnosis (MS_bl) and were reassessed after a mean interval of 3.90 years (MS_fp). Thalamic volume and thalamic nuclei were segmented using Free Surfer. 15 subjects from each group underwent DTI-MRI study of ATR. Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) maps were obtained. 12 subjects from each group underwent neuropsychological testing. One-way analysis of variance (ANOVA) with post-hoc Tukey analysis was performed.

Results: Comparing MS_bl and HCs we found no significant difference in mean age, female-to-total ratio and level of education, no significant difference in mean EDSS between MS_bl and MS_fp, an increase in Symbol Digit Modalities Test (SDMT) score ($p<0.05$) emerged. We observed that right thalamus volume was smaller in MS_bl than in HCs ($p=0.006$), while there was a reduction of left ($p=0.011$) and right thalamic volume ($p<0.001$) between HCs and MS_fp. We found a relative sparing of 11 nuclei between HCs and MS_fp in left thalamus, including medial magnocellular part and lateral parvocellular part of MDT (MDm and MDl). MDm and MDl were the only nuclei relatively spared in right thalamus. We saw an increase in left FA ($p=0.05$) between MS_bl and MS_fp. Significant correlations emerged between left FA, MDm and MDl ($p=0.002$, $p=0.004$). We observed a significant correlation between left FA and SDMT score ($p=0.001$).

Discussion and conclusions: Our data confirmed the presence of global thalamic atrophy in RR-MS [1]. However, we observed a relative sparing of MDT nuclei and an increase in left FA of ATR over time. During the time of observation, the cognitive function of RR-MS patients remained stable and the SDMT score was positively correlated with left MDT volume and left FA. Our study is the first to verify the correlation between cognitive functions and MDT-ATR-prefrontal cortex network in cognitively spared RR-MS patients.

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NEUROIMMUNOLOGY AND NEUROINFECTIVOLOGY
SAFETY, EFFICACY, AND PHARMACOKINETICS OF ARGX-117 IN ADULTS WITH MULTIFOCAL MOTOR NEUROPATHY: A GLOBAL, MULTICENTER, PLACEBO CONTROLLED PHASE 2 STUDY (ARDA)

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Objective: Multifocal motor neuropathy (MMN) is a chronic, immune-mediated neuropathy characterized by progressive asymmetric weakness predominantly affecting the distal upper limbs. MMN is often associated with anti-GM1 IgM antibodies targeting the axolemma at the node of Ranvier, leading to activation of the classical complement pathway which drives subsequent damage to the axon. IVIg is the only proven effective therapy. ARGX-117 is a novel monoclonal antibody that inhibits complement factor 2 (C2).[1] Using an in vitro model for MMN, ARGX-117 was shown to block IgM-mediated classical pathway complement activation on both motor neurons and Schwann cells.[2] This Phase 2, multicenter, randomized, placebo controlled, parallel-group study (ARDA, NCT05225675) will assess the safety, efficacy, PK, and PD of ARGX-117 in adults with MMN.

Materials and methods: Forty-eight participants will be recruited and assigned to one of two dosing cohorts (24 participants each) and randomized 2:1 to receive either ARGX-117 or placebo. Key inclusion criteria include: diagnosis of probable or definite MMN per 2010 EFNS/PNS guidelines, stable IVIg regimen, and IVIg treatment dependency. The primary objective is safety based on adverse event monitoring and other safety assessments. Secondary objectives include assessment of efficacy measured as strength and functional disability, pharmacokinetics, pharmacodynamics (C2 and CH50), and

immunogenicity of ARGX-117. After completing the 16-week treatment period, participants may enroll in an open-label extension study or enter the safety follow-up period.

Conclusions: This ongoing phase 2 study will assess the safety and efficacy of ARGX-117 in participants with MMN and will direct future studies in this patient population.

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COVID -19 -ASSOCIATED ACUTE MYELITIS WITH ANTI-MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODIES

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Introduction: Acute myelitis related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is rare and thought to be para or post-infectious. Anti myelin oligodendrocyte glycoprotein (MOG) antibodies associated disorders (MOGAD) can be preceded by infections [1].

Case Report: Case 1: a 48year-old man was admitted for progressive ascending lower limb and perineal hyperesthesia, sphincter dysfunction, difficulty walking, ten days after a paucisymptomatic SARS-CoV-2 infection confirmed by antigen detection on a nasal swab. Case 2: a 30-year-old man was admitted for distal upper and lower limb paresthesia ascending to perineal region, urinary retention and difficulty walking following a febrile state 30 days after SARS-CoV-2 mRNA vaccination.

Methods and Results: Neurological examination identified sensory abnormalities, bilateral pyramidal tract involvement and bladder dysfunction in both cases. Brain MRI was normal in case 1 and documented rare small aspecific hyperintense T2/FLAIR subcortical lesions in case 2, while spinal MRI identified a T2 medio-thoracic (D6) hyperintense central spinal cord lesion in case 1, and aT2 centro-lateral C6 and ventral D4 lesion with mild gadolinium enhancement in case 2. Cerebrospinal fluid (CSF) analysis revealed pleiocytosis (5 and 60 mononucler cells respectively) with normal glucose and protein levels and some oligoclonal bands with positive intrathecal synthesis only in case 1. Systemic autoimmune and infection makers were unremarkable; serum and CSF analysis for Borrelia, Syphilis, Tuberculosis, HIV, Herpes simple virus, Varicella Zoster virus, Toxoplasma, Cytomegalovirus, Epstein-Barr were negative in both cases; serum and liquoral aquaporin-4 and MOG antibodies were detected by fixed cell-based immunofluorescence assay (CBA) with negative results for Aquaporine-4 and high titre positive anti MOG IgG1 (1:640) in both cases. SARS-CoV-2 PCR was negative in CSF in both cases, with positive antibody markers of recent SARS-CoV-2 infection in serum in case 1. Intravenous methylprednisolone 1 gr/die for five consecutive days was administered followed by oral prednisolone tapering in the following 3 months. The follow-up at three months documented an improvement of sensory and motor deficit with persistent urinary hesitation in patient 1, a complete recovery in case 2 and the resolution of gadolinium enhancement on spinal MRI in both cases.

Discussion: The clinical presentation of our cases is comparable with the phenotype of MOGAD previously described [2,3]. CSF SARS-CoV-2 PCR test was negative, supporting the role of immune-mediated process rather than direct viral damage, raising the question of the role of SARS-CoV-2 infection/vaccination as a potential trigger for MOGAD.

Conclusions: SARS-CoV-2 infection, even in paucisymptomatic cases, might have a relationship with MOGAD.

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A CASE OF GAIT DISTURBANCE IN A PATIENT WITH MS-LIKE LESIONS AND RHEUMATOLOGICAL DISEASE

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A 60-year-old woman was evaluated for weakness in right lower limb and gait deficit, slowly progressing for two years. She reported tingling, bandaging-like paraesthesia, dysesthesia prevalent in the anterolateral region of the thigh, leg and foot, with a sensation of "stiff limb" during walking. Upon neurological examination she presented weakness prevalent in proximal muscular districts (3/5 MRC), mild distally (4/5 MRC), limb fall in antigravity tests, tactile hypoesthesia, paraesthesia, spastic hypertonia, brisk deep tendon reflex, paretic gait. She reported history of recurrent bilateral anterior uveitis from the age of 48, with severe progressive visual impairment and deformation of the pupil. Six years before diagnosis of undifferentiated connectivitis with arthralgia, xerostomia, xerophthalmia, Raynaud's phenomenon, reticularis livedo in lower limbs, detected ANA (1/320 homogeneous pattern, 1/320 nucleolar), anticardiolipin IgM, borderline ACPA. Initially treated with low dose of prednisone and chloroquine, suspended due to ocular comorbidities. Cervical and dorsal spine MRI detected multiple white matter areas of altered signal between brainstem and spinal cord and at level of C3, C4-C5, C6-C7, D2-D3, D4, D5-D6, D7, D8-D9 and D10, without contrastographic enhancement. Brain MRI revealed multiple areas of hyperintensity in T2 / flair in the periventricular, subcortical and deep white matter of cerebral hemispheres, in the corpus callosum and at subtentorial level in cerebellar and periventricular bihemispheric white matter, possible inflammatory lesions. At CSF: normal cytochemical, cytological examination, negative culture for bacteria and fungi, viral PCR, search for Borrelia and Treponema, increased total IgG, increased Link index (0.91), normal barrier index. Presence of CSF oligoclonal bands and additional identical bands in serum and CSF. Not detected on serum AQP4 and anti-MOG, HIV, HTLV, slight increase in inflammation indices, normal chest x-ray. VEPs not evaluable, SSEPs with increase in central conduction time. ENG was normal. She was re-evaluated from a rheumatological point of view with confirmation of positivity of ANA (1/640 nucleolar,1/320 homogeneous), ACLA and ACPA, HLA B 49 and B58, autoimmune thyroiditis with anti-TPO positivity, mild microangiopathy at capillaroscopy, confirmation of raynaud phenomenon, photosensitivity and reticularis livedo. Overall, the evaluation of the complex clinical picture, time course of neurological symptoms and inflammatory lesions, was found to be compatible with Behcet's disease with neurological and ocular involvement [1]. The lesion load in MRI remained stable, without contrast enhancement,

at 3, 6, 12 months. Therapy with azathioprine was undertaken with resolution of the uveitis and stability of the clinical and radiological neurological picture.

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SUDDEN UNEXPECTED DEATH IN EPILEPSY AND ICTAL ASYSTOLE IN PATIENTS WITH AUTOIMMUNE ENCEPHALITIS: A SYSTEMATIC REVIEW

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Objective: Sudden unexpected death in epilepsy (SUDEP) is an important cause of death in people with epilepsy. Its mechanisms are uncertain, but a link with ictal asystole (IA) has been suggested. To shed light on the pathogenesis of SUDEP, we systematically reviewed the existing literature on SUDEP and IA cases in patients with autoimmune encephalitis (AE).

Material and methods: We searched four databases (MEDLINE, Scopus, Embase, and Web of Science) for studies published between database inception and May 11, 2022, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We selected all articles reporting cases of definite SUDEP, definite SUDEP plus, probable SUDEP, probable SUDEP plus, possible SUDEP, near-SUDEP, and near-SUDEP plus [1], or IA [2], in patients with possible/definite autoimmune limbic encephalitis [3], or with histopathological signs of AE.

Results: Of 207 records, we included 11 cases: 7 of SUDEP or near-SUDEP and 4 of IA. Two patients were male, 8 female, and one unknown. All patients with IA were female. The median age at AE onset was 30 years (range: 15-65), and the median delay between AE onset and SUDEP was 11 months; it was 0.9 months for IA. All the patients presented new-onset seizures (median frequency: 2/month, range: 0-120), and 10/11 also manifested psychiatric, cognitive, or amnesic disorders. Cerebrospinal fluid analysis was pathological in 7/11. In patients with SUDEP, 2/7 showed positivity for LGI-1, and anti-GABABR antibodies, respectively; all IA cases were antibody-positive, 1 anti-GAD65 and 3 anti-NMDA-R antibodies. MRI showed temporal alterations in 6/11. After the diagnosis of AE, 6 patients received steroid bolus, 3 intravenous immunoglobulins, and 3 plasmapheresis. Three patients did not receive immunotherapy. A pacemaker was implanted in 3 patients with IA. The 6 patients who survived the event improved after treatment.

Discussion: SUDEP and IA can be linked to AE, suggesting a role of the limbic system in their pathogenesis. IA (but also SUDEP) tends to manifest early in AE, highlighting the importance of early diagnosis and initiation of treatment (antiseizure medications and immunotherapy). Our findings confirm that new-onset IA is predominantly linked with temporal lobe epilepsy (TLE) and the female gender.

Conclusions: To better understand the pathogenesis of SUDEP and IA, more preclinical and clinical research is required, with particular attention to their potential link with AE and TLE.

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PROGRESSIVE POST-INFECTIOUS NEUROLOGICAL SYNDROMES: CLINICAL PROFILE AND NEUROFILAMENT LIGHT CHAIN QUANTIFICATION

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Introduction: Postinfectious neurological syndromes (PINS), among which acute disseminated encephalomyelitis (ADEM), are inflammatory and mostly monophasic CNS disorders. We previously reported that PINS patients can show relapses, or even disease progression without neuroradiological/laboratory signs of overt inflammation. We aimed to describe a cohort of patients with progressive-PINS, providing laboratory evidence of axonal damage.

Methods: Among 90 patients presented to our center with PINS in 2001-2021, we identified 7 with disability progression not explained by new relapses (stable MRI lesions and negative cerebrospinal-fluid analysis). Neurofilament light chain (NfL) serum levels were determined using EllaTM in age-sex-matched patients with progressive-PINS, ADEM, secondary progressive multiple sclerosis (SPMS), amyotrophic lateral sclerosis (ALS) and healthy controls.

Results: Patients presented with encephalomyelitis (2), encephalomyeloradiculitis (4) or myeloradiculitis (1). Median age at presentation was 51(IQR, 42,5-64,5). Minimum follow-up was 6,2 years. Progression occurred after a median of 11 months from onset (in 4 cases after 1/more relapses) and led to maximum disability in about a year in 1/7. In 5/7 patients clinical progression involved the previously spared upper limbs, and in 5/7 the bulbar and or respiratory function requiring tracheostomy and/or percutaneous gastrostomy. All patients received immunotherapy (high dose steroids and/or IvIG) and 6/7 additional immunosuppressive drugs (4 Rituximab, 2 cyclophosphamide), with no clinical modification. NfL levels were significantly higher in patients with progressive-PINS compared to ADEM (p=0.023) and healthy controls (p=0.004), but not to ALS or SPMS.

Conclusion: PINS can show a progressive course unresponsive to immunotherapy. NfL levels in these patients are comparable to those found in neurodegenerative conditions characterized by persistent axonal damage.

SPATIAL ASSOCIATION BETWEEN GENE EXPRESSION AND BRAIN DAMAGE IN NEUROMYELITIS OPTICA SPECTRUM DISORDERS

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Objectives: Antibodies in autoimmune disorders of the central nervous system (CNS) target antigens with different expression across CNS regions. A former study suggested that typical brain lesions in aquaporin-4 positive Neuromyelitis Optica Spectrum Disorders (AQP4+NMOSD) occur at areas with high AQP4 expression. However, this represents a partial view of both brain damage and NMOSD pathogenesis, since the former also includes atrophy and microstructural abnormalities, and the latter involves other elements of the immune system such as complement and granulocytes. In this study we sought to investigate the spatial association between brain damage and gene expression in NMOSD.

Materials: 3.0 and 1.5 T brain magnetic resonance imaging (MRI) scans were acquired from 80 AQP4+NMOSD and 94 controls at two European centers.

Methods: In patients, brain damage was assessed through (i) T2-hyperintense lesion probability map, (ii) white (WM) and grey matter (GM) atrophy at voxel-based morphometry on 3D T1-weighted sequences, (iii) WM microstructural abnormalities at tract-based spatial statistics on diffusion-tensor imaging. The spatial association between the previous maps and gene expression according to the Allen Human Brain Atlas was obtained with the MENGA platform. The Open Target Platform was consulted to find a list of 414 genes associated with NMOSD. We performed a functional-enrichment analysis to investigate the overrepresented biological processes involving the genes significantly associated with the different types of brain damage.

Results: T2-hyperintense lesions were mainly located in the periventricular WM; GM atrophy was observed in the visual, prefrontal cortex, and insula, WM atrophy selectively involved the optic tracts; patients also had a widespread increase of WM mean diffusivity and no fractional anisotropy abnormalities. Among significant genes, the expression of AQP4 and C5 associated with all types of brain damage, IL6 family signal transducer associated with brain atrophy only, and CD59 was protective. Interferon-gamma, interleukin-4 and -13 signalling and activation of C3/C5 were associated with both lesions and microstructural abnormalities. A number of pathways, sometimes not specific for NMOSD pathogenesis, were associated with brain atrophy.

Discussion: Brain lesions and WM microstructural abnormalities are associated with biological processes specific of AQP4+NMOSD, including complement activation and eosinophils/neutrophils recruitment. More complex mechanisms contribute to atrophy.

Conclusions: A joint application of MRI quantitative measures and available gene expression atlases may pave the way to a novel type of imaging analysis able to underpin ongoing pathophysiological processes in antibody-mediated autoimmune disorders.

SIGNIFICANCE OF MOG ANTIBODIES IN CSF: A RETROSPECTIVE MULTICENTRE STUDY

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Background and Objectives: Although the diagnosis of myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) is based on serum MOG antibodies (MOG-Abs) positivity, patients with coexisting or restricted MOG-Abs in the CSF have been reported. The aim of this study is to characterize the relevance of CSF MOG-Abs positivity in clinical practice.

Methods: Eleven medical centres retrospectively collected clinical and laboratory data of adult and pediatric patients with suspected inflammatory CNS disease and MOG-Abs positivity in serum and/or CSF, using live cell-based assays. Comparisons were performed using parametric or non-parametric tests, as appropriate. Potential factors of unfavourable outcomes were explored by Cox proportional hazard models and logistic regression.

Results: The cohort included 255 patients: 139 (55%) females and 132 (52%) children (i.e. <18 year-old). Among them, 145 patients (56.8%) had MOG-Abs in both serum and CSF (MOGs+c+), 79 (31%) only in serum (MOGs+c-), and 31 (12%) only in CSF (MOGs-c+). MOGs-c+ predominated in adults (22% vs 3% of children), presented more commonly with motor (n=14, 45%) and sensory symptoms (n=13, 42%), and all but 4 (2 MS, 1 polyradiculoneuritis, 1 Susac syndrome) had a final diagnosis compatible with MOGAD. When comparing seropositive patients according to MOG-Abs CSF status, MOGs+c+ patients had a higher EDSS at nadir during the index event (median 4.5, IQR 3.0-7.5 vs. 3.0, IQR 2.0-6.8, p=0.007) and presented more commonly with sensory (45.5% vs. 24%, p=0.002), motor (33.6% vs 19%, p=0.021), and sphincter symptoms (26.9% vs 7.8%, p=0.001) than MOGs+c-. At last follow-up, MOGs+c+ cases had more often persistent sphincter dysfunction (17.3% vs 4.3%, p=0.008). Compared with seropositive patients, those with MOGs-c+ had higher disability at last follow-up ($p \leq 0.001$) and MOGs-c+ status was independently associated with an EDSS ≥ 3.0.

Conclusion: Paired serum and CSF MOG-Abs positivity is common in MOGAD and is associated with a more severe clinical

presentation. CSF only MOG-Abs positivity can occur in patients with a phenotype suggestive of MOGAD and is associated with a worse outcome. Taken together, these data suggest a clinical interest in assessing CSF MOG-Abs in patients with a phenotype suggestive of MOGAD, regardless of the MOG-Abs serostatus.

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LATE ONSET OF NEUROMYELITIS OPTICA SPECTRUM DISORDER IN A PATIENT PRESENTING WITH A HISTORY OF PROGRESSIVE SYMPTOMS DEVELOPMENT

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Background: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease of the central nervous system mostly affecting women around their third decade of life and characterized by an acute onset. Presentation in more advanced age is rare and therefore related information is scanty.

Case report: A 72-year-old female experienced a progressive loss of limbs coordination. Her symptoms had started in October 2021, when she noticed loss of grip and precision in movements associated to tingling of the right upper limb and interscapular pain. Initially treated as a cervicalgia, symptoms did not improve and progressively deteriorated till February 2022 when she was admitted to our Neurology ward. On physical examination, hypotonia, muscular weakness, severe ataxia, thermo-tactile anaesthesia and apallesthesia in upper limbs were found. Lower limbs were affected by milder ataxia, apallesthesia and hypoesthesia. Tendon reflexes were diffusely abolished, tingling-like paraesthesia and dysaesthesia were present in all limbs. The patient could not stand up autonomously or rolling in the bed without aid. Recent or past visual disturbances were not reported. The patient did not complain of vomit, nausea, or urinary incontinence. Spinal cord MRI showed a signal enhancement in long TR sequences extending from C1 to T4, coherent with a longitudinal extensive transverse myelitis (LETM). Brain MRI was normal. The cerebro-spinal fluid examination revealed hypeproteinorrachia (583 mg/L) and mononuclear pleocytosis (21 cells/μL). Because of long-standing course of symptoms, a paraneoplastic cause was reputed unlikely and then ruled out by imaging and absence of major paraneoplastic antibodies. Infectious causes were also excluded. Visual evoked potentials were carried out to investigate the subclinical involvement of optic nerves and revealed an increased latency of the right eye cortical response. At this point, an antibody screening for NMOSD was requested and resulted positive for anti-aquaporin 4 antibodies.

Results: The presence of LETM, the positivity for anti-AQP4, and the exclusion of alternative diagnosis were conclusive for NMOSD. The patient started methylprednisolone and then she was put on rituximab.

Discussion and conclusion: NMOSD was not initially considered as a first differential diagnosis, because of the age of the patient and the unusual subacute development of symptoms, and an arteriovenous malformation of the spinal cord or an infectious cause were considered more probable. NMOSD must be considered in cases of late onset LETM, even when the clinical presentation is atypical like in presented case.

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LONG-TERM-VIDEO MONITORING EEG AND 18F-FDG-PET ARE USEFUL TOOLS TO DETECT RESIDUAL DISEASE ACTIVITY IN ANTI-LGI1-ABS ENCEPHALITIS: A CASE REPORT

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Background: The use of CD20-depleting monoclonal antibodies has shown to improve the long-term outcome of patients with anti-leucine-rich glioma-inactivated protein 1 antibodies (anti-LGI1-Abs) encephalitis after first-line immunotherapy, but currently predictive markers of treatment response and disease activity are lacking.

Case presentation: A 75-year-old man presented cognitive impairment and faciobrachial dystonic seizures (FBDS), with mild abnormalities at electroencephalography (EEG), normal brain magnetic resonance and cerebrospinal fluid (CSF) analysis. Anti-LGI1-Abs were detected in serum and CSF, and corticosteroids and intravenous immunoglobulins were administered. Despite partial cognitive improvement, 18F-fluoridesoxyglucose-positron emission tomography (18F-FDG-PET) showed the persistence of temporo-mesial hypermetabolism, and FBDS were still detected by long-term monitoring video EEG (LTMV EEG). Rituximab was therefore administered with FBDS disappearance, further cognitive improvement, and resolution of 18F-FDG-PET temporo-mesial hypermetabolism.

Conclusions: Our experience supports the use of 18F-FDG-PET and LTMV EEG as useful tools to measure disease activity, evaluate treatment response and guide therapeutic decisions in the long-term management of anti-LGI1-antibody encephalitis.

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INCIDENCE AND CLINICAL CHARACTERISTICS OF MYASTENIA GRAVIS PATIENTS AFTER COVID-19

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Introduction: Myastenia Gravis (MG) is a rare neurological immune-mediated disease characterized by defective transmission at the neuromuscular junction (NMJ). Experimental and clinical evidence suggests that some forms of MG are initiated in the thymus, where acethilcolyne receptor expression is

activated through cytokine and receptor signalling, potentially triggered by a virus. Since the emergence of Covid-19 pandemia, SARS-CoV2 has been implicated in the development of a range of autoimmune diseases, notwithstanding the association between immunological diseases and infections is still poor understood. In this observational study we aimed to describe the incidence and clinical features of patients with new-MG diagnosis after Covid-19 burden.

Methods: Out of 220 MG outpatients evaluated at our neuroimmunological center, 44 cases (20%) had a new diagnosis of MG after SARS-CoV2 infection outbreak (February 2020). Demographic and clinical data were extracted from digital records and compared to a control group of 57 patients (26%) diagnosed with MG from January 2017 till January 2020.

Results: Patients with MG diagnosis after Covid-19 onset showed similar age (61.1 + 15.2 vs 61.3 + 16.5, p=0.940), sex distribution (female %, 42.3% vs 52.6%, p= 0.843), and history of immunological diseases (%, 20.5% vs 15.8%, p=0.605) compared to the control cases. Acetylcholine-receptor antibody positivity rate and the prevalence of thymic disorders, namely thymic hyperplasia and thymoma, were similar in the two groups. Clinical features at onset in the patients diagnosed with MG after Sars-CoV2 diffusion showed the same percentage of ocular (68.4% vs 63.6%, p= 0.674) and bulbar (19.3% vs 27.3%, p=0.352) phenotypes, with no differences in terms of Myasthenia Gravis Foundation of America (MGFA) classification, compared to MG patients diagnosed before Covid-19 outbreak.

Discussions: Our observational single-center study showed a similar incidence of MG cases before and after Covid-19 pandemic diffusion, with comparable clinical features at onset. Historically, viral infections have had a complex relationship with a variety of autoimmune systemic and neurological diseases, including MG. To date, it is speculated that SARS-CoV-2 can disturb self-tolerance and trigger autoimmune responses through cross-reactivity with host cells; the consequence of this immune dysregulation ranges from the production of autoantibodies to the onset of immunological disease, namely thyroiditis, vasculitis and arthritis.

Conclusions: Extensive long-term studies are warranted to shed light on pathogenesis of neuro-immunological disorders in order to identify predictive factors and improve therapeutic targets.

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FDG PET/MRI PATTERNS IN PATIENTS WITH NMDA RECEPTOR ENCEPHALITIS

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Objective: To describe the patterns of altered brain metabolism through fluorodeoxyglucose (FDG)-PET/MRI study in patients with anti-NMDA receptor encephalitis.

Methods: We retrospectively reviewed clinical data and brain FDG-PET/MRI scans in patients with definite anti-NMDAR encephalitis treated at a single academic medical center over a 5-year period. Three different patterns of tracer distribution were described: 1) pattern 1 with prominent limbic hypermetabolism; 2) pattern 2 with prominent occipital-parietal hypometabolism; 3) pattern 3 with diffuse hypometabolism or mixed hypo/hypermetabolism or diffuse.

Results: 10 patients with NMDAr encephalitis and with FDG PET/MRI scan were identified in this time-period. In two patients' movement artefacts interfered with appropriate evaluation and therefore data from 8 patients were recorded. Mean age was 21.5 years (8-40), 5 were females. 6/8 patients presented with epileptic seizures of different semeiology and localization (tonic-clonic seizures, focal temporal seizures, visual seizures); 3/8 with psychiatric symptoms (psychosis, catatonia); one patient presented with altered consciousness. Mean time from symptoms onset to PET-MRI investigation was 7,12±15 months. 7/8 patients received immune therapy before PET/MRI, but all patients were still symptomatic at the time of PET study. 5/8 patients had hypometabolism of the parietal- occipital regions (pattern 2) (mean age 22.2 ±13 years), 2 patients had pattern 1 (mean age 17.5±0.5 years). 1 patient presented with pattern 3 distribution (age 8 years). Type of pattern was not associated with time of PET scan respect to disease onset neither with treatment. Follow-up studies were performed in 50% of patients. In 2 patients the occipital hypometabolism disappeared after one month of efficient immune treatment, while in one of these 2 patients a third FDG-PET during a relapse revealed a recurrence of the occipital hypometabolism.

Conclusions: Occipital hypometabolism is a frequent FDG-PET finding in NMDAr encephalitis and is associated with disease activity. Pediatric patients may have a more heterogeneous pattern of altered metabolism.

COMPARISON OF FIXED AND LIVE CELL-BASED ASSAY FOR THE DETECTION OF ACHR AND MUSK ANTIBODIES IN MYASTHENIA GRAVIS

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Background and objectives: Live cell-based assay (CBA) can detect acetylcholine receptors (AChR) or muscle-specific tyrosine kinase (MuSK) antibodies (Abs) in a proportion of radioimmunoassay (RIA)-double seronegative myasthenia gravis patients (dSN-MG). [1] A commercial fixed CBA for AChR and MuSK Abs has recently become available, [2] however comparative studies on fixed and live CBA are lacking. In this study, we compared the performance of fixed and live CBAs in RIA-dSN MG patients and assessed their specificity and sensitivity in RIA-positive MG samples.

Methods: AChR and MuSK Abs were tested in 292 serum samples from two Italian MG-referral centers by live and fixed CBA: 192 from MG patients and 100 from controls. All samples had been previously assessed by RIA: 66 were AChR positive, 40 MuSK positive and 86 dSN. All controls were negative. Two independent raters assessed the CBA results. Fixed and live CBAs were compared with McNemar's test, inter-rater and inter-laboratory agreement were assessed with Cohen's kappa or interclass correlation coefficient (ICC), as appropriate.

Results: In 86 RIA-dSN samples, fixed CBA detected Abs in 10 cases (11.6%, 95%CI: 5.7-20.3) while live CBA in 16 (18.6%, 95%CI: 11.0-28.5) (p=0.0143). Of these sera, those positive by fixed CBA were also positive by live CBA. In addition, live CBA could detect MuSK Abs in 4 and AChR Abs in 2 samples that were negative by fixed CBA, providing 8% (95%C.I. 2.9-16.6) further increase in the Ab detection rate. In the RIA-positive cohort, sensitivity for AChR Abs was 98.5% (95%CI: 91.9-99.9%) for fixed CBAs, and 100% (95%CI: 94.6-100) for live CBAs (p=0.1573). For both assays,

sensitivity for MuSK Abs was 100% (95%CI: 91.2-100), and specificity was 100% (95%CI: 96.4-100). Inter-rater agreement was almost perfect for live and fixed CBAs (Cohen's kappa 0.972 and 0.978, respectively), alike inter-laboratory agreement. Inter-rater agreement for CBA score ranged from good to excellent (ICC: 0.832-0.973).

Discussion: Fixed CBA represent a valuable alternative to RIA for AChR and MuSK Ab detection in MG patients and could be considered as a first-step diagnostic test. Live CBA can be useful in the serological evaluation of RIA- and fixed CBA-negative samples.

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ASSESSMENT OF DIFFERENT CLINICAL DIAGNOSTIC CRITERIA FOR ATYPICAL CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

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Objectives: There are different definitions of the chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) variants in literature [1,2], and this may explain the conflicting results observed across studies regarding their frequency, clinical presentation, outcome, and treatment response. Recently the second revision of the CIDP guidelines of the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) addressed this issue providing specific clinical criteria for each CIDP variant [3]. In this study we aimed at comparing different clinical diagnostic criteria for atypical CIDP to clarify their ability to discriminate peculiar clinical patterns and response to therapy.
Methods: We compared the validity of different clinical criteria for atypical CIDP including those of the EAN/PNS in 473 Italian CIDP patients.

Results: Patients with a multineuropathic Lewis-Sumner syndrome (LSS) and those with a length-dependent sensory or sensorimotor demyelinating acquired distal symmetric (DADS) neuropathy had distinct demographic and clinical features, less severe disability, less frequent response to treatment and to intravenous-immunoglobulin (IVIg) compared to patients with typical CIDP. There was no relevant difference when non-multineuropathic asymmetric CIDP or distal but non-length-dependent sensorimotor CIDP (distal CIDP) were compared with typical CIDP. When splitting DADS in sensory and sensorimotor DADS, only the former group showed lower response to treatment and to IVIg compared to typical CIDP. When considering patients with exclusively sensory symptoms those with a length-dependent sensory CIDP (sensory DADS) but not those with a non-length-dependent sensory CIDP (pure sensory CIDP) had a lower response to treatment and to IVIg compared to typical CIDP.

Conclusions: The use of different diagnostic criteria for atypical CIDP leads to a discrepant identification of patients groups. In this large series of CIDP patients, only those with multineuropathic LSS or with length-dependent sensory CIDP had clinical and therapeutic features that distinguished them from patients with typical CIDP, possibly suggesting that they may represent different clinical and pathological entities.

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IMMUNE CHECKPOINT INHIBITOR-RELATED CEREBELLAR TOXICITY: CASE REPORT AND SYSTEMATIC LITERATURE REVIEW

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Objectives: (i) To characterise cerebellar toxicity following immune checkpoint inhibitor (ICI) administration, including clinical and paraclinical

features, response to immunosuppressive therapy, neurological and oncological outcome; (ii) to compare ICI-related cerebellar toxicity to paraneoplastic cerebellar degeneration (PCD).

Materials and methods: Systematic review of the literature following PRISMA guidelines. We included adult patients developing new-onset, isolated or predominant cerebellar dysfunction within 12 months from the last ICI infusion. Pubmed was searched on May 9th, 2022, using the search string: (cerebellitis OR pancerebellitis OR cerebellar encephalitis OR cerebellar) AND (ipilimumab OR nivolumab OR pembrolizumab OR atezolizumab OR avelumab OR durvalumab OR cemiplimab OR immune checkpoint inhibitor). Forty-seven papers were retrieved and 15 selected for review; overall, we identified 20 patients, to which an additional unpublished case of ICI-induced cerebellitis was added.

Results: Most patients were males (17/21; 80.9%) and the median age was 63 (range: 20-82). The most frequent tumour was non-small cell lung cancer (NSCLC, n = 8). Anti-PD1 was adopted in most cases (13/21, 61.9%), with nivolumab being the most frequent (7/13; 53.8%). Cerebellar toxicity developed a median of 10 weeks (range: 0.1-69) after ICI onset. Full-blown neurological symptoms were pancerebellar in 7/21 (33.3%), predominant trunk/gait ataxia in 7/21 (33,3%), predominant limb ataxia in 1/21 (4.8%) and isolated limb and gait ataxia in 1/21 (4.8%). Symptoms could not be further characterized in 5/21 (23.8%) patients. Antibody testing was not available in 4 patients; positivity was detected in 8/17 (47.1%) cases. Lumbar puncture was not available in 2 patients; CSF findings included raised proteins (17/19, 89,5%) and pleocytosis (11/19, 57,9%). The most common pathological MRI finding was cerebellar hyperintensities (5/21, 23.8%). Immune-modulating therapy was administered in 20/21 patient (95.2%). Concerning neurological outcome, 10/21 (47.6%) patients improved with residual disability, 7/21 (33.3%) returned to pre-ICI condition, 1/21 (4.8%) did not improve and 3/21 (14.3%) worsened. Tumour regression or no progression was observed in 10/21 (47.6%), while 6/21 (28.6%) relapsed; oncological outcome was not specified in 5/21 (23.8%).

Discussion: ICI-related cerebellar toxicity more commonly associated to male sex, NSCLC and nivolumab, developing a median of 10 weeks after ICI start. Pancerebellar or predominant trunk/gait symptoms prevailed at disease peak. ICI-related cerebellitis appeared to be responsive to immune-suppressive treatment.

Conclusions: In contrast with PCD, ICI-mediated cerebellar toxicity typically develops after cancer diagnosis. While treatment of the underlying cancer is of paramount importance in PCD, neurological symptoms appear to be tumour response-independent in ICI-related cerebellar toxicity.

SUBACUTE MYELITIS OF POSSIBLE VASCULITIC ORIGIN AFTER SARS-COV2 AND VZV INFECTIONS: A CASE REPORT

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Introduction: Transverse myelitis represents a rare neurological complication following SARS-CoV2 infection, extensively described in literature. On the other hand, CNS post-infectious vasculitis characteristics and incidence remain undefined.

Case Report: We describe the case of a 53-year-old man with a history of cryptogenic ischaemic stroke, recent SARS-CoV2 and VZV infections who presented with a 1-month history of distal lower limbs paresthesias, nocturnal muscular spasms, urinary incontinence and Lhermitte's sign. At admission, neurological examination showed a mild ataxic gait, bilateral paresthesias from the knees downwards and a left Babinski sign. Routine blood tests including autoimmune screening and vitamin deficiency were normal. CSF analysis showed a mild protein increase (76 mg/dl) with normal white cell count (1 leucocyte/microL). Blood and CSF PCR film-array for pathogens research were negative. Spinal MRI with gadolinium was unremarkable. The patient was discharged with oral corticosteroid therapy (Prednisone 1 mg/kg). He returned 4-days later with sensitive symptoms worsening, new-onset slurred speech and right lower limb clumsiness. Neurological examination showed a severe ataxic gait, bilateral paresthesias from the knees downwards, bilateral apallesthesia from the iliac crests downwards, bilateral lower limbs hyperreflexia with ankle clonus and Babinski sign, right dysdiadochokinesia, motor clumsiness of the right lower limb and dysarthria. Brain MRI showed a new left thalamic ischaemic stroke, while spine MR was unchanged. Echo-doppler of the supra-aortic and intracerebral vessels displayed no stenosis. CSF analyses showed again only a mild protein increase (64 mg/dl) with 5 leucocytes/microL. Despite a 5-day intravenous high dose corticosteroid therapy (1g/die) the patient reported worsening of the paresthesias up to the thighs, the appearance of finger paresthesias and bilateral lower limbs muscle weakness. Spine MR was repeated after 11 days with the evidence of inflammatory-like centro-medullar lesions from C2 to C7 and from T3 to the conus medullaris with no gadolinium enhancement. Plasmapheresis was started with clinical stabilisation.

Conclusion and Discussion: This case shows a simultaneous development of an ischemic stroke lesion and a subacute myelitis, in a patient with a previous ischemic stroke and recent SARS-CoV2 and VZV infections. No blood test abnormalities and a moderate proteinorrhachia without pleocytosis in two different CSF analyses. These results, even though are not diagnostic, seem to suggest a CNS vessel inflammatory process. The association of myelitis and ischemic stroke is unusual, but it is possible that the close occurrence of viral infections in a predisposed subject have triggered a vasculitis process with brain and spinal involvement.

EVALUATION OF HUMORAL AND CELLULAR RESPONSE TO THIRD DOSE OF BNT162B2 MRNA COVID-19 VACCINE IN MULTIPLE SCLEROSIS PATIENTS TREATED WITH B-CELL DEPLETING THERAPY

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Objective: To investigate the responses to mRNA COVID-19 vaccines in a cohort of immunosuppressed patients affected by immune-mediated inflammatory diseases (IMID).

Methods: We have measured humoral and cellular immunity using quantitative IgG anti-SARS- CoV-2 Spike antibody (anti-S-IgG), neutralization assays and specific interferon-gamma (IFN-g) release assay (IGRA) before and after the third dose of BNT162b2. The response of those on anti-CD20 (n=18) was then compared with healthy controls (HC, n=18) and IMID naïve to anti-CD20 drugs (n=13).

Results: A third BNT162b2 dose is highly immunogenic in IMID patients naïve to anti-CD20, as 100% of the subjects seroconverted compared to the 55% in anti-CD20. The rate of IGRA response was of 79% in anti-CD20, 50% in IMID naïve to anti-CD20, 100% in HC. Among those who have seroconverted, IMID patients had significantly reduced anti-S-IgG and neutralization titers compared to HC, whereas no significant difference was observed when comparing anti-CD20 and HC.

Conclusion: These data draw attention to the immunogenicity of COVID-19 vaccination in treated IMID, taking specific groups into consideration for vaccination program.

PEDIATRIC NEUROMYELITIS OPTICA SPECTRUM DISORDER: CASE SERIES AND LITERATURE REVIEW

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Objective: In this report, we present cases of seven pediatric patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) and we review the clinical and neuroimaging characteristics, diagnosis, and treatment of NMOSD in children.

Material and methods: NMOSD is a central nervous system (CNS) inflammatory demyelinating disease characterized by recurrent inflammatory events that primarily involve optic nerves and the spinal cord, but also affect other regions of the CNS, including hypothalamus, area postrema and periaqueductal gray matter. The aquaporin-4 antibody (AQP4-IgG) is specific for NMOSD. Recently, myelin oligodendrocyte glycoprotein antibodies (MOG-IgG) have been found in a group of AQP4-IgG negative patients. NMOSD is rare among children and adolescents, but early diagnosis is important to start adequate therapy.

Results: This is a narrative review in which we have included original studies and case reports exclusively on pediatric patients with NMOSD.

Discussion and Conclusion: We have reviewed recent literature to provide a tool for diagnosing and treating children with NMOSD. These case reports are an example of the diagnostic and therapeutic complexity of pediatric NMOSD. Our cases, although limited in number, offer a wide range of personalized therapeutic strategies for the individual patient. Furthermore, our series also discusses AQP4-negative patients, unlike the other reviews that focus on AQP4-positive pediatric patients.

THERAPY WITH NATALIZUMAB IN PATIENT WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS AND CROMOSOMALLY-INTEGRATED HHV-6 (ci HHV-6)

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Background: Natalizumab is an humanized monoclonal antibody directed against the a4-integrin (VLA-4) involved in the migration of peripheral inflammatory cells through the blood-barrier into the CNS. The drug is highly efficacy in the treatment of relapsing-remitting multiple sclerosis (MS), although progressive multifocal leukoencephalopathy (PML) due to JC poliomavirus (JCV) reactivation and related to immune surveillance impairment is reported. In the same way of JCV, human herpesvirus-6 (HHV-6) is able to establish lifelong latency in the host and a genomic integration is reported in about 1% of the general population (ci HHV-6) [1].

Cases report: We describe a 41 years old woman with relapsing-remitting MS started at age of 28 and diagnosed after eight years. At the time of diagnosis, brain MRI showed multiple T2-hyperintense lesions, one of them gadolinium enhancing. Hematological screening for collagenopathies, vasculitis and thrombophilias were negative in the patient and P100 latency bilaterally increased. CSF analysis revealed pattern 3 Oligoclonal Bands (OCBs), with five bands speculate in blood and CSF plus 3 exclusively in the CSF. Real-time PCR (rt-PCR) excluded neurotrophic viruses in the CSF, except for the HHV6-DNA (2700 copies/ml). High levels of HHV6-DNA were concurrently found in the whole blood, peripheral blood mononuclear cells, plasma and hair follicles, suspecting for a ci-HHV6. According to McDonald' Criteria, diagnosis of relapsing-remitting MS was made and therapy with Glatiramer Acetate was used for one year. Because persistence of relapses, on September 2018 Natalizumab was started. Stratify at this time was negative and remained unchanged over the time. To date, after 36 infusions of Natalizumab, clinical and radiological MS was stable. During the time HHV6 values in the whole blood, peripheral blood mononuclear cells and plasma samples were slightly modified.

Discussion: HHV-6 is a neurotrophic virus present in some MS patients, even its role isn't still clear. HHV-6 reactivation was reported in MS patients treated with Natalizumab [2] and an encephalitis due to ci HHV-6 reactivation was also referred in patients who underwent to allogenic hematopoietic cell transplantation (allo-HCT) [3]. In our patient ci HHV-6 was detected concurrently with MS and therapy with Natalizumab was started even the possibility to an HHV-6 reactivation. To date, after four years, there was an optimum control of the MS with any side effect. In particular no reactivation of HHV6 was observed.

Conclusions The use of Natalizumab was efficacy and secure in this patient with MS associated with ci-HHV6. Anyway, further follow up is necessary.

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PROGNOSTIC RELEVANCE OF QUANTITATIVE AND LONGITUDINAL MOG ANTIBODY TESTING IN PATIENTS WITH MOGAD: A MULTICENTER STUDY OF 354 SAMPLES

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Objectives: IgG antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) define a specific subset of associated disorders (MOGAD) that can have a relapsing course.[1] However, information on relapse predictors is scarce. Despite the diagnostic value of MOG-IgG, the utility of retesting them over time and measuring their titres is still uncertain.[2] We aimed to evaluate the clinical relevance of quantitative and longitudinal evaluation of serum MOG-IgG in patients with MOGAD.

Materials and Methods: In this retrospective multicenter study, we included patients with MOGAD and available longitudinal samples (at least one > 3 months after disease onset) and tested them using a live cell-based assay with endpoint titration. MOG-IgG titers ≥1:160 were considered positive, and titres between 1:20 and 1:80 "low-titre negative". Samples were classified as "attack samples" if taken within 30 days since attack onset (N=59; 17%) and "remission samples" (N=295; 83%) if taken ≥31 days after attack onset.

Results: We included 102 patients with MOGAD [58 adults (57%) and 44 (43%) pediatric] with a total number of 354 samples [295 from remission (83%) and 59 from attack (17%)]. Median titers were higher during attacks [median: 1:1280, interquartile range (IQR): 1:320-14480] compared to remission (median: 1:640, IQR: 1:160-2560; p=0.001). Median titers at onset did not correlate with attack-related disability or age and did not predict disease course. Titers at remission were higher in relapsing patients (p=0.02). When considering the first remission sample available for each patient, titres >1:2560, they were a predictor of relapsing course in survival (log rank, p<0.001) and multivariate analysis (p<0.001, HR: 4.095, 95%CI: 1.968, 8.525). Similar results were obtained considering the highest remission titre for each patient (log rank, p=0.021). Conversion from positive to negative MOG-IgG serostatus occurred in 27 patients, and we observed a 95% relapse incidence rate reduction after a negative/low-titre negative sample was detected (incidence rate ratio: 0.05, p<0.001).

Discussion and conclusions: Quantitative and longitudinal MOG-IgG testing provides useful information in clinical practice as (a) titers correlate with the disease phase, (b) remission titers >1:2560 associate with a higher risk for a relapsing course and (c) relapses are rarer after seroconversion.

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THE NINA-FLOW: A PILOT PROJECT TO IMPROVE THE LABORATORY DIAGNOSTICS IN NEUROIMMUNOLOGY IN ITALY

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Objectives: Autoimmune Neurology is an expanding area covering rare neuroimmunological disorders that can affect the nervous system, such as autoimmune encephalitis, neuromyelitis optica and MOG associated disorders, and Myasthenia Gravis (MG).[1] Often characterized by the presence of diagnostically relevant antibodies, these pathologies' management requires the combination of clinical and laboratory expertise. Laboratory diagnostics in this field is crucial, but poorly standardized. Unreliable results are relatively frequent and related to: a) issues in the interpretation of the assays likely due to scarce expertise; b) the wide use of commercial assays that are easier to perform, but, in some areas at least, that can have lower accuracy vs in-house assays.[2] These problems have a dramatic impact on patient care, as delayed or wrong diagnosis translates into suboptimal treatments. Our aim was to implement a project to directly address the current limitations of laboratory diagnostics in this field.

Materials and methods: NINA-Flow is a pilot, diagnostic-oriented project born within the "Network Italiano per lo studio della Neurologia Autoimmune (NINA)", a group established by AINI in collaboration with SIN. The project exploits an "Hub&Spoke" model applied to laboratories performing neuroimmunology tests. The diagnostic areas covered in 2022 are CNS acquired demyelinating disorders (MOG and AQP4 antibodies) and MG (AChR and MuSK antibodies). Other diagnostic areas will be included in future years. "Hub" centres have been selected according to expertise and availability of the current diagnostic gold standard techniques. "Spoke" centres are the neurological institutions that can only offer standard diagnostics based on commercial assays. Any neurology department in Italy can join as "spoke" centre, even without offering standard diagnostics (www.nina.aini.it). The project, aimed to perform second level testing, covers all the costs to ship critical samples from "spoke" to "hub" centers. Critical samples will include those providing results not fitting the clinical phenotype, or those providing results hard to interpret by the "spoke" laboratory. "Hub" and "spoke" centres will interact through a web application, that will be used to book the sample shipment, collect clinical information, and visualize the assays results.

Results: 4 "Hub" laboratories and over 25 "spoke" centres have been selected for the first year of the project, with an estimated flow of 100 samples.

Conclusion: NINA-Flow presents as a virtuous network to improve laboratory diagnostics in neuroimmunology. It also provides a unprecedented service to the Italian neurological community and to patients, ensuring them an easy access to a high-level diagnostics.

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IGLON5-ASSOCIATED DISEASE: FOUR NEW CASES

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Objective: To report the clinical features of four new cases of IgLON5 associated disease [1,2].

Material: Between December 2018 and May 2022, 380 patients with various neurologic disorders (including autoimmune encephalitis, classic paraneoplastic syndromes, neurodegenerative diseases, neuromuscular and movement disorders) were assessed for neuronal surface antigens. IgLON5 antibodies were assessed in serum and CSF by antigen-specific cell-based assay and tissue-based assay. Clinical information was obtained by the investigators and included prodromal symptoms, neurologic manifestations, results of ancillary studies, and immunotherapy.

Results: Four patients with IgLON5 antibodies were identified. Patients were 2 males and 2 females with a median age of 73 years (range 66-84). Median duration of symptoms by the time of diagnosis was 1.5 (1-6) years. Symptoms at presentation included bulbar syndrome, sleep disorders, ptosis or diplopia, parkinsonism and sensory symptoms. Symptoms fluctuations were reported in 3 cases. Initial diagnoses included myasthenia (n=3) and parkinsonism. During the disease course, other clinical features included ataxia (n=2), parkinsonism (n=4), sleep disorders (n=3), dyskinesia (n=2), dysautonomia (n=4). CSF analysis showed blood-brain barrier disruption (n=3) and increased proteins (n=2). Brain MRI showed normal findings in one case, white matter hyperintensities in two cases and mesencephalic atrophy in one case. Three out of three assessed cases carried the DQB1*0501 and DRB1*1001 HLA haplotype. All patients received first-line immunotherapy, followed by rituximab in three cases. Three cases required percutaneous endoscopic gastrostomy due to severe dysphagia, and two patients underwent tracheostomy. At the last follow-up (median 13 months) all patients reported a clinical improvement, particularly after second-line therapy, but none experienced a complete recovery. IgLON5 antibodies were found in serum and CSF at high titers in all cases. The main IgG subclass was IgG4 followed by IgG1 in all cases.

Discussion: IgLON5 antibodies are associated with complex symptoms, and misdiagnoses are frequent, with consequent delay in identifying this disorder. Our patients showed a variable response o immunotherapy but support the possible utility of second-line therapies in patients not responding to first-line interventions.

Conclusion: IgLON5 disease could be an important differential diagnosis in patients presenting with ocular and bulbar symptoms reminiscent of myasthenia. Further studies are needed to understand the role of immunotherapy in the management of these patients.

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SIX-MONTH HUMORAL AND CELLULAR RESPONSE TO MRNA SARS-COV-2 VACCINES IN PATIENTS WITH AUTOIMMUNE NEUROLOGICAL DISORDERS AND ROLE OF THE THIRD DOSE

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Objectives: Longitudinal studies of SARS-CoV-2 vaccine-induced immune responses in patients with autoimmune neurological conditions (ANC) requiring immunotherapy are needed to optimize clinical care. Therefore, our aim was to report data on the longitudinal durability of two dose mRNA vaccination and the T cell response in ANC patients. Additionally, humoral and T cell responses were assessed in a subgroup of patients who received a third dose of mRNA-1273 or BNT162b2.

Material: The ANCOVAX is a longitudinal study including ANC patients vaccinated with two doses of BNT162b2 or mRNA-1273 between March and August 2021[1]. Serum samples were collected 1 (T1), 3 (T3), 6 (T6) months after the second dose. PBMCs were collected in a subset of patients at T6.

Methods: IgG antibodies to the spike receptor binding domain protein (anti-RBD IgG) were measured using the Elecsys® anti-SARS-CoV-2 ECLIA assay (Roche). SARS-CoV-2-specific T cell immunity was determined using a T-SPOT Discovery SARS-CoV-2 kit (Oxford Immunotec).

Results: 294 patients were included in the follow-up study. Before T6, 86 patients received a booster dose. One month after the two-dose primary vaccination (T1), 265 patients (91%) had anti-RBD IgG antibodies, whereas 29 (9%) were seronegative. The highest non-responder rate was associated with anti-CD20 therapy and BNT126b vaccine ($p<0.0001$). Antibody titers progressively declined three ($p<0.0001$) and six months ($p<0.0001$) after vaccination in the non-booster group. However, most patients receiving immune therapies including steroids, AZA, IVIG and DMTs remained seropositive at 6 months; those who became seronegative were mainly in the anti-CD20 group. In the booster group, antibody levels significantly increased, with an overall seropositivity rate of 95.2%. Three previously seronegative patients, all on anti-CD20 therapy, remained seronegative. The T cell response was assessed in 57 patients. A logistic regression model showed that, independently from the booster dose, a positive T cell response was associated with anti-CD20 therapy. The T cell response did not correlate with antibody levels at T6.

Discussion: Antibody levels declined over time in ANC patients. However, only in patients treated with anti-CD20 therapy antibody levels declined below the threshold of detection within six months after the second dose. However, despite a blunted humoral response, the T cell response was increased in patients receiving anti-CD20 therapy. In addition, the booster dose, significantly increased antibody levels.

Conclusions: Our study shows variation in antibody responses across ANC patients receiving different immunotherapies and supports the need of immunomonitoring and individualized vaccination schedules in ANC patients.

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COEXISTENCE OF LAMBERT-EATON MYASTHENIC SYNDROME AND AUTOIMMUNE ENCEPHALITIS POSITIVE FOR BOTH ANTI NMDAR AND ANTI AMPAR-2 ANTIBODIES: A CASE REPORT

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Background: Lambert-Eaton myasthenic syndrome(LEMS) is an autoimmune neuromuscular disease with progressive muscle weakness and diminished tendon reflex associated with tumor in about 50-60% of cases [1]. Autoimmune encephalitis (AE) is a paraneoplastic autoimmune-mediated disorder characterized by memory impairment, behavioural changes and seizures [1]. LEMS and AE share the same etiology and pathophysiology with autoantibodies that target respectively peripheral and central neuronal proteins (CNP) in order to modify synaptic transmission. To date, there are no published reports of LEMS associated with AE with both N-metyl-D-aspartate receptor (NMDAR) and alpha-amino3-hydroxy-5-metyl4-isoxazopropionic acid receptor(AMPAR-2) antibodies, which target antigens on the neuronal cellular surface. Herein, we describe a patient with LEMS and AE who did express both antibodies.

Case report: A 70-year-old man with dropped head and generalized weakness came to our hospital for investigation. He noted weakness of all extremities for one year. The weakness gradually worsened until he became unable to go upstairs and to keep his head up. In his past medical history was reported arterial hypertension, pacemaker holder, diabetes and a single episode of membranous glomerulonephritis treated with immunosuppressants. At physical examination, he showed bilateral eyelid ptosis, weakness of the neck and upper limbs, hyporeflexia of limbs. Electrophysiological study showed a 600% increment response to post-exercise facilitation. Serum anti-P/Q voltage gate calcium channel (VGCC) antibody research was positive and LEMS was confirmed. Then he started 3,4diaminopyridine with relief. Ten months later the patient suddenly started to complain insomnia, memory loss, irritability, confusion and dizziness after postural changes. He performed a routine head TCscan was normal and an electroencephalogram showed slow background activity. AE was then diagnosed after detection, in serum and cerebrospinal fluid, of NMDAR and AMPAR-2 antibodies. So the patient was treated with intravenous immunoglobulin without relief and after one month he started rituximab. At 6 months-follow-up the patient reported a significant improvement of his symptoms with full recovery of behavioral disturbances. At 2 years-follow-up, no tumor was found at total body TCscan and PETscan.

Conclusions: Our patient is the first case in which LEMS was followed by cognitive, behavioral and autonomic disturbances due to AE with multiple antibodies against CNP. In literature [2] several cases of LEMS associated with cognitive and psychiatric disorders have been reported but only recently coexistence of LEMS and AE with antibodies against CNP has been described [3].

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A PROBABLE CASE OF WEST NILE NEURO-INVASIVE DISEASE IN KROTON'S AREA (SOUTHERN ITALY)

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West Nile Neuro-invasive disease (WNND) is a rare complication of West Nile virus (WNV) infection, that should be considered in differential diagnosis in patients with fever and neurological signs without better explanation, especially in endemic areas.

Objective: To describe a case of WNND in Kroton's area, Calabria region.

Case report: A 40 years fireman who received oral cyclosporine ad steroids for alopecia, complains headache and fever started the last week of February 2022. After few days he developed mental confusion and was admitted in neurology ward on 16 March. He also developed a caudo-cranial bilateral weakness with absent deep tendon reflexes about 15 days after fever onset, with subsequent quadriplegia and respiratory failure. Brain MRI showed bilateral FLAIR hyper-intensity of caudate nucleus without gadolinium enhancement; after 12 days, displayed reduction of previous alterations with a "swollen" aspect of fronto-temporal cortex bilaterally. From lumbar puncture was obtained a clear ("rock water"), normal pressure cerebrospinal fluid (CSF) with hyperproteinorrachia, 75 cells (97% lymphocytes) and mild hypoglicorrachia (40 mg/dl). Electroneurography showed initially only F-waves diffusely absents; after 7 days displayed a severe axonal sensory-motor polyneuropathy. EEG showed non-specific diffuse slowing. A full panel of infective exams including CSF filmarray, cultural exam, onconeural and surface cells antibodies search for autoimmune encephalitis were performed and resulted all negative. A thoraco-abdominal CT scan with contrast medium showed only pulmonary thrombo-embolism. Serology highlighted WNV IgM and IgG positivity. WNV real time RT-PCR was negative on blood, CSF and urine (search performed about 15 days after symptoms onset). He received empirical antibiotics and antiviral drugs, intravenous immunoglobulin and high dose steroids. He gradually improved in cognitive and respiratory function and restarted to move upper limbs. On 04 April he was discharged to rehabilitative ward.

Discussion: Formerly Kroton's territory was signalled for WNV infection in equines, but no human cases were reported. This patients had clinical features similar to other WNND cases described elsewhere, without a better explanation. Serum IgM e IgG were positive for WNV, but without evidence of viral genome presence in CSF or blood. However, in previous cases direct RNA detection was infrequent, especially after more than 10 days after onset.

Conclusions: To our knowledge, this may be the first case described of probable WNND in Calabria region. We suggest to investigate any febrile pathology associated with neurological symptoms of unclear origin with WNV serology, in order to better understand the real epidemiology of this infection.

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VISUAL SYSTEM INVOLVEMENT IN GFAP ASTROCYTOPATHY: A CASE REPORT AND REVIEW OF THE LITERATURE

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Objectives: We report a patient with GFAP-positive severe bilateral optic neuritis and present a literature review to evaluate available evidence of visual system involvement in GFAP astrocytopathy.
Materials: Clinical, imaging, and neurophysiologic data from our Neurology Unit and review of available literature.
Method: We describe our case report. We then present a review of signs and symptoms of optic system involvement in GFAP astrocytopathy.

Results: A 33-year-old woman presented with severe, rapidly progressing bilateral optic neuritis (ON) with marked vision loss (OD: No light perception; OS: 0.2). Cerebrospinal fluid (CSF) examination found 96 lymphomonocytoid cells and a mirror pattern of oligoclonal bands (Type 4). Brain and spinal cord MRI were negative. Visual Evoked Potentials (VEPs) showed absent cortical responses in OD and reduced amplitudes with preserved latencies in OS, indicating an axonal pattern of optic nerve damage. Treatment with intravenous steroids, plasma exchange and immunoglobulins was scarcely effective. We tested a stored CSF sample for GFAP antibodies which were positive, and retrospectively made a diagnosis of GFAP-antibodies related severe bilateral ON. We found 506 patients among 69 papers (50 case reports, 19 case series) and gathered information on visual symptoms and optic system involvement. Visual symptoms, mainly blurred vision, were reported in 88/506 (17%), while bilateral optic disc edema was found in 55/506 (11%). ON was reported in 36/506 (7%), with two cases of severe bilateral ON with poor prognosis.

Discussion: In recent years, most GFAP studies have included the characterization of visual symptoms. Some cohorts report up to 60% of patients with visual symptoms. Optic disc edema is probably underestimated, as most affected patients (69%) are asymptomatic for visual impairment and fundoscopy is not performed. Some evidence suggests optic disc edema as a specific marker of GFAP rather than AQP4 astrocytopathy. A rare presentation is bilateral, severe optic neuritis, which has a high disabling potential and shows limited treatment response. The neurophysiology of optic nerve damage indicates axonal damage, and resembles optic neuritis in NMOSD, another astrocytopathy; therefore, pathological mechanisms could be similar.

Conclusions: Visual system involvement in GFAP astrocytopathy is growing in relevance. Visual symptoms and optic disc edema are frequent and could have a specific value for diagnosis. Testing for GFAP antibodies should be considered for cases of bilateral optic neuritis of unknown origin. Disease severity can be high, and prognosis poor, even with swift and aggressive treatment.

NEUROFILAMENT LIGHT-CHAIN AND CSF PARAMETERS DO NOT CHANGE AFTER SARS-COV-2 VACCINATION

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Background: Coronavirus disease 2019 (COVID-19) ranges from paucisymptomatic course to severe pneumonia and life-threatening conditions although several neurological manifestations have been commonly reported [1,2]. In this scenario, vaccines against-SARS-COV-2 represent an important public health tool in reducing morbidity and mortality. The efficacy and safety of that vaccines in counteract COVID-19 have been already established, but patients with neurological disease are still concerned about vaccination thus, a great deal of daily requests reach Neurologists about the link between vaccination and worsening of a pre-existing neurological condition. Hence, the aims of this study are to compare the CSF parameters and neurofilament light chain (NfL) between unvaccinated and vaccinated participants and to evaluate whether these parameters differ according to underlying neurologic disease.

Materials and Methods: We enrolled patients admitted to the Neurologic Unit of University Hospital "Paolo Giaccone" who underwent lumbar puncture (LP) between February 2021 and December 2021. CSF parameters and NfL were compared between unvaccinated and vaccinated patients at three different intervals from vaccination (<4 weeks, 4-8 weeks, >8 weeks) as well as according to the underlying diagnosis (Multiple sclerosis, Dementias, Parkinson disease and atypical parkinsonisms) a not-dependent time manner from vaccination. Data are reported as median and interquartile range within squared brackets. The analysis was conducted by using non-parametric test.

Results: A total of 116 patients underwent LP (median age 59 years, [37-51]; 50% females); n=14 (<4 weeks), n=10 (4-8 weeks), n=25 (>8 weeks) and n=25 (unvaccinated) respectively were included in the final analysis. No significative differences emerged between vaccinated and unvaccinated patients for total protein content (p=0.2), CSF glucose (p=0.5), CSF/Serum Glucose ratio (p=0.3), number of cells per mm3 (p=0.7) and CSF-NfL (p=0.6). When comparing vaccinated and unvaccinated patients according to underlying diagnosis, no further differences emerged between groups (overall p>0.5). Total protein content and NfL positively correlated with participants' age (p=0.03) while number of cells per mm3 was inversely correlated (p<0.0001).

Discussion: The impact of the vaccination among clinical outcomes is easy to assess, but the early and subtle alterations such as inflammation and neuro-axonal loss of the nervous system may be investigated through the analysis of CSF parameters and NfL [3]. We observed that CSF parameters and NfL are not different in vaccinated patients compared to the unvaccinated ones, even when considering the underlying neurological conditions leading to LP or stratifying by time from vaccination.

Conclusion: NfL and CSF parameters did not differ between vaccinated and unvaccinated patients. COVID-19 vaccines are not associated with neuroinflammation and neuro-axonal degeneration in people with neurological diseases.

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ELSBERG SYNDROME: ATYPICAL VIRAL INFECTION WITH HYPOGLYCORRHACHIA

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Introduction: Elsberg syndrome (ES) is a cause of acute lumbosacral radiculitis with myelitis related to reactivation, or occasionally, primary herpes virus infection [1]. In the case of Cauda Equina Syndrome (CES), with superimposed clinical and radiological findings of myelitis, ES should be considered. We describe a patient with an ES due to reactivation of varicella-zoster virus (VZV).

Case description: A 68-year-old man with a history of symptomatic benign prostate enlargement presented to our institution's Emergency Department (ED) with acute urinary retention and lower abdominal pain. Urological examination revealed stenosis of the neck bladder. Abdominal x-ray showed hydroaeric levels and fecaloma. After 3 days, he presented gait impairment and dysarthria. Neurological examination revealed dysarthria, dysphagia, right-sided peripheral facial nerve palsy, and right deviation of the protruded tongue associated with mild atrophy of the same side; in addition, he presented diplopia in primary position of gaze. Furthermore, he had mild left-sided hemiparesis, absent reflexes in the legs, hypoesthesia in the perineal region (saddle hypoesthesia), urinary and bowel incontinence. He had not meningeal irritation signs, fever, or skin lesions. Magnetic resonance imaging (MRI), lumbar puncture, and electromyoneurography (EMNG) were performed. MRI of the brain and spine showed spinal cord lesions in the thoracic region and nerve roots enhancement of the cauda equina; cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis (980 Cells /μL with 100% lymphocytes), glucose 33 mg/dL (serum glucose was normal); EMNG showed acute denervation in the right side of the tongue. Intravenous antibiotics and antiviral treatments were promptly started. The protein chain reaction (PCR) CSF analysis later revealed 190837 gv/mL copies of VZV. Therefore, the antiviral treatment (acyclovir) was administered for 21 days. Discussion: ES is poorly defined and rarely reported but it is probably frequent unrecognized [1]. This case-report describes the case of an immunocompetent 68-year-old man who presented CES, myelitis and cranial polyneuropathy associated with VZV infection without skin rash [3]. This case underlines the importance of searching VZV in CFS analysis in patients with suggestive symptoms of ES and with an atypical viral infection with hypoglycorrhachia [2].

Conclusions: ES should be considered in all cases of CES, even in an immunocompetent patient without rash suggestive of VZV. Early diagnosis is important to start immediately antiviral treatment to avoid the severe outcome.

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PREDICTORS OF WELL-BEING IN MS PATIENTS

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Introduction: Multiple sclerosis (MS), due to its chronic and unpredictable course, may cause physical, cognitive, and behavioural changes, which greatly impact on patients' well-being and their everyday functioning [1].

Objectives: The objective of this study was to assess the variation in measure of well-being as predicted by individual differences in health status, risk factors and healthy behaviours, physical environment and social support in patients affected by multiple sclerosis (MS).

Methods: PGWBI was used to assess well-being. Objective measures of patient's state of health were body mass index (BMI), hypertension, handgrip, cognitive functioning (MoCA), functional independence and locomotion (FIM), comorbidity (SCQ), anxiety (STAI), depression (BDI-II), duration and severity of disease (EDSS). Risk factors and healthy behaviours were smoking, alcohol consumption, fruit and vegetable consumption, physical activity (EPIC-PAQ). Environmental and social support were assessed as number of close people to count on and perceived social support (MOS-SSS). A linear regression model was fitted targeting well-being as outcome; health measures, risk and healthy behaviours, characteristics of physical and social environment, and age were the predictors.

Results: 151 participants (93 females) were included, with a mean age of 51.6 years (sd=5. 8) and 12 years (sd=8.7) since diagnosis; 130 patients had relapsing-remitting MS (RRMS), 21 had a progressive MS; mean EDSS score was 2.6 (sd=1.6). PGWBI mean score was 72.3 (sd=17.5). EDSS, STAI-S, STAI-T, and BDI-II were predictors of PGWBI, with the model explaining 66.8% of PGWBI variation ($R2=.668$; $F(4.146)=76.3$; $p<.001$).

Discussion: We found that MS severity, anxiety and depression predicted 73% of well-being variation in adults with MS. Anxiety and depression can be secondary to MS chronic and unpredictable course, which in turn determines increased symptom burden and slower recovery process, reducing psychological well-being in general [2]. Anxiety and depression can also increase fatigue, pain, and sleep problems in people with MS [2]. Including anxiety and depression symptoms, in association with MS severity, as part of routine screenings and rehabilitation programmes can impact on up to 67% of MS patients' experienced disability.

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DISEASE MODIFYING THERAPY SPECIFICALLY IMPACTS ON MICRORNAS EXPRESSION

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Objectives: Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system with heterogeneous clinical phenotypes, disease progression and response to disease-modifying therapies (DMTs). Among DMTs, drugs depleting immune cells emerge for their efficacy, such as Ocrelizumab (OCRE), a monoclonal anti-CD20 antibody, and the purine analog Cladribine (CLA). The identification of diagnostic or prognostic biomarkers is of extraordinary interest for early diagnosis and appropriate therapeutic choice. The impact of DMTs on gene expression is still unknown. Thus, we investigated the microRNAs profiling and their response to the Cladribine or Ocrelizumab treatment, proposing them as possible diagnostic and prognostic biomarkers for MS.

Materials and Methods: 20 relapsing-remitting MS (RRMS) patients who started a therapy with Cladribrine or Oocrelizumab were enrolled (10 CLA, 10 OCRE). Serum samples were obtained before treatment (T0) and 6 months post treatment (T1). Inclusion criteria: MS diagnosis, age⩾18 years, <65years. Exclusion criteria: other concomitant neurological or immunological pathologies. RNA extraction was performed with miRNeasy Tissue/Cells Advanced Mini Kit (QIAGEN©). MiRNAs microarrays: Agilent protocol (Version 3.1.1, 2015). Data analysis tools: Limma, R-Bioconductor (USA). Normalization by the quantile and median alignment.

Results: Fourteen miRNAs were differentially expressed in subjects treated with CLA meanwhile the OCRE treatment had an effect on one miRNA only (miR-3653-3p). Among the differentially expressed miRNAs in CLA-treated subjects, some significant correlations were found with disease duration (miR-23b-3p, miR-27b and miR-326), frailty index, EDSS and the presence of urinary symptoms. In response to both treatments, naive patients differentially clustered then ones that underwent previous treatments with other DMTs. The comparison of miRNAs expression in pre-treated population (CLA T0 and OCRE T0 subgroups) showed that 24 miRNAs were differentially expressed, of which miR-186 and miR-155 seems to define a more neurodegenerative and a more inflammatory pathway respectively.

Conclusions: Results highlight a specific microRNAs response to DMT, which involves differentially expressed microRNAs of the neuroinflammatory, immune-regulator, myelin production (miR-29 and miR-23b-3p) and neurodegenerative pathways. These microRNA candidates, integrated with clinical and imaging data, might allow to optimize the therapeutic response to DMT.

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LABORATORY DIAGNOSTIC STRATEGIES FOR IDENTIFICATION OF ANTIBODIES AGAINST NEURONAL SURFACE ANTIGENS IN AUTOIMMUNE ENCEPHALITIS

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Background: Detection of neuronal surface antibodies (NSAbs) is crucial to diagnose autoimmune encephalitis (AE). Most laboratories rely on commercial fixed cell-based assays (C-CBA), that are easy to perform and include the most common NSAbs targets. It has been suggested that home-made techniques, including immunohistochemistry on lightly fixed rat brain (IHC), live CBA (L-CBA) and live rat neuronal cultures (LNC) might provide a higher accuracy. Some patients show uncharacterized staining on IHC not associated with any known NSAbs (unc-NSAbs), but the clinical relevance of such finding is unclear.

Materials and methods: We prospectively tested 1112 consecutive samples from patients with suspect AE sent to our laboratory using IHC and C-CBA. IHC positive samples were additionally tested with specific L-CBA according to the staining pattern detected, and with LNC. We only included patients with sufficient clinical information. Analytic performance was assessed using sensitivity, specificity, accuracy, positive and negative predictive values. IHC staining pattern distribution and intensity (0-4) was retrospectively systematically evaluated.

Results: Among the 778 included patients, 57 had AE with characterized NSAbs (NSAbs+AE), 77 had NSAbs-negative possible/probable AE (NSAbs-AE) and 644 had alternative diagnosis. IHC had a higher sensitivity (98,2% vs 66,7%) and negative predictive value (99,8% vs 97,4%) compared to C-CBA to identify patients with NSAbs+AE. L-CBA had both a higher sensitivity (98,2% vs 67,7%) and specificity (99,0 % vs 98,3%) compared to C-CBA. The combination of IHC and L-CBA provided a higher accuracy compared to C-CBA (99,7% vs 97,3%). Fifty patients had unc-NSAbs, and only 8 were finally diagnosed with AE. A LNC positivity was found only in 1/7 patients with AE, but also in 3/31 other neurological disorders (p=0.698). Among patients with unc-NSAbs, a higher staining intensity was the main predictor of a final AE diagnosis.

Discussion: Our data show that the combination of IHC, used as a screening test, and L-CBA as a confirmation test provides a diagnostic advantage compared to C-CBA, both in terms of sensitivity and specificity. In patients with unc-NSAbs, evaluating the staining intensity might be helpful to predict an AE diagnoses. Conversely, the use of LNC does not seem to provide further useful information in clinical practice.

Conclusions: Re-evaluating critical samples tested with C-CBA using home-made techniques including IHC and L-CBA is recommended to increase diagnostic accuracy.

A CASE OF ACUTE NECROTISING ENCEPHALOPATHY IN A YOUNG ADULT WITH POSITIVE FAMILY HISTORY

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Objectives: Acute Necrotising Encephalopathy (ANE) is a rare and rapidly progressive condition following a viral febrile infection. Brain magnetic resonance imaging (MRI) reveals symmetric, bilateral grey and white matter lesions, often involving the thalami [1]. Most familial and recurrent cases are associated with mutations in the Ran Binding Protein 2 (RANBP2) gene that is coding a nuclear pore protein [2]. We are presenting a case of adult-onset ANE with a previously affected brother.

Materials: Our 20-year-old woman developed mild confusion and focal sensory-motor symptoms after preceding fever and upper respiratory tract infection 5 days before. 15 years before her older brother at the age of 15 presented rapidly progressive alteration of consciousness after a febrile episode. Brain MRI showed bilateral hyperintense lesions in T2 at thalamus and external capsule that resolved on follow-up scans. He recovered partially with persistent mild-to-moderate tetraparesis, cerebellar syndrome and cognitive impairment.

Methods: Neurological examination showed confusion and concentration difficulties, bilateral visual blurring and paraesthesia to her upper right arm. Brain MRI showed bilateral symmetrical T2 hyperintense lesions in the thalami, the external capsules, the optic tracts and the mammillary bodies. Blood tests (including infective and autoimmune screening, autoimmune encephalitis and anti-myelin oligodendrocyte glycoprotein antibodies) were normal except for increased alanine aminotransferase. Cerebrospinal fluid analysis was normal (including negative herpes and West Nile viruses). At the moment the genetic analysis carried out by whole exome sequencing excludes point mutations of pathological significance at RANBP2.

Results: The patient was treated with high-dose intravenous steroids for 5 days and immunoglobulins, recovering partially soon after. A second MRI showed a significant reduction (almost a resolution) of the previously reported lesions. According to Mizuguchi criteria [1] we concluded for ANE and suspected for a genetic predisposition (single-gene mutation other then RANBP2 are described [2]).

Discussion: ANE is a rare condition mostly described in children, and uncommonly presenting in young adults. Our patient had a mild course in comparison to his brother, and recovered almost completely. Younger age, late treatments and brain stem lesions have been related to a poor prognosis.

Conclusions: Our case represents a clinical rarity despite genetic test are not conclusive yet. Family history, anamnestic data and specific neuroimaging was relevant to suspect ANE despite the altered state of consciousness was slight and no seizures were witnessed.

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AGE RELATED PROGNOSIS AND RE-CHALLENGE IN NEUROLOGICAL COMPLICATIONS OF IMMUNE CHECKPOINT INHIBITORS (ICI)

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Objectives: ICI-based regimens for the treatment of older patients with melanoma were reported to decrease the risk of disease progression and death by more than 20%^1. Neurological immune related adverse events (n-irAEs) reportedly occur in up to 6% of patients. However, little is known about the impact of age^1. We analyse a large cohort of adult melanoma patients treated with ICI to investigate the prevalence of n-irAEs in different age groups.

Materials: Patients with advanced stage melanoma treated in our institution from 1/1/2015-31/12/2021 were identified and extensive data from their electronic clinical records were collected.

Methods: The patients were classified into three age groups, group 1: 18-60 years old, group 2: 60-70, group 3: 70 and over.

Results: n-irAE occurred in 4.36% of patients (n=74/1,694). Mean age was 65.9 in males, 59.8 years in females. Median number of ICI doses prior to n-irAE onset was 2 cycles and was not different between age groups. Severity scale was 3 or higher in 39% of patients and similar between groups. Common n-irAE phenotypes were myositis (45.9%), followed by encephalitis (9.4%), and peripheral neuropathy (8.1%). Age was an important predictor of total number of irAEs with fewer AEs in group 3 (p=0.04). Second ICI treatment after a n-irAE was administered in 18.9% of patients with 28.5% of them developing n-irAE again. All patients responded to immunosuppression.

Discussion: The increased usage of ICI is resulting in increased presentation of n-irAE, leading in some cases to treatment withdrawal. We describe the more common adverse events and find that their likelihood decreases with age. There is a gap in the literature regarding the rechallenge of patients with further ICI treatments following n-irAE, however our data shows that rechallenge was a safe option in the majority of patients.

Conclusions: n-irAE is a rare complication of ICI occurring in 4% of our cohort. Some regimens resulted in more n-irAEs than others. It manifests as a wide phenotypic spectrum with distinct clinical characteristics. Older adults had lower rates of n-irAEs.

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EFFECT OF NATIONAL SHORTAGE OF IVIG ON PATIENTS WITH CHRONIC IMMUNE MEDIATED PERIPHERAL NEUROPATHIES?

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Objectives: Intravenous immunoglobulin (IVIg) can contribute importantly to management of chronic inflammatory peripheral neuropathies, including multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyneuropathy (CIDP) [1]. Disability scores show that regular administration slows disease progression [2]. Recent and current reductions in plasma donations and increased demand for IVIg have enforced restricted dosing. We retrospectively analysed the effect of 20% reduction of IVIg dose on disability scores of CIDP and MMN patients at Addenbrooke's Hospital, Cambridge.

Materials: Forty-one patients with CIDP or MMN received a reduced dose of IVIg over a 2-month UK national shortage period. Scores for the Rasch-built Overall Disability Scale (RODS), the Medical Research Council (MRC) Score, and/or the 10-meter walk test were recorded for 16 of these subjects.

Methods: We analysed available results from the months before reduction and one measurement after reduction.

Results: There were no significant changes in the various indices despite the 20% reduction in IVIg dose.

Discussion: The growing number of indications for IVIg treatment has resulted in an increase in its demand, resulting in periodic shortages. Our observation indicates that reducing IVIg dosage in times of need, such as during a national shortage, does not dramatically impact our patients' disability scores.

Conclusion: In this small cohort, our post hoc analysis detected no change in disability scores over the relatively brief period of reduced IVIg dosing. Prospective study of a much larger set of patients, with adequate between and

within patient controls, is required to firmly establish optimal IVIg dosing regimens, especially in the face of recurrent shortages.
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BIOMARKERS OF NEURONAL AND GLIAL DAMAGE IN SUSAC SYNDROME

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Aims: Susac syndrome is a rare condition characterized by possible neurological, eye and ear symptoms, with a putative autoimmune etiology. Scattered pathological studies described vascular changes with microinfarcts involving the retina, the inner ear and the brain. These vascular changes involve small vessels most severely, causing microinfarcts, cortical atrophy, and leukoencephalopathy. White and gray matter can be affected with characteristic MRI brain lesions. Serum neurofilament light chain (sNfL) and serum glial fibrillary acidic protein (sGFAp) represent two promising markers of neuronal and glial degeneration. The aim of this study is to evaluate sNfL and sGFAp levels in Susac patients.

Materials and Methods: Twenty Susac syndrome patients and 108 healthy subjects (HSs) were enrolled in the study. Blood samples were collected from 5 international centers and sNfL and sGFAP levels were assessed in each serum sample of patients and controls. We used the commercially available immunoassay kits for GFAP and NfL run on the semi-automated ultrasensitive SR-X™ Biomarker Detection System (Quanterix) following manufacturer instructions. sGFAP and sNfL values are skewed therefore their levels were log10-transformed when analyzed. Analysis of covariance (ANCOVA) was performed considering log10 sNfL and sGFAP levels as dependent variables, groups (Susac vs HSs) as fixed variables, and age and gender as covariates.
Results: sGFAp levels were higher in Susac patients (77.79, 51.10-175.43) compared to HSs (74.18, 43.73-122.74) ($p = 0.001$). sNfL levels were higher in Susac patients (35.59, 14.74-930.85) compared to HSs (7.71, 5.25-13.94) ($p < 0.0001$). sGFAp/sNfL ratio was higher in HSs (8.63, 5.88-12.84) compared to SUSAC patients (1.19, 0.22-4.29) ($p < 0.0001$).

Discussion and Conclusions: The results of this study suggest a disproportionately increased neuronal rather than glial degeneration in patients with Susac syndrome. The possible utility of sGFAp/sNfL ratio as Susac syndrome biomarker warrants further investigations.

NEUROSYPHILIS PRESENTING AS ALZHEIMER'S DISEASE: A CASE REPORT WITH HISTOLOGICAL FEATURES, NEUROIMAGING AND CSF FINDINGS

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Introduction: Neurosyphilis (NS) is the clinical result of the nervous system infection by Treponema pallidum. NS can mimic many neurological disorders and may develop during any stage after the initial exposure to syphilis. We describe a case of NS presenting as Alzheimer's disease (AD).

Case report: A 68-year-old man with a previous history of multi-embolic stroke was referred to our hospital for cognitive decline which began 2 years earlier but worsened rapidly in 4 months. At admission, he was space-time disoriented with difficulties in name-finding and comprehension and with gestural apraxia. Neuropsychological tests revealed memory and executive deficits and closing-in phenomenon (MMSE 17/30). Blood testing revealed iron-deficiency anemia and inflammation, tumour markers were negative. Brain MRI demonstrated leukoaraiosis, global cortical atrophy (GCA 2) and medial temporal lobe atrophy (MTA 3 right-side, 2 left-side). FDG-PET showed bilateral temporo-parietal hypometabolism. CSF examination revealed lymphocytic pleocytosis (52/mm3), elevated protein (86mg/dL) and normal glucose. CSF immunophenotyping and cytology excluded neoplasm. Serum/CSF research for onconeural antibodies tested negative. The Oligoclonal IgG bands (OCB) assay detected OCB in CSF plus other OCB in CSF and serum. CSF-markers for AD documented amyloidopathy (Abeta42:225ng/L, Abeta40:5227ng/L, total-Tau:709ng/L, phospho-Tau:66 ng/L). CSF-PCR for neurotropic viruses and Mycobacterium tuberculosis-DNA were negative. CSF acid-fast staining and microscopic examination were unremarkable. Treponema pallidum haemagglutination assay (TPHA) was positive on serum (title 1:5120) and CSF (title 1:640). CSF/serum Venereal Disease Research Laboratory (VDRL) were nonreactive. Funduscopic examination and ultrasound examination of the pupil were normal. Echocardiography demonstrated hypokinetic cardiomyopathy without significant stenosis on coronary angiography. Whole-body FDG-PET showed multiple hypermetabolic supra- and infra-diaphragmatic lymph nodes, a hypermetabolic nodule in the right breast and hypercaptation of the anus. Dermatologic consultation diagnosed anal condyloma lata. Patient underwent multiple biopsies (breast nodule, anal lesions, inguinal lymph node). Histologically, specimens showed follicular lymphoid hyperplasia without immunophenotypic abnormalities. Skin biopsy of the perianal region revealed infiltration of plasma cells and neutrophils, Treponema pallidum antibody immunohistochemical stain tested positive. Patient was diagnosed with latent syphilis and treated with ceftriaxone (2 g daily i.m. for 15 days). After treatment cognitive improvement in attentive tests was noted, CSF analysis was normalised, TPHA titles declined (serum 1:2560, CSF 1:160), PET-FDG showed significant decrease of lymphadenopathy.

Conclusions: Due to the clinical variability the diagnosis of NS could be challenging and easily missed. The potential interaction between the onset of NS and the development of AD is an intriguing matter for future studies.
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RARE CNS INFLAMMATORY DEMYELINATING EVENTS AFTER COVID-19 VACCINES: A CASE SERIES AND SYSTEMATIC REVIEW

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Background: The SARS-CoV-2 pandemic has led to COVID-19 vaccines development and campaign at an unprecedented magnitude and speed, providing the most effective tool to exit from global emergency. It is now well established that COVID-19 vaccines are unequivocally safe in the general population. However, data are now being collected for Rare Adverse Events, negligible from a statistical viewpoint but potentially relevant to single out

specific risk factors and to gain insight about CNS disease pathophysiology. With respect to CNS Inflammatory Demyelinating Events (CIDEs) various cases have been described following COVID-19 vaccines. Although observational studies are showing that these events are rare and vaccines' benefits highly overcome the risks, collecting and characterizing post-COVID-19 vaccines may, at some point, disclose disease-relevant mechanisms.

Methods: Here we describe 6 CIDEs (2 Acute Transverse Myelitis (ATM), 3 Multiple Sclerosis (MS) and 1 Neuromyelitis Optica Spectrum Disorder (NMOSD)) occurring within 35 days from COVID-19 vaccines and perform a systematic search of post-COVID-19 vaccine CIDEs -including ATM, ADEM, MS and NMOSD/MOGAD- published worldwide from 1st December 2020 to 31st December 2021. Demographic/clinical/MRI/CSF/serum characteristics were extracted from reviewed studies and summarized.

Results: Forty-nine studies were included in the systematic review, reporting a total number of 85 CIDEs. Considering our additional 6 cases, a total of 91 CIDEs were summarized, including 24 ATM, 11 ADEM, 47 MS (15 new diagnosis and 32 relapses), 8 NMOSD (7 new diagnosis and 1 relapse), and 1 newly diagnosed MOGAD. CIDEs occurred after both mRNA-based (n=46), adenoviral-vectored (n=37) and inactivated vaccines (n=8). Adenoviral-vectored vaccines accounted for the greatest number of ADEM and NMOSD/MOGAD, suggesting their possible higher tendency to trigger antibody-mediated diseases. Age was heterogeneous (19-88 years old) and female sex was prevalent. Time from vaccine to symptoms onset was highly various: interestingly 73% of very early onset CIDEs (within 3 days from vaccine) followed an mRNA-based vaccine and post-mRNA-vaccine ATMs occurred on average earlier compared to those following other vaccines (3 vs. 8 median days), with the same trend observed in MS relapses. Recovery was complete/almost complete in the majority of MS and ADEM, while ATM and NMOSD/MOGAD reached good outcome in 44% of cases.

Conclusions: While epidemiological studies have assessed the safety of COVID-19 vaccines, detailed clinical descriptions and systematic reviews of sporadic cases may be valuable for a better understanding of the pathophysiology of CNS inflammatory demyelinating events.

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A CASE OF POSSIBLE NEUROSARCOIDOSIS PRESENTING WITH RAPIDLY EVOLVING NEUROLOGICAL DETERIORATION

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Background: Neurosarcoidosis has an incidence of 1/100.000/year and its diagnosis is considered possible in presence of compatible clinical, MRI, CSF, and/or neurophysiological findings and exclusion of other causes [1]. We report a case of isolated neurosarcoidosis that initiated with mild symptoms and rapidly worsened.

Case Report: a 66 year-old woman developed tingling and hypoesthesia of the tongue, limb extremities and perineum. Four weeks later, she was admitted to Castelfranco Veneto's Neurology Unit, with lower limbs hyposthenia, bladder dysfunction, ataxic gait, loss of right eye visual acuity. Routine blood tests and brain CT were normal; however, brain and spine MRI showed FLAIR and post-contrast T1 hyperintensities involving the leptomeninges and ventral midbrain, pons and medulla oblongata, mainly on the right side. Such abnormalities were also present in the anterior part of the upper cervical (C1-C3) and lower dorsal (D8-D12) spinal cord, involving both the white and grey matter. After rachicentesis, antibiotic, antiviral and steroid therapies were initiated (methylprednisolone 1g/day x 6 days). Repeated CSF analyses showed >100 lymphocytes/microliter, 130 to 76 mg of proteins/dL, angiotensin-converting-enzyme 9 U/L (n.v.:0-5), markedly elevated CD4/CD8 ratio (7.8), CSF oligoclonal bands, whereas microbiological CSF tests, immunophenotypic analyses and the most common encephalitis-associated antibodies were negative. The patient rapidly developed ascending tetraplegia, global ophthalmoparesis, facial diplegia, dysphagia, C5 sensory level, acute urinary retention and, eventually, respiratory pauses. The patient was intubated and transferred to the intensive-care unit. Control MRI showed additional enhancements of III, V, VII, VIII cranial nerves bilaterally. During the following 2 months, due to persistence of symptoms, she underwent the third steroid cycle, one intravenous immunoglobulins treatment cycle and plasmapheresis. The diagnostic work-up also included the finding of normal CSF IL-2-R, elevated serum IL-2-R, slightly elevated serum and CSF IL-6. Serial neurophysiological studies showed sensory-motor demyelinating neuropathy to all four limbs, gradually improving to the upper limbs and worsening, with axonal involvement, to the lower limbs. The diagnosis of possible neurosarcoidosis of CNS and PNS was made, according to Stern et al.'s criteria [1], hence starting long-term methotrexate and steroid therapy. Ultimately, she was transferred to a rehabilitation Hospital, gradually regaining spontaneous breathing, deglutition, visual acuity and partial upper limbs mobility, while paraplegia, hypoesthesia of limbs and urinary catheter-dependency persisted. Control MR showed gliotic degeneration of previously active lesions.

Conclusions: Neurosarcoidosis may cause rapid clinical deterioration and can involve brainstem, spinal cord and/or peripheral nerves, posing a number of differential diagnosis in the emergency setting.

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CSF OSTEOPONTIN IS ASSOCIATED WITH CORTICAL DAMAGE ACCUMULATION AND DISEASE ACTIVITY IN EARLY MULTIPLE SCLEROSIS

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Objective: Preliminary data suggested that the intrathecal inflammatory profile and especially the osteopontin levels represent prognostic factor of multiple sclerosis (MS)-related long-term cortical damage and disability accumulation [1,2]. We evaluate possible cerebrospinal fluid (CSF) inflammatory markers of accumulation of cortical damage as well as disease activity in early relapsing remitting MS (RRMS).

Methods: CSF levels of 69 inflammatory markers were assessed using immune-assay multiplex technique in 89 RRMS patients (22M/67F, mean age 38,7 ± 12,5 years). All patients underwent regular clinical assessment and yearly 3T MRI scans. White matter (WM) lesion number and volume,

cortical lesions (CLs) and volume (CLv) and global cortical thickness (CTh) were evaluated together with the 'no evidence of disease activity' (NEDA-3) status, defined by no relapses, no disability worsening and no MRI activity.
Results: Throughout a random forest approach to all markers, 10 molecules were significantly associated with changes in global Cth, especially Osteopontin (OPN) and CXCL13. Among CSF markers, linear regression confirmed CXCL13 ($p<0.001$), sTNFR1 ($p<0.01$), OPN ($p<0.013$) as associated with accumulation of cortical atrophy. Finally, the 10 selected molecules were added in a multivariable regression model with demographical, clinical and MRI measures of WM damage. Here, increased CXCL13 (Beta -4.15x10-15, $p<0.001$) and OPN (Beta -1.56x10-8, $p<0.001$) associated with CTh changes. When adding also variables associated to GM damage (CLs and CLv), increased levels of OPN (Beta-1.38x10-8, p 0.014) and sTNFR1 (Beta-2.692x10-7, $p<0.047$) provided additional value in predicting Cth changes (adjusted R-squared 0.62) when compared to the same model but without CSF markers (adjusted R-squared 0.20). OPN and CXCL13 revealed also as the best associated to the NEDA status (44/89 reached NEDA).

Discussion: Intrathecal inflammation at the time of diagnosis associates with accumulation of Cortical Atrophy. CXCL13 is confirmed as a significant prognostic factor for accumulation of cortical atrophy and disease activity. Moreover, Osteopontin emerged as a possible marker of disease activity and accumulating cortical damage, supporting its role in intrathecal inflammatory responses: OPN is released by CNS residents and infiltrating cells, associated with survival of myelin-reactive T cells, IFN and IL12 proinflammatory activity and inhibition of IL10-mediated responses [3]. Evaluation of CSF markers could so provide further value to the commonly adopted measures of disease severity in clinical practice.

Conclusion: CSF inflammatory markers provide prognostic information in predicting changes in cortical pathology. Particularly OPN is a possible candidate in predicting such changes, in addition to clinical, demographic and MRI variables.

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CENTRAL NERVOUS SYSTEM IMMUNE-RELATED DISORDERS AFTER SARS-COV-2 VACCINATION: A MULTICENTER STUDY

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Objectives: To characterize the clinical spectrum and immunological features of central nervous system (CNS) immune-related events following SARS-CoV-2 vaccination.

Materials: Data were retrospectively collected from medical records and consisted in date of vaccination, vaccine type and dose number, neurological symptoms, cerebrospinal fluid (CSF) characteristics, antibody presence and type, brain/spinal cord magnetic resonance and electroencephalography features, final diagnosis and treatment strategies adopted. Disability was evaluated using the modified Rankin Scale (mRS) at disease onset, clinical nadir and last available follow up.

Methods: We considered patients referred to the participating centers between December 1st, 2020 to April 30th, 2022 and fulfilling the following criteria: (1) de novo CNS disorders developing after SARS-CoV-2 vaccination satisfying the highest level (i.e. probable) in the criteria for labelling causality in neurological adverse events following immunization [1]. (2) Evidence for an immune-mediated etiology, as per (i) 2016 Graus criteria for autoimmune encephalitis [2]; (ii) 2015 Wingerchuk criteria for neuromyelitis optica spectrum disorders [3]; (iii) criteria for myelitis. (3) Patients with insufficient medical information to assess causality or lacking an immune-mediated etiology, patients with new-onset multiple sclerosis or those with pre-existing CNS autoimmune disorders were excluded.

Results: We included 8 patients (4 men, 4 women; median age 52; range: 35-73). Five patients over eight received an mRNA-based vaccine (Pfizer n=4, Moderna n=1) and 3/8 received a vector-based vaccine (Astra-Zeneca n=3). The median time lag between vaccine exposure and neurological symptoms development was 13 days (range: 2-22). CSF testing was inflammatory in 7/8; onconeural, surface antigen and demyelination-associated antibodies were negative in all patients. Four patients were diagnosed with autoimmune encephalitis, 2 with acute disseminated encephalomyelitis and 2 with myelitis. Immunemodulatory therapy was administered to 7/8 patients. At last follow-up (median 134 days; range: 43-276), 1/8 patient was asymptomatic, 5/8 were left with no significant disability and 2/8 with slight disability.

Discussion: Neurological adverse events tend to develop approximately 2 weeks after vaccination, more frequently after mRNA-based vaccines, probably reflecting their widespread adoption as compared to adenovirus-based vaccines. Seronegative autoimmune encephalitis was the most frequent presentation. All patients either improved or stabilized following immunemodulatory therapy.

Conclusions: We reported a case-series of CNS immune-mediated adverse events, demonstrating that such complications may not only occur after Sars-CoV-2 infection, but less frequently following vaccination as well. Therefore, it would be worth exploring their epidemiology and immunopathogenesis in a population-based study.

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GAD ANTIBODY-ASSOCIATED SUBACUTE CEREBELLAR ATAXIA RELATED TO THYMIC LYMPHOMA

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Objectives: Paraneoplastic neurologic syndromes (PNS) are rare, immune-mediated disorders, related to an underlying tumour, as both cancer and central nervous system may share similar antigens that triggers an immune-mediated response [1,2]. Among these, paraneoplastic cerebellar degeneration (PCD) is one of the most common and is often related to onconeural proteins [1,2]. Prognosis is driven largely by the treatment of the underlying tumour [1,2]. Here, we report a case of a rapidly progressive cerebellar ataxia associated with anti-GAD-65 antibodies (anti-GAD-65-Abs) in a patient with lymphoma.

Materials: A previously-health 63-year-old woman had an 8-week history of progressive dizziness, blurred vision, gait instability. She needed support to walk. Neurologic examination revealed severe gait ataxia, multidirectional nystagmus, intention tremor, slight adiadochokinesia in the upper limbs. She had no family history of neurologic disorders.

Methods: An extensive clinical, neurophysiologic, and imaging work-up was carried out. We also investigated antibodies against onconeural proteins and neuronal surface antigens on serum and cerebrospinal fluid (CSF).

Results: Routine blood analysis, EEG, EGM, brainstem auditory-evoked potentials and brain MRI were unremarkable. CSF detected high level of IgG (46 mg/l, normal range: 8,50-34). The antibody panel revealed high serum levels of anti-GAD-65-Abs that was confirmed by tissue-based immunofluorescence. A whole-body CT scan revealed a neoplasm in the anterior mediastinum. Histopathologic study revealed a thymic lymphoma. After tumour treatment, the patient showed a striking clinical and laboratory improvement.

Discussion: Progressive cerebellar ataxia associated with high levels of GAD antibodies is a very rare entity, which is usually associated with concomitant organ-specific autoimmune disorders, such as diabetes mellitus type 1, thyroiditis, pernicious anemia, or vitiligo, that usually precede the onset of ataxia by several years. [3] Even more rare is the association with malignancies, and it has been disputed its role in PNS [2,3], the clinical and laboratory findings in our patients strongly favor a pathogenic link between anti-GAD-65-Abs and cerebellar ataxia and the relationship with the underlying lymphoma. Thus, our case illustrates the need to consider a paraneoplastic etiology in patients with pathologic titers of anti-GAD-65-Abs. In our patient, the early removal of the tumor lead to a better prognosis.

Conclusion: Our study provides new insight into the pathophysiology of anti-GAD-65-Abs, including anti-GAD-65 cerebellar ataxia as clinical presentation of lymphoma. Interestingly, the clinical improvement after tumor removal further confirms the need of a cancer screening in such patients. An early detection and treatment of the underlying etiology may contribute to resolution of the clinical picture.

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NEURO-ONCOLOGY

NEURO-PSYCHOLOGICAL AND METABOLIC COMPLICATIONS OF CRANIOPHARYNGIOMA: A RETROSPECTIVE STUDY

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Objectives: To identify factors associated with neuropsychological and metabolic complications of craniopharyngiomas (CP).

Materials: Data from patients who underwent CP resection in our center from 2000 to 2021

Methods: Retrospective analysis. IBM SPSS v26 was used for statistical analysis.

Results: 54 patients were included in the analysis (32 males). 33 subjects showed a significant weight gain (>10% of body weight) after surgery. 15 patients showed neuropsychological complications after surgery. Neuropsychological complications correlated with volume of the lesion ($p<0.001$), weight gain ($p<0.001$), hyperphagia and overweight before surgery ($p<0.005$). Significant increase in body weight correlated with neuropsychological complication, hyperphagia, post-operative diabetes insipidus ($p<0.001$) and hypopituitarism ($p<0.005$). Post-operative overweight correlated with pre-operative overweight, pre-operative hyperphagia, post-operative hypopituitarism ($p<0.005$). A logistic regression was performed to ascertain the effects of volume and location of the lesion, hyperphagia, BMI before and after surgery on the likelihood of neuropsychological complications. The logistic regression model was statistically significant ($p<.0001$), the model explained 49.1% of the variance in neuropsychological complications (Nagelkerke R2) and correctly classified 83.0% of cases. Greater volumes were associated with increased likelihood to exhibit neuropsychological complications with an increase of 1.006 times for a 1-unit change in volume.

Discussion: Hypothalamic obesity (HO), neuropsychological deficits, and disturbances of circadian rhythms occur at the time of diagnosis in 35% of patients with CP and in up to 65% following treatment [1]. No specific treatment is currently available for HO and neuropsychological complications, which severely impact the quality of life and prognosis of CP patients [2]. The pathogenesis of these alterations is complex and has not been fully elucidated. Besides of obvious structural damage to the hypothalamus and nearby regions, it has been proposed that other mechanisms such as effects on other regions, e.g. an impaired activity of frontal lobes, and the disruption of the oxytocinergic network might participate to these manifestations. Indeed, oxytocin plays an important role in controlling social and emotional behavior, body weight and metabolism as well as reproductive functions [3].

Conclusions: Accordingly with previous studies, our data confirms the association between post-operative increase in body weight and neuropsychological complication, hence supporting the hypothesis of common and possibly synergic mechanism underlying these manifestations. In the regression analysis, the volume of the lesion emerged showed a significant association with the likelihood of development of neuropsychological complications: studies implementing functional neuroimaging to assess the effects of CP in other regions are needed to further understand the pathophysiology of these manifestations and identify possible therapeutic targets.

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NON PARANEOPLASTIC SENSORY GANGLIONOPATHY AS THE FIRST CLINICAL PRESENTATION OF LEPTOMENINGEAL CARCINOMATOSIS: A CASE REPORT

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Purpose: Meningeal carcinomatosis is a rare complication of neoplasms, often in an advanced stage, characterized by leptomeningeal dissemination of cancer cells. We present the case of an atypical presentation of meningeal carcinomatosis, characterized by sensory ganglionopathy as the first clinical manifestation in a patient with breast cancer recurrence.

Case Report: A 56 y.o. woman was admitted to our Neurology Department because of tingling-type paresthesias for about 7 months, onset in the hands and then extended to the feet, with uncertainty in balance and walking. She had an history of breast cancer at 33 y.o. treated with mastectomy, adjuvant chemotherapy and hormonal drugs. The oncological follow-up shows no other recurrence of disease. Neurological examination showed an autonomous but slightly ataxic walking possible on tips and heels but impossible in tandem, Romberg's sign, impairment of touch, vibratory perception, and proprioception, more pronounced in the lower limbs but with asymmetrical distribution, absent tendon reflexes; Lasegue sign was bilaterally absent. ENG/EMG showed a slight reduction of amplitudes of SNAPs with relative sparing of sensory latencies and conduction velocities, a slightly increased minimal latency of F wave from left tibial nerve and normal motor-nerve conduction and needle electromyography studies. CSF analysis demonstrated hypoglycorrhachia, increased protein and cell count; the cytomorphological examination revealed breast cancer derived cells; paraneoplastic antibody detection in serum and CSF was negative. Spine MRI showed diffuse leptomeningeal and radicular thickening with contrast enhancement, minimal in the cervical site and marked in the dorsal and in lumbosacral tract.

Discussion: Paraneoplastic forms of sensory ganglionopathies are due generally to cytotoxic T cells cross-reactivity with epitopes on sensory ganglia neurons induced by neoplastic antigens. However, the continuum with the dorsal roots could make the ganglion susceptible to a direct perineural infiltration of the neoplastic cells. Cancer cells within the CSF upregulate production of complement component that leads to disruption of the BBB and entry of plasma growth factors into CSF, promoting cancer cell growth: the fenestrated endothelial cells that form the permeable blood–nerve barrier of the ganglia, could increase their susceptibility to this process.

Conclusion: Sensory ganglionopathy may be associated with systemic neoplasms not only as paraneoplastic syndrome but also as a meningeal carcinomatosis. Rarely, as in our patient, it is the first clinical manifestation, simulating a polyneuropathy, but without electrophysiological strong correlation and can be revealed only by spinal MRI and CSF analysis.

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BRAIN TUMOUR-RELATED EPILEPSY: IMPACT OF GRADING AND TREATMENTS IN A COHORT OF MOLECULARLY DEFINED LOWER-GRADE GLIOMAS

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Introduction: Brain-tumour related epilepsy (BTRE) is associated with lower-grade gliomas (LGGs) in up to 70-90% of cases. Our study aims to identify which factors are related to seizure control in a large cohort of grade 2 and 3 LGGs patients.

Methods: We retrospectively collected clinical data of LGGs patients with history of BTRE. We retained information about seizure-freedom after surgery, adjuvant treatments, and at recurrence.

Results: 280 patients with LGGs diagnosed between 1988 and 2021 were included. Oligodendrogliomas IDH-mutant 1p19q-codeleted, astrocytomas IDH-mutant and IDH-wildtype were 106 (54.9%), 40 (20.7%), and 47 (24.4%), respectively. Grade 2 and 3 tumours were 199 (71.1%) and 81 (28.9%). Gross-total resection (GTR) accounted for 117 (41.8%) cases. In a multivariable model, seizure-freedom after surgery was positively related to age ≥40 years (OR 2.173, p=0.012) and GTR (OR 2.006, p=0.022), and negatively related to temporal lobe location (OR 0.440, p=0.007) and grade 2 histology (OR 0.271, p<0.001). Similarly, grade 2 histology and temporal lobe location were negative predictors of seizure-freedom after adjuvant treatments (OR 0.169, p<0.001, and OR 0.353, p=0.006, respectively). FLAIR response to adjuvant treatments (complete/partial vs stable disease/progression) was associated with seizure-freedom (84.2% vs 59.4%, p=0.040) regardless of tumour grade. Seizures were a symptom at recurrence in 134 (59.6%) patients. Previous RT significantly reduced the risk of seizures at recurrence (OR 0.343, p=0.010).

Discussion and Conclusion: These data suggest that grade 2 histology increases the risk of seizure persistence after treatment among LGGs. Conversely, GTR and RT are associated with seizure control regardless of tumour grade.

CLINICAL CHARACTERISTICS, TREATMENT MODALITIES, AND OUTCOME OF A COHORT OF 42 ADULT PATIENTS WITH EPENDYMAL TUMOURS OF THE BRAIN: A PILOT ANALYSIS WITHIN MOLECULAR SUBGROUPS

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Background: The 2021 WHO Classification lists two molecularly defined types of supratentorial ependymomas (STEs), i.e., ZFTA and YAP1 fusions,

and posterior fossa ependymomas (PFEs), i.e, PFA and PFB. Based on retrospective data, ZFTA fusion and the PFA subtype seem to correlate with a poorer outcome. However, prospective data on large cohorts of adult patients are lacking, and the role of treatments is uncertain. The aim of our study was to investigate the clinical characteristics, response to treatment, and outcome of a cohort of adult patients with STEs and PFEs across different molecular subtypes.

Patients and Methods: Clinical data of patients >/=18 years with STEs and PFEs were retrospectively collected. ZFTA and YAP1 fusions were detected by FISH, while PFA and PFB subtypes were defined by anti-H3K27me3 immunohistochemistry.

Results: We collected 42 adult patients with STEs (11, 26.2%) and PFEs (31, 73.8%) diagnosed between 1984 and 2021. Median age was 45 years. Extent of resection (EOR) was gross-total (GTR) in 6/11 (54.8%) STEs and 17/31 PFEs (54.8%). 4/11 (36.4%) STEs and 9/31 (29.0%) PFEs received radiotherapy (RT). ZFTA and YAP1 fusions were found in 5 (45.5%) and 1 (9.1%) case of STEs. PFA and PFB subtypes accounted for 9 (29.0%) and 22 (71.0%) cases of PFEs. Median progression-free survival (mPFS) and overall survival (mOS) were both 172 months for STEs patients, and not reached (NR) and 332 months for PFEs. For patients with STEs, the presence of ZFTA fusion correlated with a shorter PFS (64.0 months vs NR, p = 0.05) and with a trend for shorter mOS (168.0 months vs NR, p = 0.307). The only patient with YAP1 fusion had a very long PFS (33 years). In a multivariable analysis, EOR and adjuvant RT did not significantly affect survival of STEs patients. For patients with PFEs, PFA and PFB subtypes did not differ significantly in terms of mPFS (NR vs 137.0 months, p = 0.513) and mOS (NR vs NR, p = 0.132). Conversely, GTR was associated with a significantly longer mPFS (NR vs 63.0 months, p = 0.007) and with a trend for longer mOS (NR vs 332.0 months, p = 0.146).

Discussion and Conclusion: STEs and PFEs of the adult are very rare entities. Our preliminary data on a real-life cohort of adult patients confirm the worse prognosis of STEs harbouring the ZFTA fusion and suggest an impact of the EOR among PFEs regardless of molecular subtypes. Larger populations are needed to better define the role of treatment modalities within molecular subgroups.

LEVETIRACETAM PROPHYLAXIS THERAPY FOR BRAIN TUMOR-RELATED EPILEPSY (BTRE) IS ASSOCIATED WITH A HIGHER PSYCHIATRIC BURDEN

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Purpose: Brain tumor-related epilepsy (BTRE) is a condition characterized by the development of seizures in the context of an undergoing oncological background. Some authors indicate that the high incidence of BTRE justifies the use of prophylactic anti-seizure medications (ASM). Levetiracetam (LEV) is a third-generation ASM widely used in BTRE prophylaxis. The study aims to evaluate LEV neuropsychiatric side effects in BTRE prophylaxis.

Materials and Method: Twenty-eight patients with brain tumors were consecutively selected from 2017 to 2019 and divided into two groups: patients with an ascertain diagnosis of BTRE on anti-seizure treatment (BTRE group) and patients with brain tumor who never had epilepsy and were on prophylactic anti-seizure treatment (PROPHYLAXIS group). Demographics, clinical, neurophysiological, and neuroradiological data of patients of the two groups were assessed. BTRE features, including seizure type, seizure frequency, and anti-seizure therapy, were also evaluated. Neuropsychiatric side effects (SE) of anti-seizure treatment were monitored using the Neuropsychiatric Inventory Questionnaire (NPI-Q) at the baseline visit and 6-month and 12-month follow-up.

Result: 18 patients in the BTRE group and 10 patients in the PROPHYLAXIS group were included. Compared to the BTRE group, the PROPHYLAXIS group showed higher incidence and severity of neuropsychiatric symptoms as assessed by NPI-Q score. According to Linear Mixed Models, a multiplicative effect for the interaction between group-treatment for time (p-value=0.02) was observed. For the caregiver distress score (CDS) only a Time-effect was observed (p=0.001) whereas no additive or multiplicative effect was found.

Discussion: The mechanisms through which LEV can determinate psychotic symptoms is largely unknown and not necessarily related to synaptic vesicle protein SV2A blockade. LEV exhibits broad pharmacological effects due to the interaction with various receptors, including α-amino-3-hydroxy-5-methyl- 4-isoxazolepropionic acid (AMPA) glutamate receptors (AMPAr). AMPAr modulation can also modulate the onset of psychiatric symptoms. Behavioral changes, agitation, anxiety, psychosis, and aggressive behavior, as well as depression, have been largely described in experimental and clinical settings with the use of AMPAr blockers. AMPAr are also largely expressed in the epileptic foci and contribute to the intrinsic excitability of epileptic neurons. The higher AMPAr expression in BTRE patients may explain the reduced burden of LEV-related psychiatric side effects in this group.

Conclusions: Prophylactic anti-seizure treatment with LEV is associated with increased neuropsychiatric adverse effects. These results stress the importance of accurate epileptological evaluations in patients with brain tumor to carefully select the ones who would benefit most from anti-seizure therapy.

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NEUROLOGICAL ADVERSE EVENTS IN MITOTANE TREATMENT OF ADRENOCORTICAL CARCINOMA

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Our study is aimed to investigate the relationship between mitotane blood levels and central neurological toxicity because of few cases are described in literature [1] in cancer patients. Mitotane is the only drug approved by FDA for the treatment of patients affected by adrenocortical carcinoma (ACC) and can be used in adjuvant monotherapy or in combination with other cytotoxic drugs in the metastatic disease. It acts by inhibiting adrenocortical steroid synthesis and inducing carcinoma cells apoptosis [2]. Despite its efficacy, mitotane is associated with several side effects. Some of them are well known (endocrinological and gastrointestinal toxicity). Other ones, such as neurotoxicity, are rare and less known since they are associated to higher doses administration. They are: ataxia, somnolence, muscle tremors, vertigo and cognitive deficits [3]. Neurotoxic sequelae appear to be reversible after treatment discontinuation. We studied 4 patients mean age 50, 3 females and 1 man, with diagnosis of ACC and no previous cognitive impairment or neurological diseases, treated with mitotane. We examined them when neurotoxicity due to increased plasma values mitotane (therapeutic range 14- 20 mg/L) was suspected. They

underwent to neurological examination (NE), neuropsychological assessment (NA), EEG (electroencephalogram)and event related potentials (P300). We evaluated them at T0, T1 (three months) and T2 (twelve months) times with T0 mitotane toxic concentrations. At T0 we found that all patients showed EEG abnormalities and increased latency of P300; three patients had selective visual-constructive deficit and one patient had ideo-motor slowdown. At T1 plasma mitotane levels were normal for all patients after reduction dosage therapy except in one. The only patient with mitotane toxic concentrations showed ideo-motor slowdown concentration and abnormal NA. In two patients, despite normal plasma value of mitotane, abnormalities of EEG and P300 persisted. At T2 a second mitotane toxicity was observed in 3 patients that had normal NE, NA and EEG but abnormal P300. In the patients with normal mitotane concentration all the neurological exams were normal. The preliminary results of our ongoing study evidence neurophysiological and visual-constructional abnormalities associated to above thresholds mitotane values, in particular P300 and EEG showed a greater sensitivity. In fact, the electrophysiological abnormalities persisted overtime, despite normalization of mitotane values and it could be the sign of a prolonged toxicity. Our study, furthermore, showed an interesting result on the neuropsychological deficit that was restricted only to visual-constructional domain. Further studies will be needed to better understand the toxic effects of mitotane on neurocognitive function

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GLIOMAS AND INFLAMMATORY DEMYELINATING DISEASES: CASUAL OR CAUSAL ASSOCIATION? CASE REPORT AND LITERATURE REVIEW

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Aims: Several studies showed higher incidence of brain tumors in multiple sclerosis (MS) patients. Although a surveillance bias may contribute to this finding, this data is well known and described in approximately one-hundred patients. In most cases MS diagnosis preceded glioma by years. Glioblastomas or high-grade astrocytomas are the most frequently reported. We describe a MS patient who developed an astrocytoma and we discuss some hypotheses about the possible reason for this association.

Materials and Methods – Case Report: A 52-year-old patient was admitted in August 2021 for seizures. Patient was affected by Primarily Progressive MS since 2013. Over the years, he was treated with Cyclophosphamide and Azathioprine, with partial benefit. From 2020 patient had epileptic secondary seizures. A brain MRI showed, in addition to demyelinating disease, a bilateral frontal lesion with enhancement, suspected for high-grade glioma. A brain biopsy showed an IDH1-mutated anaplastic (WHO grade III) astrocytoma. Temozolomide was started, and the indication for radiotherapy was discussed.

Results and Discussion: Several studies hypothesized that gliomas in MS may arise as a result of gliosis following an inflammatory demyelinating process. During and after active inflammation, there is a proliferation first of the oligodendrocytes involved in the repair process of the myelin sheath and, secondarily, of the astrocytes involved in the process of gliosis. During these processes, immunosuppressive factors (such as NGF and IL-10) are overexpressed. These factors limit the inflammatory injury but increase the risk of tumor transformation [1]. Other authors have highlighted the role of JC virus. The virus regulates the expression of some oncoproteins, and it would seem able to modulate the expression of oncosuppressors p53 and pRB [2]. This virus, founded more frequently in MS patients and also in glioma cells, could have an oncogenic role, also in association with the processes of inflammatory modulation as already described [3].MS therapies could also increase the risk of developing glial lesions. Many therapies promote an anti-inflammatory Th2 cytokine profile and inhibit the pro-inflammatory response. High-grade gliomas use a similar mechanism to evade the immune response, suppressing the antitumor cytotoxic response through IL-10 and TGF-β secretion. Therefore, pharmacological and tumor immunosuppression can contribute to promoting gliomatogenesis.

Conclusions: Although the coexistence of glioma and demyelinating disease is rare, there is probably a causal relationship between the two. Several hypotheses have been proposed, mainly based on the role that chronic inflammation and the immune response modulation have in oncogenesis.

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EMPLOYMENT OUTCOME AFTER BRAIN TUMOR DIAGNOSIS IN PATIENTS AND CAREGIVERS. A SINGLE INSTITUTION STUDY

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Brain tumors (BT) affect a patient's ability to work. Many BT patients are employed at the time of diagnosis but frequently the decision to stop working may represent a subsequent event driven by brain tumor (BT) diagnosis. This retrospective study highlights the ongoing need of information targeting BT patients ability to work and to facilitate the management of employment

and financial issues early in the BT trajectory. Moreover, caregivers have also a significant burden of disease with strong influences on employment.

Methods: 213 BT patients assisted at Regina Elena Cancer Institute of Rome between April 2015 and May 2018 and their Caregivers (CG) were included in this study. Employment status was assessed during social work visit at baseline (first visit after diagnosis) and at follow up visit after a mean time interval of 12 months.

Results: Patients: at baseline 81 patients (38%) resulted employed and 106 (50%) resulted retired. 12% resulted unemployed (student; housewife; out of work). At follow-up assessment 67 (31%) were still employed (58 with reduction of work ability) and 136 (64%) were retired.

Caregivers: At baseline among 81 caregivers evaluated 52% resulted employed, while at follow-up assessment 43% were still employed and 8% reported a reduction of work activity

Discussion: The results of this study show that work ability and return to work is a significant issue, as approximately 50% of patients have jobs at the time of diagnosis. In addition, modification of employment status needs to be better evaluated in order to facilitate patients social recovery. To support return to work represents not only recovery of financial ability but also improvements in patients and caregivers quality of life.

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STAT3 EXPRESSION IN BRAIN METASTASES FROM BREAST CANCER: CORRELATIONS WITH DIFFERENT MOLECULAR SUBTYPES AND CLINICAL OUTCOME

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Background: STAT3 expression in peritumoral reactive astrocytes (RA) of brain metastases (BM) may favor a pro-metastatic environment. The aim of the study was to evaluate in a retrospective cohort of surgically resected BM from breast cancer (BC) the expression of pSTAT3 in RA of peritumoral tissue of BM, identify different patterns of expression according to molecular subtypes, and correlate with intracranial progression-free survival (i-PFS).

Material and Methods: Patients with histologically proven BM diagnosis from BC were identified from the biobank of Pathology Unit of University of Turin and Spanish national BrM network (RENACER). pSTAT3 expression was evaluated and scored in RA of peritumoral tissue using GFAP and STAT3 immunohistochemistry, according to Priego et al. [1]. Data on histological diagnosis, molecular subtypes, and i-PFS were retrieved by chart review. Intracranial progression was defined based on the reports of MRI examinations.

Results: Eighty-five BM specimens from BC of 85 female patients with a median age of 54 years (range 30–81 years) were available for analysis. Immunohistochemistry for GFAP and pSTAT3 was feasible in 68/85 (80%). Fifteen out of 68 patients (21.1%) had BM from luminal BC, 27/68 (39.7%) from HER2-positive BC, and 26/68 (39.2%) from TNBC. Fifty-six out of 68 (82.4%) showed positive staining of pSTAT3 in peritumoral RA, of which 9/68 (13.3%) scored with 3, 26/68 (38.2%) with 2, and 21/68 (30.9%%) with 1, while pSTAT3 expression was negative (score 0) in 12/68 (17.6%). High pSTAT3 expression (score 2-3) was observed in 17/27 (62.9%) BM from HER2-positive BC and in 15/26 (57.7%) BM from TNBC, while most of BM from luminal BC (12/15 – 80%) had low or absent pSTAT3 (score 0-1) (p=0.021). Overall, i-PFS was 16 months (range 7-41): low pSTAT3 BM (score 0-1) had a median i-PFS of 21 months versus 12 months for high pSTAT3 BM (score 2-3). A shorter median i-PFS was observed in high pSTAT3 BM from TNBC (4 months) as compared with low pSTAT3 BM (11 months). Conversely, i-PFS of high pSTAT3 BM (7 months) was similar to low pSTAT3 BM (6 months) in HER2-positive BC.

Conclusion: pSTAT3 expression in RA of peritumoral tissue of BM from TNBC and HER2-positive BC is higher than in BM from luminal BC. Of note, patients with high pSTAT3 BM from TNBC progressed earlier in comparison with those with low pSTAT3, suggesting that pSTAT3 expression has an influence on the outcome.

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PLASMA CFDNA LIQUID BIOPSY IN THE FOLLOW-UP OF HIGH-GRADE GLIOMAS

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Background/Aims: As highlighted by the 2021-WHO classification of brain tumors [1], molecular characterization of gliomas is now critical to complement histopathology. However, intratumor heterogeneity may lead to surgical biopsies not fully-representative of whole tumors and tissue analyses are not repeatable over time, limiting the possibility to monitor therapeutic response. In this context, non-invasive molecular profiling of body fluids may support patients' management [2]. To investigate the potential value of cell-free DNA (cfDNA) in plasma as marker of high-grade glioma evolution, we collected

patients' blood samples at 4 time points (TP) during clinical follow-up and analyzed plasmatic cfDNA concentration/molecular status.

Materials and Methods: A reproducible pipeline was optimized for blood-withdrawal, centrifugation, plasma-storage, cfDNA-extraction from plasma by QIAamp MinElute-ccfDNA Midi-Kit and cfDNA fluorometric quantification by Qubit [3].

Results: We analyzed plasma-cfDNA of 35high-grade glioma patients and 14healthy subjects. Blood samples were collected from all 35patients at radiological diagnosis before surgery (TP0), from 15patients after surgery before starting radio-chemotherapy (TP1), from 8patients after completing radio-chemotherapy (TP2), from 2patients at the first radiological progression (TP3). At T0, a significantly higher plasma concentration of cfDNA was detected in high-grade gliomas than in controls($p<0.0001$). when comparing 5IDH-mutant with 20IDH wild-type gliomas, we found a trend toward higher basal cfDNA in the latter group($p=0.169$). Digital-droplet-PCR, performed at T0 on plasma of 4/5 patients with IDH mutations in tumor tissues, identified the same IDH1R132H mutations in all cases. When cases were considered singularly and cfDNA content at TP0 was compared to that at TP1 of the same patient (n=15), there was a significant reduction of cfDNA after surgery, mirroring the extensive tumor resection shown by Magnetic Resonance Imaging (MRI) (paired-comparison $p=0.0006$). At T1, cfDNA concentration in patients became similar to healthy controls. Finally, plasmatic concentration of cfDNA was evaluated in 2patients with glioblastomas at their radiological progression, suggested by enlarged area of T2-MRI hyperintensity and boosted contrast-enhancement in T1-MRI. A mild increase of relative-cerebral-blood-volume in Perfusion MRI was visible in the first patient, not in the second one, but it was not sufficient to discriminate between real progression or radionecrosis. Interestingly, cfDNA plasmatic concentration raised by 50%in the first case, while decreased by 58%in the second one, strengthening the probability of real-progression in the first case, pseudoprogression in the second case.

Conclusion: Our preliminary results suggest that plasma cfDNA content may be an informative tool to complement brain tumor follow-up. Further studies will help to clarify whether evaluating cfDNA at patients' radiological progression may help to discriminate real-progression and pseudoprogression.

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CAR-T RELATED NEUROTOXICITY: A SINGLE CENTER EXPERIENCE AND APPLICATION OF MULTIVARIABLE PREDICTIVE SCORES

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Objectives: The "immune effector cells-associated neurotoxicity syndrome" (ICANS) is a recognized complication of Chimeric antigen receptor T cells (CAR-T)-based therapies for hematologic cancers. Usually, it develops post or in occurrence with the "cytokines-release syndrome" (CRS) [1]. Predisposing risk factors for ICANS are not yet fully understood. The Boston group developed a score (cut-off=6) based on clinical and blood parameters [2]. Moreover, Endothelial Activation and Stress Index (EASIX) score may predict severe toxicity [3]. The aim of this study is to evaluate the incidence of neurotoxicity and to applicate the predictive tools in our cohort of patients.

Methods: The BioCAR-T BS study (ClinicalTrials.gov: NCT05366569) is an observational, prospective study, enrolling patients treated with CAR-T cells from April 2021 to May 2022 at ASST Spedali Civili of Brescia. Both clinical and laboratory data before lymphodepletion and after CAR-T infusion were collected in order to be related with ICANS.

Results: A total of 11 patients entered the study (female= 6, median age: 59). Eight patients were diagnosed with DLBCL, two with PMBCL and one with ALL. The Boston score was ≥6 in 8 patients (72.7%); 2 of latter developed ICANS (grade 2 and 3), showing diffuse slowing at EEG. Among the analysed parameters, lower levels of IL-6 at baseline ($p=0.04$) and of ferritin post-infusion ($p=0.03$), as well as late onset CRS ($p=0.04$) were associated with neurotoxicity. Conversely, post-infusion IL-6 levels correlated with CRS. A trend between post-infusion high-score (HS) EASIX and CRS has been noted, while no relation with ICANS was observed.

Discussion: 18.2% of patients developed ICANS. These patients presented a high risk of neurotoxicity according to Boston score. However, only 2 of the 8 patients with Boston score higher than 6 developed ICANS. Interestingly, low levels of ferritin and IL-6 were associated with ICANS development, confirming that other inflammatory patterns than the ones usually related with CRS are involved in ICANS development. Endothelial damage may also play a crucial role in CRS and ICANS development. In our study, HS-EASIX was related with CRS only, but larger studies are needed to better investigate the endothelial involvement in neurotoxicity post CAR-T cells infusion.

Conclusion: ICANS is a challenging neurological side effect post CAR-T cells infusion. Scores predicting its development are needed. Our study confirms that inflammatory markers usually used for CRS are not useful in predicting ICANS. On the other hand, it confirms ICANS relationship with late-onset CRS. Larger studies exploring different inflammatory patterns and endothelial activation are needed.

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PITUITARY METASTASIS AS A PRESENTING MANIFESTATION OF SILENT GASTRIC CARDIA ADENOCARCINOMA

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Background: Pituitary metastases (PM) represent only 0.4% of cerebral metastases and up to 3.6% of pituitary tumors. They usually occur in patients with a known metastatic disease, but may rarely be the first presentation of the primary tumor. They often originate from breast, lung, kidney and prostate tumors. Here we describe the case of a patient in whom symptoms of pituitary metastasis represented the first manifestation of an occult gastroesophageal junction adenocarcinoma.

Materials and Methods: We present the case of 58 years-old-man who reported a three-month history of polyuria-polydipsia syndrome, generalized asthenia, panhypopituitarism, and bitemporal hemianopsia. Brain-MRI showed a voluminous pituitary mass (18.5x19.5x15.5 mm diameter) causing posterior sellar enlargement and compression of the surrounding structures including pituitary stalk, optic chiasm, and optic nerves.

Results: The patient underwent neurosurgical removal of the mass. Histological examination revealed a poorly differentiated adenocarcinoma of uncertain origin. A total-body CT scan showed a mass in the left kidney that was subsequently removed. Histological features were consistent with a clear cell carcinoma. However, endoscopic examination of the digestive tract revealed an ulcerating and infiltrating adenocarcinoma of the gastric cardia. Total-body PET/CT scan with 18F-FDG confirmed an isolated area of accumulation in the gastric cardia, with no hyperaccumulation at other sites.

Discussion and Conclusion: To the best of our knowledge, there is no report of pituitary metastases from gastroesophageal junction adenocarcinoma. Our patient presented with symptoms of sellar involvement and without evidence of other systemic metastases. Therefore, sudden onset of diabetes insipidus and visual deterioration should lead to the suspicion of a rapidly growing pituitary mass, which may be the presenting manifestation of a primary extracranial adenocarcinoma. Histological investigation of the pituitary mass can guide the diagnostic workup, which must however be complete.

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WHITE MATTER DENSITY PREDICTS OVERALL SURVIVAL IN GLIOBLASTOMA: A NEW CONNECTIVITY FRAMEWORK FOR BRAIN TUMORS

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In this study we hypothesize that the impact of the tumor is not independent from white matter (WM) organization and that tumor localizing where the tracts density is higher are associate to a worst outcome. The aim was to explore the relationship between the impact of GBM to WM tracts and the outcome. To this scope we computed a new connection density index to quantify the average number of white matter connections affected by a GBM. The study was conducted retrospectively on two independent GBM datasets: discovery dataset from the University Hospital and the Venetian Institute of Oncology of Padova, Italy. A second dataset (referred as the replicative dataset) from the Department of Neurosurgery - Charité University of Berlin, Germany. An average diffusion map was computed from the Human Connectome Project dataset, using the available data from 170 healthy controls probabilistic tractography to reconstruct WM streamlines. The resulting average map represented the mean number of WM streamlines passing for each voxel of the brain. Normalized GBM of each patient was then over imposed to this average streamline map and used as a mask to compute a density index. The density index corresponds to the mean number of streamlines (per voxel) within the tumor mask. We explore the statistical relationship between density index and overall survival (OS), the prediction of OS from density index with linear correlations, linear and Cox regression, Kaplan-Meyer analysis, in both datasets. In a first cohort of GBM patients (n=92) we found that the connectivity density index significantly correlated with overall survival (OS) ($r=-0.46$, $p<0.001$), and that this relationship was stronger than other prognostic factors (i.e. age, MGMT methylation, surgery extension, performance status). When we added the density index to the prediction model of survival, the variance explained increased by 10% with a log-rank $p < 0.001$ in a Kaplan-Meyer analysis. Similar results were found in the replicative dataset. When we tested this connectivity density index in an independent cohort (n=52), OS prediction showed an overall accuracy of 84%. Our results suggest that GBM prognosis strongly depends on the location of the tumor. The analysis of brain connections affected by GBM can be a useful presurgical predictor of OS and a necessary covariate for disease-modifiers clinical trials. This study supports from a perspective in which GBMs are isolated from the brain architecture to one in which they interact with it.

PATTERNS OF CORTICAL AND WHITE MATTER NETWORKS' INVOLVEMENT IN GLIOBLASTOMA MULTIFORME: INDIRECT MAPPING FROM CLINICAL MRI SCANS

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Objectives: The brain is organized in "networks" of functionally interconnected grey and white matter regions. Resting-state functional MRI (R-fMRI) studies have identified a small number of cortical brain networks (CNs) identified by the temporal correlation of the blood oxygenation level dependent (BOLD) signal, the so-called resting-state networks (RSNs) [1]. Similarly, an emerging body of literature identified corresponding white matter functional networks, so called white matter networks (WMNs) [2]. The aim of this study was to describe and quantify the impact of glioblastoma multiforme (GBM) lesions and the brain's functional organization in terms of relative overlap with cortical and white-matter functional networks. While future studies will consider the patterns of disconnection, the current study is limited to the primary locus of GBM lesions.

Materials: Inclusion criteria: histopathological diagnosis of GBM, and pre-surgical routine MRI acquisitions.

Method: GBMs were segmented and normalized to a standard space (MNI). Networks were defined accordingly with Yeo's 7 CNs and Peer's 12 WMNs parcellation. For each functional network we computed the percentage of voxels hit by GBM, weighted for the overall size of the networks. Statistical analyses included linear correlations, ANOVA, t-tests and Bonferroni's correction for multiple comparisons. The significance level (alpha) used was 0.05.
Results: N=92 patients were included in the study. GBMs variably overlapped with brain networks: the DMN and superior longitudinal fasciculus (N5) were most frequently involved networks at the individual level (91/92 and 87/92 patients), whereas VIS and the posterior cerebellar tracts (N9) were the least frequently involved (45/92 and 33/92). VAN and the ventral front-parietal tracts (N12) had the highest mean percentage overlap (7.43% and 7.08%), while VIS and N9 the lowest (1.8% and 0.17%). ANOVA showed significant differences in mean percentage network overlap ($F=11.2$, $p<000.1$, between CNs; $F=9.9$, $p<0.0001$, between WMNs; $F=9.96$, $p<0.000.1$ among all networks). GBM lesions hit in a joint manner multiple association networks like VAN, DAN, FPN, and underlying white matter tracts involved in cognitive functions. These cortical and white matter networks were strongly correlated in terms of their overlap with GBMs.

Discussion: GBMs hit predominantly cognitive networks involved in memory (DMN), attention (DAN, VAN), executive functions (FPN) and associated white matter networks. Our findings are consistent with the cognitive profile of these patients.

Conclusions: This pattern of network impairment may guide surgery and rehabilitation.

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HEALTH PROFESSIONAL INVOLVEMENT IN THE FORMULATION OF THE CLINICAL QUESTIONS: THE GUIDELINE ON PALLIATIVE CARE IN ADULTS WITH GLIOMA

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Background: In 2017, the European Association for Neuro-Oncology (EANO) published the guideline for palliative care (PC) in adults with glioma [1]. The Italian Society of Neurology (SIN), the Italian Association for Neuro-Oncology (AINO), and the Italian Society for Palliative Care (SICP) joined forces to update the guideline, and adapt it to the Italian context. To obtain this, we involved patients, caregivers and (herein presented) health professionals in the formulation of the clinical questions [2].

Methods: Online survey of health professionals experienced in the care of patients with glioma. Participants rated the importance of 14 pre-specified intervention topics on a 0/10 scale, and gave their free comments.

Results: Of 244 participants, 149 (61%) were PC health professionals and 95 other health professionals. Their mean age was 48.9 years, 63% were women, and 48% had over 12 years of experience in the care of glioma patients. Physicians were 68%, followed by nurses (28%), psychologists (7%), therapists (3%), and social workers (2%). Most professionals rated the pre-specified topics as 'important' (score ≥ 7) or 'critical' (score ≥ 9), with some differences across the two groups. Specifically, a significantly higher proportion of PC professionals (vs. other professionals) gave a 'critical' score to the following 6 topics: spiritual/existential support, advance care planning, end-of-life, bereavement, health professional's psychological support, and health professional's training in PC. There were 41 free comments: 36 (88%) on 9 of the pre-specified topics, and 5 on new topics, 3 of which were guideline-pertinent (caregiver's support and education, general practitioner's training in neuro-oncology, and PC health professional's training in neuro-oncology).

Conclusions: Participation in the survey was high, and information-rich. The differences between the two health professional groups in scoring reflect their background. These data will inform the formulation of the guideline clinical questions.

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PATIENT AND CARER INVOLVEMENT IN THE FORMULATION OF THE CLINICAL QUESTIONS: THE GUIDELINE ON PALLIATIVE CARE IN ADULTS WITH GLIOMA

A. Solari[1], S. Veronese[2], E. Bertocchi[2], B. Lissoni[3], L. De Panfilis[4], G. Dalla Verde[2], R. Merli[5], R. Rudà[6], A. Silvani[7], A. Pace[8]

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Background: Stakeholder involvement in clinical practice guideline development is recommended to increase guideline trustworthiness and relevance [1,2]. In 2017, the European Association for Neuro-Oncology (EANO) published the guideline for palliative care (PC) in adults with glioma [3]. The Italian Society of Neurology (SIN), the Italian Association for Neuro-Oncology (AINO), and the Italian Society for Palliative Care (SICP) joined forces to update and adapt these guidelines to the Italian context; and (herein presented) to involve patients and carers in the formulation of the clinical questions.

Methods: Semi-structured interviews with glioma patients and focus group meetings with family carers of deceased patients. Participants were invited to appraise the importance of 14 pre-specified intervention topics produced by the guideline panel, share their experience, and suggest additional topics. Interviews and focus group meetings were audio-recorded, transcribed, coded and analysed (framework and content analysis).

Results: We held 20 interviews and five focus group meetings (29 carers). Patients and carers considered communication and psychological support as the most important topics, and reported difficulties in dealing with behavior and personality changes. Patients emphasized the impact of focal neurological and cognitive deficits. Carers focused on the importance of preservation of functioning via rehabilitation and social support. Both affirmed the importance of a dedicated health care path and patient's involvement in the decision-making process.

Conclusions: Interviews and focus group meetings were well informative but emotionally demanding. Participants confirmed the importance of all the pre-specified intervention topics, with no additional issues identified. Our findings strengthen the importance of a comprehensive care approach in glioma patients, and of addressing the needs of patients as well as of their family carers.

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TELE-NEUROREHABILITATION: A REPORT FROM THE NEURO-ONCOLOGY OF "REGINA ELENA"

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Introduction: Malignant gliomas patients frequently experience cognitive deficits along the disease course, leading to significant functional limitations [1]. Attention, memory and executive deficits are the most frequent ones [2]. Furthermore, the increased patients' survival, due to treatment improvements, often determines a longer coexistence with cognitive sequelae. Thus, neuropsychological rehabilitation has become relevant in disease management and tele-rehabilitation can have positive implications in terms of adherence to treatment and effectiveness [3]. The aim of this retrospective observational study was to evaluate the impact of tele-neurorehabilitation in malignant gliomas patients.

Methods: Among patients followed by the neuro-oncology unit of Regina Elena National Cancer Institute between 2018 and 2021, 40 patients (mean age: 54.2; HGG:29) underwent neurocognitive baseline and follow-up assessment (median interval: 7 months) tapping on 7 cognitive domains. A subgroup of 20 patients (mean age: 50.9; HGG: 15) who could undergo cognitive tele-rehabilitation was treated twice a week for 2 months. Demographical and clinical data were collected. Training comprised exercises from the software ERICA (Giunti Psychometrics), mixed with psychoeducation and teaching of compensatory strategies.

Results: Patients in the treated subgroup resulted to be younger (mean age:50.9 vs 57.5 years) and with a longer illness duration (median: 18 vs 11 months) than non-treated ones. No differences were found about tumor grade. At baseline, all patients showed at least 1 impaired cognitive domain (median:1), without significant differences between the two groups. Most affected cognitive domains were executive functions (n: 24) and long-term memory (n:19). At follow-up assessment, treated patients performed significantly better than untreated ones (p: 0.001), who showed a further deterioration. 13 out of the treated patients improved their performance (7 showed no deficit) and 7 remained stable. Conversely, in the group of untreated patients 13 showed stable status, 6 resulted deteriorated and 1 improved.

Conclusions: Our results confirm the positive effect of neurocognitive tele-rehabilitation in brain tumor patients but highlight the importance of improving its accessibility for older and more fragile patients that often face technical problems resulting excluded from benefits.

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CARBOPLATIN IN MALIGNANT GLIOMAS AFTER FAILURE OF DIFFERENT LINES OF TREATMENT

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Purpose: Patients with relapse of recurrent glioma have a poor outcome and limited treatment options. The aim of this study is to investigate the clinical benefit and tolerability of weekly intravenous administration of carboplatin-based monotherapy in adult glioma patients who had progressed from previous chemotherapy lines.

Methods: We included progressive or recurrent malignant glioma after radiotherapy and chemotherapy-based treatments and Karnofsky Performance Status (KPS) > 60 with failure of two lines of chemotherapy.

Results: 53 patients (median age: 43.5 y), 38 male (72%) and 15 female (28%) were enrolled to receive weekly carboplatin monotherapy in intravenous mode of administration. 32 patients received carboplatin as third line, 21 after four lines. 45% are glioblastoma and 29 are other gliomas. Median progression-free survival (PFS) was 2.3 months while overall survival (OS) was 5.6 months. Patients that received carboplatin at third line have a better prognosis than other. Glioblastoma at a median PFS at 4 months than 2 months of other gliomas.

Conclusions: Our findings show that single agent, weekly, intravenous carboplatin may have a role in the treatment patients with recurrent malignant glioma, in particular GBM at third lines

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MPGIRE: MOLECULAR PROFILE IN GLIOMA PATIENTS AT THE REAL WORLD STUDY AT REGINA ELENA NATIONAL CANCER INSTITUTE

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Since the update of the 5th edition of the WHO Classification of Central Nervous System 2021, particular molecular characteristics are part of the definition of a subset of these neoplasms. This combined 'histo-molecular' approach allows for a much more precise diagnosis of especially diffuse gliomas. Defining molecular markers for diffuse gliomas are IDH1/IDH2 mutations, 1p/19q codeletion and mutations in histone H3 genes. In the new who classification IDH mutation it is important while diagnostic factors. It has been found to be an inciting event in gliomagenesis and to have a profound effect on the molecular and genetic route of oncogenic progression and on clinical outcome. The aim of the study is evaluate the role of MGMT and IDH1 mutation and the role of histology.

Results-Participants: We analysed data of 284 patients (168 males, 116 females) with a mean age of 55.4 ± 15.3 years who received a diagnosis of glioblastoma (n=183), astrocytoma (n=67), oligodendroglioma (n=34); Therefore, patients with glioblastoma were older than those with astrocytoma and oligodendroglioma ($p<0.001$), as well as patients with astrocytoma were older than those with oligondendroglioma ($p=0.015$). There was no significant differences across tumour subtypes in the remaining demographic and clinical characteristics at baseline. Overall, 195 (68.7%) patients died, of whom 150 (92.0%), 34 (50.7%), and 11 (32.4%) were affected by glioblastoma, astrocytoma, and oligodendroglioma, respectively. The median OS was 1.3, 9.3 and 21.5 years for glioblastoma, astrocytoma, and oligodendroglioma, respectively. A total of 230 (81.0%) patients experienced disease progression over the follow-up, of whom 164 (89.6%), 44 (65.7%), and 22 (64.7%) were affected by glioblastoma, astrocytoma, and oligodendroglioma, respectively. The median PFS was 0.9, 4.8 and 8.6 years for glioblastoma, astrocytoma, and oligodendroglioma, respectively. When we add the IDH1 mutation and for GBM mgmt. METHYLATION we observed that gbm are poor prognosis according to literature. Also astrocytoma WT have poor prognosis than Astrocitoma mutant but have a better prognosis than Glioblastoma. Oligodendroglioma has the best prognosis between these groups but difference we observed between ologodendroglioma mutant and WT ($p<0.001$).

Conclusion: This preliminary result confirm the role of IDH1 mutation and MGMT methylation on OS and PFS but it is important the role of histology. According to new classification is very important larger clinical studies are necessary to confirm preliminary data.

CLINICAL NEUROPHYSIOLOGY

CLINICAL METHODOLOGY FOR THE APPLICATION OF THE PROCESS OF COGNITIVE NEUROMODULATION

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Introductions: This can't be a clinical's study but a short introduction of the method throw wich we realize the cognitive-behavioural neuromodulation. In this presentation will be explained all the algorithms used to develop the neuromodulation's method.

Materials and Methods: Will be showed the meanings of the following elements:

1. how we register the EEG traces, the VEP AEP and visual AND auditory ERP

2. how we execute the followings analysis: a. mapping EEG/ERP; b: wavelet analysis; c: COHERENCE of EEG TRACES, d: non-linear analysis. Will be explained how these data are useful to build a neuromodulation's process

Comments: The author will give preliminary data how the method work and how they can be treated. Some example of the method will be show in another presentation.

Reference:

– Event Related Potentials (A Methods Handbook) Todd C, Handy MIT PRESS (2005)

COGNITIVE NEUROMODULATION CLINICAL APPLICATION

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Introduction: The theoretical bases for the application of "Cognitive Neuromodulation" were the subject of extensive description in another presentation. In this study, we will describe the results for the following clinical classes: - ADHD, PARKINSON, DEPRESSION.

Material and Methods: 1 subject was included for each clinical class randomly chosen by the author by entering the diagnosis and choosing the first of the list of each class .all subjects had received a diagnosis with adequate tests for: ADHD, Parkinson's M, depression, later they were subjected to the following investigations: 1.EEG With Frequency Maps, 2.VEP AEP P300 Visual, P300 Auditory, 3. Analysis of the Coherence of EEG Tracks, 4. Wavelet Analysis of visual potentials tracks and visual and auditory ERPs. This work made it possible to identify the frequencies and location for both EEG tracks with frequency maps and the latency and amplitude values of the visual AEP P300 and P300 auditory VEP. The following instruments were used for the analyses: 1. Micromed EEG recorder, 2. coherence software, 3. Tought Techonology equipment.

All the data collected have allowed us to build a Neuromodulation protocol that is completely peculiar to the patient. Each subject followed a cycle of 12 sessions of Neuromodulation lasting 45 minutes. Every 4 sessions the recording of visual EEG VEP AEPp300 P300 auditory and related analysis was performed with the aim of verifying the modification of the frequencies / location, if the modification had occurred, the quality was evaluated to decide whether to do another cycle.

Results: The evaluation made it possible to significantly modify the clinical situation both with regard to global variations (EEG) and local ones (VEP AEP P300 VISUAL P300 AUDITORY). The target parameters have changed significantly and we plan to expand the subjects of these groups for a more exhaustive presentation both in terms of the size of the different samples and for statistical analysis. this method appears to us in the light of the results produced a good model even if the algorithms used are complex, but has a low invasiveness and does not require complex and expensive equipment.

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ELECTROENCEPHALOGRAPHY, MULTILEVEL ANALYSIS AND THEIR CORRELATIONS. METHODOLOGICAL AND CLINICAL ASPECTS

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Introduction: The first EEG recording dates back to 1875, when Caton recorded brain electrical activity in the monkey and dog. 50 years later in 1924, H. Berger recorded the brain bioelectric activity with the discovery of alpha and beta rhythms. The recording of the EEG over time has evolved, with the acquisition of new and powerful computational tools, which have brought out aspects of the track that are not visible to simple visual inspection. These include a special attention to the experience of the authors of the work: 1. Analysis with frequency maps; 2. Frequency coherence analysis; 3. Nonlinear dynamic analysis.

Materials and methods: The authors developed a series of algorithms, already known in the literature, to correlate them with each other in order to obtain a verifiable system for both clinical definition and therapy. The methods described are: a. EEG recording with mean reference; b. analysis with frequency maps c. Calculating coherence in the 4 frequency bands defined in the maps d. Nonlinear dynamic analysis with calculation of the following parameters: delay, embedding dimension, correlation dimension, large Lyapunov exponent.

Conclusions: This data set shows the possibility of integrating the different EEG signal analysis algorithms in a clinically meaningful way, thus allowing us to verify possible changes in relation to the different therapies. In this presentation we will describe the different electrophysiological parameters in relation to normal subjects, with minimal cognitive impairment. The data highlight a clear difference between normal and MCI subjects, confirming the clinical usefulness of the parameters described.

References:

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NEUROPHYSIOLOGICAL CHANGES IN CIDP PATIENTS DURING SCIG TREATMENT: RESULTS FROM A SINGLE CENTER POPULATION

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Objectives: To evaluate changes in nerve conduction studies (NCS) in patients affected by chronic inflammatory demyelinating polyneuropathy (CIDP) during treatment with subcutaneous immunoglobulin (SCIg) [1, 2].

Materials: We analyzed electroneurographic data of patients followed at our Neuromuscular Diseases Center with a diagnosis of definite CIDP (as defined by EFNS/PNS criteria [3]), treated with SCIg.

Methods: We performed sensory and motor conduction studies, analyzing sensory nerve action potential (SNAP) and compound muscle action potential (cMAP) distal sensory and motor latency (dL, DML), distal negative peak amplitude (dA), conduction velocity (CV) and motor conduction blocks (calculated as CMAP amplitude or area reduction of more than 50%) of median, ulnar, tibial, peroneal and sural nerves. NCS were performed before SCIg treatment (t0) and every 12 months during the treatment (i.e., t1, t2, etc). Results were analyzed using Mann-Whitney U test.

Results: We included 21 patients (12 men and 9 women, 56 +/- 11.5 years) with typical CIDP at baseline. At the time of the analysis, 4 patients completed 1 year follow-up, 7 patients completed two years follow-up, and 2 patients completed 3 years follow-up. 8 patients did not reach one year of treatment. We observed that all the parameters studied did not change significantly during all the evaluations (each p value >0.05). We noted just a slight non-significant mean increase of CV recorded from

right peroneal (t0 29.4 +/- 13.2 m/s vs t1 35.54 +/- 20.8 m/s; p= 0.10) and left sural nerve (t0 44.4 +/- 5.5 m/s vs t1 52.5 +/- 19.7 m/s; p= 0.10).

Discussion: SCIg was proven to be a safe and effective maintenance treatment for CIDP patients. However, there are no available data in literature regarding long-term efficacy. Our work shows that nerve conduction parameters remain stable even after 3 years of treatment. This may prove that SCIg therapy effectively controls disease activity, preventing relapses and further demyelinating damage. Longer follow-up periods and wider populations are needed for a better validation of these findings.

Conclusions: SCIg treatment could be an effective long-term maintenance therapy in CIDP patients, able to stabilize neurophysiological findings.

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"ALL TIBIAL FOOT": A NEUROPHYSIOLOGICAL AND NEURORADIOLOGICAL STUDY

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Introduction: Lower limbs' innervation is provided by Sciatic Nerve (SCN), dividing into two branches: Common Peroneal Nerve (CPN) and Tibial Nerve (TN). CPN typically provides Deep Peroneal Nerve (DPN) and Superficial Peroneal Nerve (SPN). Several anatomic variants have been reported, whose the most frequent is the presence of Accessory Peroneal Nerve (APN) innervating Extensor Digitorum Brevis (EDB) muscle. A very rare anatomic variant is here reported. We describe the case of a patient with the right foot totally innervated by TN. This condition is known as "All Tibial Foot" and it has been reported in only three cases. [1,2,3] We performed both neurophysiological and neuroimaging studies of the anatomic variant with the aim to understand the physiology of this rare condition.

Case Presentation: A 39-year-old man was admitted to our department for a calf asymmetry. Neurological examination showed only right gastrocnemius hypertrophy. Brain and spinal MRI were normal. ENG and EMG were also performed. The absence of right DPN CMAP, recorded with surface electrode on EDB was observed, despite of normal toes dorsal extension. Therefore, we performed an EMG/ENG examination with concentric needle electrode that confirmed the absence of DPN CMAP, also stimulating posterior lateral malleolus to exclude the presence of APN. DPN CMAP was obtained stimulating TN both at ankle and at popliteal fossa and recording on EBD. DPN SNAP recorded between first and second toes was present. EMG/ENG evaluation of the left foot was normal. Therefore, we decided to perform MRI and Doppler-ultrasound of muscles and nerves of both feet, confirming right gastrocnemius hypertrophy and also showing a normal anatomy of DPN and TN.

Discussion and Conclusions: Neurophysiological features here reported confirmed the diagnosis of "All Tibial Foot". This condition has been described for the first time by Yamashita and colleagues,1 showing that TN innervates muscles of both tibial and peroneal domains, despite of DPN sensory task preservation. Neuroimaging studies confirmed the anatomical integrity of the peroneal bundle suggesting that DPN could conduct only sensory impulses, not permitting motor conduction. Furthermore, these features could justify clinical and radiologic evidence of right gastrocnemius muscle hypertrophy, as a compensative mechanism due to a "prevalent" TN innervation of right foot compared to the left. Our study is the first to analyze "All Tibial Foot" with concentric needle electrode ENG, avoiding the hypothesis of volume conducted potentials, and the first with a radiological description of a rare anatomic variant.

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CORTICO-CORTICAL SIGNAL TRANSMISSION AND BRAIN CONNECTIVITY IN HEALTHY INDIVIDUALS AS A MODEL FOR STUDYING ALZHEIMER'S DISEASE: A MULTIMODAL APPROACH OF TMS-EEG AND ADVANCED MRI

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Objectives: Signal spread through the cortex following transcranial magnetic stimulation (TMS) pulse can be tracked with millisecond precision

by electroencephalography (EEG). Such a measure, called TMS-evoked potential (TEP), when derived after the stimulation of a brain network's node, represents the spread of the signal over time in that specific network (time of signal transmission, STT). We wish to establish how contralateral STT (specifically the TEP's P20 latency) following a TMS pulse of specific brain nodes (within default mode [DMN] and executive control [ECN] networks) is related to the integrity of interhemispheric white matter (WM) fibers. This approach could provide a novel marker for 'disconnection syndromes' such as Alzheimer's disease (AD).

Materials: 28 healthy controls (aged 60-84 years) underwent a functional/structural MRI and a TMS-EEG session.

Methods: Resting-state fMRI maps were used to define DMN and ECN nodes to be TM stimulated: left and right inferior parietal (IPL; DMN) and dorsolateral prefrontal (DLPFC; ECN). Fiber tracking of the main intra- and interhemispheric WM tracts was performed using a probabilistic tractography algorithm (probtrackx, FSL). TEP's P20 latency for each contralateral area of the stimulated node and DTI indices (fractional anisotropy [FA] and mean diffusivity [MD]) from each tract were obtained. The ability of WM measures to predict TEP's P20 latency were explored using multiple linear regression models for each tract, WM measure, and stimulation node, accounting for subject age.

Results: We observed that lower MD values of the occipital splenium predicts lower TEP's P20 latency after left IPL stimulation (p=0.04). On the other hand, lower MD values of the parietal splenium (p=0.04), and higher FA values of parietal (p=0.02) and occipital splenium (p=0.01) were independent predictors of higher TEP's P20 latencies after right IPL stimulation.

Discussion: In healthy controls, we demonstrated that the WM integrity of the splenium predicts the interhemispheric P20 latency within the DMN following a TMS pulse of the left IP nodes. These findings were neither observed for intra-hemispheric connections (SLF) nor within the ECN, reflecting interhemispheric and network (DMN) specificity. On the other hand, when the right hemisphere was stimulated, we observed an inverse WM prediction that needs further investigation.

Conclusions: P20 latency is a promising measure of brain interhemispheric connectivity. After our initial validation, this approach could provide a novel single-subject marker of brain connectivity in early cases of AD.

Funding. Italian Ministry of Health (GR-2016-02364132). Foundation Research on Alzheimer Disease.

THALAMOCORTICAL DYSRHYTHMIA IN PATIENTS WITH DELIRIUM: A MULTICENTER-COHORT STUDY

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Objectives: Delirium is an acute clinical syndrome, characterized by confused thinking and reduced awareness of the environment due to fluctuations in vigilance, attention, and other cognitive functions possibly related to thalamo-cortical dysrhythmia (TCD). It is particularly prevalent during hospitalization, especially in old seniors. We hypothesized that in elderly patients with intact cognition, delirium during the hospitalization may be TCD reflected by on-going electroencephalographic (EEG) activity which can unveil TCD. The study aim was to identify compressed spectral array (CSA) markers of resting-state electroencephalogram (rsEEG) rhythms related to delirium.

Methods: 65 patients were admitted for various reasons in 7 Italian Neurology Clinics during the year 2021 and experienced an episode of delirium (delirium group). The patients were matched with a group of patients admitted during the same period (no-delirium group). The presence of delirium was revealed by the administration of 4AT scale and according to DSM-5. Comorbidities were evaluated by Charlson Comorbidity index. All patients underwent a rsEEG registration and spectral makers were compared between the two groups: power density at delta, theta, pre-alpha, and alpha frequency bands, dominant frequency (DF), and dominant frequency variability (DFV).

Results: All 65 (76.9 years ±12 standard deviation, SD; 49% females) suffered from delirium during the hospitalization showed abnormal CSA patterns. Among those without delirium (74.6 years ±12 SD; 39% females), a minority (28.6%) presented abnormal CSA patterns. Compared to no-delirium group, delirium group had an EEG mainly characterized by lower Mean DF and higher DFV at the pre-alpha/theta frequencies (< 8 Hz). These effects were topographically widespread. In most of the patients with delirium having a follow-up EEG, the recording showed normalization at resolution of delirium.

Discussion: Patients with delirium showed abnormal CSA markers of EEG activity supporting a strict relationship between TCD and delirium.

Conclusions: Delirium during the hospitalization may be strictly related to TCD, known to affect vigilance and awareness, and reflected by CSA markers of on-going EEG activity.

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ELECTROKINESIOGRAPHIC STUDY OF OROPHARYNGEAL SWALLOWING IN PATIENTS WITH NEUROGENIC DYSPHAGIA

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Introduction and aim: ElectroKinesiographic Study of the oral and pharyngeal phases of Swallowing (EKSS) is a useful tool for the assessment

of patients with suspected or overt neurogenic dysphagia. This electrophysiological method consists of a multichannel recording of the electromyographic (EMG) activity of the suprahyoid/submental muscle complex (SHEMG), the EMG activity of the cricopharyngeal muscle (CPEMG), the laryngopharyngeal mechanogram (LPM), and breathing activity by means of a nasal cannula connected to a piezoelectric transducer. The LPM is expression of the mechanical changes of the laryngopharyngeal structures occurring during the pharyngeal phase of swallowing. Aim of this study is to provide detailed information regarding magnitude, duration, and temporal relations of the different events that characterize oropharyngeal swallowing in dysphagic patients with different neurological disorders.

Material and Methods: A retrospective case series of 100 patients with different forms of neurogenic dysphagia (35 patients with parkinsonian syndromes, 20 patients with amyotrophic lateral sclerosis, 20 patients with multiple sclerosis, 20 patients with stroke and dysphagia) who underwent EKSS from 2017 to 2021 at IRCCS Mondino Foundation is presented. EKSS was carried out by testing on-command deglutition of 3- and 12-cc of water and 12-cc of fruit jelly.

Results: In patients with overt dysphagia, the EKSS was able to highlight at least one abnormality in almost all subjects. Although most of the alterations were not disease-specific, some alterations were more frequently observed, or were more markedly altered, in patients with a specific pathological condition. For instance, reduced or absent relaxation of the cricopharyngeal muscle was typically observed in patients with Wallenberg syndrome, while increase in both duration of SHEMG and interval between SHEMG and LPM (i.e., oropharyngeal delay) was very frequent in patients with PD, being expression of bradykinesia of the oral phase of swallowing.

Discussion and conclusions: The EKSS allows an in-depth exploration of pathophysiological features of swallowing in different forms of neurogenic dysphagia. Information provided by EKSS can be very useful to guide the choice of different dysphagia treatment strategies, allowing identification of optimal solutions for single patients. For instance, CPEMG recording can identify incomplete or absent relaxation of the upper esophageal sphincter during the pharyngeal phase of swallowing, thus suggesting a therapeutic approach based on botulinum toxin injection into the cricopharyngeal muscle.

NEUROPHYSIOLOGY AND NERVE ULTRASOUND IN BELL'S PALSY

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Bell's palsy is the most common cause of acute peripheral facial palsy. Although the etiology of the disorder is unknown, inflammation and oedema of the facial nerve probably play a key role in the pathogenesis. Most patients recover within a few months, while up to a third have a residual functional deficit with the presence of facial muscle weakness or synkinesis [1]. Despite the fact that electrodiagnostic tests are widely used for the evaluation of facial nerve paralysis, data on the predictive value of these tests are conflicting. In recent years, nerve ultrasound has gained attention as a valuable tool for the diagnosis of peripheral nervous system diseases [2-3]. In this clinical, neurophysiological and nerve ultrasound longitudinal study we aimed at assessing the utility of facial nerve ultrasound as a supportive tool for the diagnosis and assessment of Bell's palsy. Twenty-seven (age 46 ±12 years, sex 10 males) consecutive patients diagnosed with Bell's palsy were enrolled. Three consecutive clinical (neurologic examination), neurophysiological (electroneurography of the facial nerve bilaterally, blink reflex and electromyography of the muscles affected by the paralysis) and nerve ultrasound evaluations (within 15 days (T0), 1 month (T1) and 3 months (T2) from onset) were performed. The diameter of the facial nerve on the affected side was larger than on the healthy side at T0 evaluation ($p<0.05$), it did not differ at T1 and T2. Facial nerve diameter did not correlate with the degree of Bell's palsy according to the House-Brackmann facial nerve grading system and the amplitude of the Compound Muscle Action Potential stimulating the facial nerve on the affected side. We showed that the facial nerve has a larger diameter in the acute phase in Bell's palsy. The observed nerve enlargement may be due to inflammation-induced swelling of the nerve probably spreading from the geniculate ganglion. Ultrasound of the facial nerve could be a tool for evaluating the facial nerve in Bell's palsy. Further studies are needed to assess its prognostic value.

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IS FATIGUE A DISORDER OF MOVEMENT PREPARATION? A NEUROPHYSIOLOGICAL STUDY

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Background: Fatigue is a common symptom of Parkinson's disease (PD), poorly recognized and not adequately treated [1]. In MRI studies, it has been linked to motor planning impairment [2] and in other diseases, like Multiple Sclerosis, it has been linked to reduced pre-movement facilitation (PMF) [3]. Our aim was to understand whether PMF is abnormal in PD and it is related to fatigue.

Methods: Presence and the severity of fatigue were defined based on the 9-item Fatigue Severity Scale (FSS, cut-off ≥ 4). We enrolled PD patients with fatigue (PD-F), PD patients without fatigue (PD-NF) and Healthy Controls (HC). We assessed PMF with transcranial magnetic stimulation (TMS) during a simple reaction time (RT) motor task. Subjects were asked to briskly abduct their thumb after a visual go-light signal and TMS was delivered at 50 ms, 100 ms and 150 ms before the mean calculated movement onset (EMG burst).

Results: 15 PD-F patients (mean age 63.27 ± 9.8 years), 16 PF-NF patients (66.4 ± 8.2 years) and 16 HC (mean age 54.25 ± 14.4 years). The three groups were matched for gender and differed for age ($p = 0.033$*). The rmANOVA corrected for age did not show significant interactions group x side x time ($F= 0.26$, $p= 0.9$) of amplitude of MEP and at three different intervals during PMF (MEP PMF) compared to MEP REST. However, when computing the rate of MEP increase during PMF (MEP

PMF/MEP REST), all groups had a significantly higher rate of PMF at 50 ms (F =4.3, p = 0.014*), but HC significantly differ from patients with an higher rate of increase at all times during PMF (F =4.6, p = 0.01*) while PD-F and PD-NF did not differ from each other (p > 0.05). Analyses of correlation did not show any influence of FSS scores on MEP amplitude nor on rate of MEP increase during PMF (MEP PMF/MEP REST), to further strengthen our results.

Discussion: These results provide preliminary evidence PMF is abnormally reduced in PD patients compared to HC and independent from fatigue.

Conclusions: Abnormally reduced pre-movement facilitation could represents a neurophysiological hallmark of PD patients but it is not linked to fatigue in PD. Future works are necessary to disentangle the mechanisms of fatigue and to verify the meaning of reduced PMF in PD patients, its meaning in clinical and research context.

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NEUROPLASTICITY IN PEOPLE AFFECTED BY CHRONIC MAJOR UPPER LIMB AMPUTATION: A TMS STUDY

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Background and Objectives: Major upper limb amputations (mULAs) have disastrous consequences for amputees' life, in terms of mental, physical, and social well-being. The study of how the nervous system changes after mULAs can offer fundamental insights for the challenge of improving surgical and rehabilitation outcomes and prosthetic control. We wanted to study hemispheric differences in basal corticospinal excitability (CSE) in a population of subjects with chronic mULA who were using active control prostheses (AcP) and to evaluate in the same population the effects of acute neuromodulatory interventions - continuous Theta Burst Stimulation (cTBS) and Paired Associative Stimulation (PAS-10) - in terms of inhibition of CSE.

Materials and Methods: People aged >18 years, with chronic (> 1 year) stabilized mULA already using AcP (body powered or myoelectric), without contraindications to Transcranial Magnetic Stimulation (TMS) and psychiatric comorbidities were enrolled. Basal CSE was assessed through resting motor thresholds (RMTs) and Motor Evoked Potentials (MEPs) amplitude. The target muscle was the biceps for trans-radial amputations, and the biceps or trapezius for trans-humeral amputations, according to the amputation level. Electrical stimuli were delivered to the residual ulnar nerve of the amputated arm. Participants have been recruited in collaboration with INAIL.

Results: We enrolled 12 subjects (11M, 1F), age (mean+ SD)=49.6 + 17.19 years old (range 21-80), level of amputation: 6 trans-humeral, 5 trans-radial, 1 congenital forearm amputation. Years after amputation (mean+ SD)= 12,6+12,1 (range 1-49). 3/12 were affected by phantom limb (PL) pain; 10/12 reported non-painful PL sensation. Basal CSE (recorded at target muscles, bilaterally) was significantly higher for the brain hemisphere contralateral to the amputation side (CLtoAMP) (p=0.002) when assessed through MEPs amplitude (and not RMTs). cTBS (n=12), delivered over the M1 CLtoAMP, induced a significant inhibition of MEPs amplitude 5 minutes after stimulation (p=0.023) only for MEPs elicited from the brain hemisphere CLtoAMP. Significant inhibition was still present 10 min after cTBS (p=0.001). PAS-10 (n=6) did not induce significant changes in MEPs amplitude.

Discussion and conclusions: Basal CSE results confirm previous observations of a higher CSE in the hemisphere CLtoAMP and extend them to a sample representative of a younger population, with chronic mULA and using AcP. Results from neuromodulation suggest that cortical circuits responsible for cTBS are functional after chronic mULA, while circuits linked to PAS-10-induced plasticity are impaired. Further research is needed to strengthen and clarify these results.

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THE EFFECTS OF MONOPOLAR TDCS ON BRAINSTEM REFLEX PATHWAYS

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Objectives: The effects of transcranial direct current stimulation (tDCS) on deep brain structures (e.g., basal ganglia network and brainstem) is still unclear, but of key importance for stimulation protocols in several diseases (e.g. movement disorders). To evaluate the neurophysiological effect of tDCS on brainstem, Blink Reflex (BR) and Masseter Inhibitory Reflex (MIR) were assessed in healthy subjects undergone two different experimental conditions.

Materials: 10 healthy subjects (mean age: 32 ± 9.8, 5 women) underwent two stimulation protocols developed from computational realistic models predicting the current density along the brainstem. Anodal tDCS (2 mA for 20 min, single session) was delivered over right and left motor cortex (5x5 cm2 rubber pads), with rubber pads of 7x5 cm2 as reference electrode. BR was bilaterally assessed from orbicularis oculi muscle after the stimulation of each supraorbital nerve, considering the reflex

Threshold (mV) and the latencies (ms) of the two main components (RI, RII ipsilateral and RII contralateral) for analysis. MIR were recorded from the left masseter muscle after stimulation of the inferior alveolar branch of the mental nerve; we considered the reflex Threshold (mV), and onset latencies and duration of two silent periods (SP1 and SP2) for analysis.

Method: In this randomized, assessor-blinded, crossover study, each volunteer underwent biemispheric anodal tDCS with the reference either over T10 (condition A) or the right deltoid (condition B), in two different single sessions separated by a washout period (≥1 week). BR and MIR were recorded immediately before (T0) and after (T1) the stimulation.

Results: Only for condition B (reference over right deltoid), paired samples T-Test revealed a significant decrease in RI latencies [ms, right BR: t (8) =4.69, p=0.002; left BR: t (8) =3.61, p=0.007], and a significant increase in RII contralateral latency [ms, right BR: t (8) =-2.43, p=0.041]. A trend in increasing RII ipsilateral latency was found, although non-significant [ms, right BR: t (8) =-2.29, p=0.051]. No significant results were found for MIR in both conditions.

Discussion: Computational results suggest that tDCS with monopolar montages might result in electric field intensities in deep brain structure comparable to those in grey matter [1,2]. Our results suggest that pontine circuitry might be modulated by tDCS with reference over the right deltoid. However, it is not clear whether this is a direct effect of the stimulation, or and indirect effect of cortical or subcortical pathways' activation.

Conclusions: Pontine circuitry might be modulated by monopolar tDCS.

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NEUROGRAPHIC RECORDINGS AFTER SELECTIVE STIMULATION OF INTRAEPIDERMAL FIBERS

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The small afferents of the peripheral nervous system (PNS) are still seldom recorded in the clinical neurophysiology setting because of technical difficulties and the absence of a safe and reliable method of investigation. Such lack of information hampers the diagnosis in most neuropathic pain conditions where such a fiber group is involved. A new micropatterned electrode has recently been designed for selective stimulation of the intraepidermal endings of the small fibers, allowing the use of electric stimuli and providing potentially widespread access to the method. This is the first dedicated study for its application as an assessment of the peripheral nerve. Twelve healthy subjects have been studied. In order to be enrolled in the study, a preliminary check of normal conduction of the fast fibers of their radial nerve was performed with traditional methods. The commercially available micropatterned electrode with a 150 μm interrail gap (150 IDE) was used to stimulate the radial nerve innervated area of the hand dorsum between the 1st and 2nd metacarpal bone. Electric stimulation was delivered with 0.5 ms pulses of 0.5-3.0 mA intensity (adjusted to twice the sensory threshold). The subjects exclusively perceived a pinprick sensation at all used intensities. Recordings were performed with two 0.3 mm needle electrodes TeflonTM coated, inserted in contact with the radial nerve at the wrist, 20 mm apart, thus configuring a bipolar derivation. Averaging was performed offline on separate groups of responses to ascertain reliability. Stimulation with the 150 IDE yielded small amplitude responses at approximate latencies between 3 and 5 ms, suggesting the evoked activity of fiber groups conducting at 30, 20 and 17 m/s. Separate group averaging confirmed their reliability. The faster fibers tested with a traditional stimulation method conducted in the same nerve tract between 40 and 50 m/s. The assessment that we report just needs a dedicated electrode for stimulation and needle electrodes for recording, with no further specific requirement. This technique for neurophysiological small fiber assessment is therefore within the possibilities of the standard equipment usually available at any laboratory of clinical neurophysiology. We demonstrated the reliability of the method in healthy subjects, which can now be extended to the clinical practice.

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STABILITY OF REST TREMOR ELECTROPHYSIOLOGICAL FEATURES ACROSS DIFFERENT LIMB POSITIONS IN PARKINSON'S DISEASE

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Background: Parkinsonian rest tremor (RT) can be observed in several positions (seated, standing, lying down) but no study compared the electrophysiological tremor features between different tremor positions. The aim of this study was to evaluate the stability of RT electrophysiological features across different recording positions in tremor dominant Parkinson disease (TD-PD).

Methods: We consecutively enrolled 41 TD-PD patients showing upper limb RT in three positions: with the patient seated on a chair with the arm flexed at 90 degrees, the forearm fully supported against gravity, and the hand hanging down from the chair armrest (hand-hanging position), in lying down supine position and in standing position. RT electrophysiological features were assessed in all patients and compared across the three described recording conditions. Alternating or synchronous contraction of antagonistic forearm muscles were evaluated using both quantitative phase values and qualitative visual inspection of pattern on tremor recording. ANOVA for repeated measures was used for comparing features across different tremor positions.

Results: The RT amplitude, burst duration, phase values (and pattern) were similar across the three recording conditions ($p>0.05$), with the only exception of RT frequency, that was slightly lower in supine position ($p=0.01$). In all recording conditions, there was an inverse correlation between RT frequency and disease duration, and a direct correlation between RT burst duration and disease duration.

Discussion: Our study demonstrates that the RT electrophysiological features remain stable across different resting conditions.

Conclusion: Our findings suggest common pathological bases for hand-hanging, supine and standing RT in Parkinson's disease, and enable clinicians to perform the RT evaluation for diagnostic purposes in these different recording conditions.

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ABNORMAL SENSORIMOTOR CORTEX AND THALAMO-CORTICAL NETWORKS IN FAMILIAL ADULT MYOCLONIC EPILEPSY TYPE 2: PATHOPHYSIOLOGY AND DIAGNOSTIC IMPLICATIONS

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Background: Familial Adult Myoclonic Epilepsy (FAME) is a hereditary condition characterized by cortical tremor, myoclonus and epilepsy. It belongs to the spectrum of cortical myoclonus and the sensory-motor cortex hyperexcitability represents an important pathogenic mechanism underlying this condition. Besides pericentral cortical structures, the impairment of subcortical networks seems also to play a pathogenetic role, mainly via the thalamo-cortical pathway. However, the mechanisms underlying cortical-subcortical circuits dysfunction, as well as their impact on clinical manifestations, are still unknown.

Objective: To systematically study with an extensive electrophysiological battery the sensory-motor hyperexcitability in FAME2 patients and to establish reliable neurophysiological biomarkers for the diagnosis.

Materials and Methods: We evaluated the facilitatory and inhibitory circuits within the primary motor cortex (M1) using single and paired-pulse transcranial magnetic stimulation (TMS) paradigms. We also probed the excitability of the somatosensory (S1) cortex as well as the thalamo-S1 connection by using ad hoc somatosensory evoked potential (SEP) protocols in a cohort of genetically confirmed (Intronic ATTTC repeat expansions in STARD7 gene) Italian FAME2 patients, a group of patients with Juvenile Myoclonic Epilepsy (JME) and a subset of healthy control subjects. The sensitivity, and specificity of TMS and SEP metrics were derived from receiver operating curve analysis.

Results and Discussion: Twenty-six FAME2 subjects, 17 JME patients and 22 healthy controls (HC), were evaluated. Overall, FAME2 patients displayed increased facilitation and decreased inhibition within the sensory-motor cortex compared with JME patients (all $p>0.05$) and HC (all $p>0.05$). SEP protocols also displayed a significant reduction of early high-frequency oscillations and less inhibition at paired-pulse protocol, suggesting a concomitant failure of thalamo-S1 circuits. Disease duration, age and myoclonus severity (Unified Myoclonus Rating Scale), and surface EMG did not correlate with sensory-motor hyperexcitability (all $p>0.05$). Finally, FAME2 condition was reliably diagnosed using TMS, demonstrating its superiority as a diagnostic factor compared to SEP measures.

Conclusion: Sensory-motor cortical and thalamo-cortical circuits are involved in the pathophysiology of FAME2. In addition, TMS displays an overall higher accuracy than SEP to reliably distinguish FAME2 from JME and HC.

CLINICAL AND NEUROPHYSIOLOGICAL BIOMARKERS OF DISEASE PROGRESSION IN MULTIPLE SCLEROSIS

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Objectives: Secondary progressive multiple sclerosis (SPMS) diagnosis is retrospective and markers of conversion from relapsing-remitting MS (RRMS) are still lacking. A recent neurophysiological study in MS showed that the short intracortical inhibition (SICI)- a transcranial magnetic stimulation (TMS) variable testing inhibitory interneuron excitability in primary motor cortex- and the somatosensory temporal discrimination threshold (STDT) – the shortest interstimulus interval at which a subject is able to discriminate two stimuli as separate testing inhibitory circuits in primary somatosensory cortex- are both altered in patients with MS (pwMS). The abnormalities were present to a higher extent in pwSPMS as compared to pwRRMS and an objective neurophysiological index (NI) to discriminate SPMS from RRMS was proposed. Frailty represents a vulnerability to stressors due to an adaptation impairment to physiological changes. Frailty index (FI), a quantitative frailty indicator based on clinical and laboratory data, was able to discriminate pwSP from pwRRMS.

The aim of this pilot study was to evaluate possible correlations between the NI and the FI in pwMS.

Materials and Methods: 19 MS patients (13RR, 6SP) were enrolled. Participants underwent to clinical and neurophysiological examinations. SICI, STDT and FI were assessed using the procedures used in previous studies (1-2). NI was calculated by using the following formula based on SICI and STDT values for each patient: $P(X=1) = (e^{(-5.95503+0.00056*SICI(\%)*Age+0.00073*STDT*Age)}) / (1 + (e^{(-5.95503+0.00056*SICI(\%)*Age+0.00073*STDT*Age)}))$

Statistical analyses: Mann-Whitney U test for independent samples was performed to evaluate differences in NI and FI between SP and RR. Spearman's correlation was used to evaluate possible correlations between NI and FI.

Results: Confirming previous studies, NI ($p<0.001$) and FI ($p=0.02$) significantly differed between pwRRMS and pwSPMS. The novel finding of the present study was that FI and NI were positively related ($\rho=0.55$; $p=0.014$).

Discussion and conclusions: The observation that both NI and FI differ in pwRRMS and pwSPMS and that NI and FI correlate to each other in pwMS suggests that both variables reflect pathophysiological mechanisms involved in disease progression in MS.

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AN UNUSUAL CASE OF TARSAL TUNNEL SYNDROME RESULTING FROM A NECROTISING VASCULITIS

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Objectives: Necrotizing vasculitis is a term used to describe vessel wall necrosis due to neutrophil infiltration. Vessels may be involved, leading to specific signs or symptoms, in a wide range of organs, with those of the skin, kidney, joints, and gastrointestinal tract leading the list [1]. Why vessels of different sizes or locations become involved in individual patients is unknown. However, to discern signs and symptoms concerning less frequently involved organs (i.e. kidneys, multiple peripheral nerves, joints, and the heart) may represent a turning point for case management and patient outcome

Materials: A 44-year-old female, known asthmatic, came to our attention with intense left foot pain and paresthesia occurring in the previous 40 days. She underwent neurophysiological assessment in a local clinic. Nerve conduction studies (NCS) showed small compound muscle action potential (cMAP) amplitude of the left tibial nerve; concentric needle electromyography (EMG) registered abundant spontaneous activity with isolated motor unit potentials (MUP) in the left abductor hallucis. Diagnosis of Tarsal Tunnel Syndrome, an entrapment neuropathy of the tibial nerve within the fibro-osseous tarsal tunnel beneath the flexor retinaculum, was proposed.

Methods and Results: We repeated NCS and needle EMG 16 days after the former test. Previous findings were confirmed, furthermore we detected a small cMAP amplitude of the left peroneal nerve and abundant spontaneous activity with giant MUP and neurogenic pattern in the left extensor digitorum brevis. Blood tests, autoimmune screening and imaging scans were performed. Primarly axonal mononeuritis multiplex combined with asthma, eosinophilia (60%) and positive ANCA prompted us to suspect eosinophilic granulomatosis with polyangiitis (EGPA) formerly known as Churg Strauss Syndrome, a rare systemic vasculitis that occasionally (10-60%) [2,3] affects the peripheral nervous system. Chest CT scan revealed patches of ground glass opacities in both lungs with sub centimeter nodules. Skin biopsy showed necrotizing vasculitis associated with tissue infiltration by eosinophils and extra-vascular granulomas, confirming the diagnosis of EGPA.

The patient was treated with an initial course of pulse steroid therapy with Methylprednisolone for 3 days and was started on Rituximab. On the nineth day, she was able to ambulate around the room and denies pain or paresthesia.

Discussion and Conclusions: This case highlights that necrotising vasculitides must be considered a differential diagnosis of rapidly progressive mononeuritis multiplex with eosinophilia and asthmatic history. Early diagnosis is essential to reduce the risk of further disease progression and morbidity. Prompt treatment with immunosuppressive therapy is often successful.

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CLINICAL NEUROPSYCHOLOGY

AN HISTORICAL CONFIRMATION FOR LANGUAGE IMPAIRMENT IN ALS AND MOTOR NEURON INVOLVEMENT IN PROGRESSIVE APHASIC SYNDROMES

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Objectives: Among clinicians and researchers, it is common knowledge that frontotemporal cognitive involvement in ALS started to be acknowledged in the late '90s of the 20th century. Relatedly, language impairment within the spectrum of primary progressive aphasia (PPA) [1] was fully recognized as semiotically and diagnostically relevant only in the 2017 revision of consensus criteria for frontotemporal-spectrum disorders in ALS [2]. By contrast, a considerable body of PPA-spectrum language dysfunctions in ALS and motor neuron (MN) involvement in progressive aphasic syndromes can be traced in the literature as early as the late 19th century [3].

Materials: Worldwide reports on language impairment in ALS dating from 1893 to 1981 were retrieved thanks to Biblioteca di Area Medica "Adolfo Ferrate", Sistema Bibliotecario di Ateneo, University of Pavia, Pavia, Italy and through online databases.

Methods: Reports addressing either 1) ALS patients presenting with language dysfunctions or 2) aphasic patients developing motor neuron involvement were included. Data were qualitatively synthetized.

Results: Out of 88 reports published between 1893 and 1981 and describing cognitive/behavioural involvement in ALS/MN involvement in dementias, 23 were included (N=30 patients; 11 female; age range=22-70). Neuropsychological symptoms preceded or co-occurred at onset with motor symptoms in 22 cases. Phonological, lexical-semantic and morpho-syntactic deficits were described, as well as both dysgraphic and dyslexic features. Isolated language deficits were detected in 3 patients, whereas the remaining ones also showed extra-linguistic involvement. Behavioural dysfunctions were comorbid in all patients but one. Probable PPA, resembling either progressive non-fluent aphasia or semantic dementia, was describe in 9 patients. Bulbar involvement was present in 21 patients, whereas extrapyramidal signs in 2. Disease duration ranged from 6 months to 7 years. Neuropathological data, available for 16 patients, revealed diffuse cortical-subcortical alterations, although predominantly in frontotemporal structures, with left-greater-than-right involvement described in 4 patients and Pick's bodies being reported in 5. In vivo evidence of morphological/functional brain abnormalities

was detected in 6 out of the 12 patients for which such information was available. Familiarity with ALS, dementias or other brain disorders was detected in 9 patients.

Discussion: 19th- and early 20th-century reports on language impairment in ALS and MN involvement in probable PPA strikingly resemble the current clinical, pathological and genetic knowledge on the association between the two nosological clusters.

Conclusions: The association between ALS and language deficits, as well as the possibility of MN involvement occurring in progressive aphasic syndromes, has been acknowledged more than a century ago.

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RESPIRATORY FUNCTION AND COGNITIVE DECLINE IN AMYOTROPHIC LATERAL SCLEROSIS: SEX-RELATED DIFFERENCES

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Introduction: Aim of the study was to evaluate the possible association between respiratory function and cognitive performances in patients with Amyotrophic Lateral Sclerosis (ALS) also exploring possible sex-related differences.

Methods: Patients with "probable" or "definite" ALS were enrolled. Respiratory function was assessed by spirometry. Patients with Forced Vital Capacity (FVC) ≤75% were considered to have "reduced respiratory function". A "comprehensive" neuropsychological battery was performed. Sex-stratified analysis was carried out.

Results: Ninety-six patients (59 men, mean age 66.9±9.6 years) were enrolled. Fifty patients (52.1%) had FVC≤75%. Patients with FVC≤75% presented significantly lower scores at the Frontal Assessment Battery-FAB (13.2±2.8) than patients with FVC>75% (14.4±2.6; OR 0.8; 95%CI 0.71-0.99; p-value 0.039). Moreover, patients with FVC≤75% presented significantly lower scores at the Rey Auditory Verbal Learning Test (RAVLT)-immediate recall (32.2±7.9) than patients with FVC>75% (36.4±8.0; OR 0.9; 95%CI 0.88-0.98; p-value 0.015). At sex-stratified analysis, reduced FVC was found to be significantly associated with low scores at both FAB and RAVLT only in women.

Conclusion: In women, an association between ventilatory function and cognitive performance was found.

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IMPAIRED EXECUTIVE FUNCTION IN ADDICTION: A NOVEL NEUROCOGNITIVE SCREENING BATTERY

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Aims: Given their role in supporting self-monitoring/regulation and top-down control of cognitive processes, executive functions (EF) are a primary mediator of both typical and atypical functioning, influencing progress of psychopathology. Recent models suggest that EF impairments may negatively contribute to the functional decline of patients with substance use disorder (SUD), aggravating secondary affective and social symptoms [1,2,3]. Despite these potential implications, the tools now typically used to outline neurocognitive, and specifically EF, impairments in patients presenting addiction are not specific for such clinical population, them being originally devised to assess cognitive or dysexecutive deficits in neurology or geriatric patients. Given their different clinical focus, such tools are often unable to fully delineate the dysfunctional EF profile of patients with addiction. We here discuss the development and validation of a novel specific screening battery for neurocognitive disorders in addiction.

Method: The battery was tested on 151 patients with SUD and 55 control subjects.

Materials: It consists of five digitalized neuropsychological tests (focus: short/long-term memory, working memory, focused attention, verbal/non-verbal cognitive flexibility) and two computerized neurocognitive tasks (Stroop and Go/No-go tasks adapted for the evaluation of inhibition mechanisms, executive control, and attention bias towards drugs of abuse).

Results: Statistical analyses showed worse performance in patients with SUD compared to controls, both in tests of cognitive flexibility, focused attention and verbal memory and in computerized tasks, suggesting the presence of a deficit of inhibitory mechanisms and regulation of cognitive resources. The analysis of Cohen's d values has pointed out that the clearest deficits concern short/long-term memory and focused attention, followed by verbal/non-verbal fluency and inhibitory control.

Discussion and conclusion: Assessment of EF dysfunctions associated with addiction should represent a crucial – as well as currently underrepresented – step of the diagnostic process in drug assistance/treatment services. Early profiling of cognitive vulnerabilities and preserved skills would complement clinical interviews and help designing the therapeutic plan, possibly planning a parallel cognitive rehabilitation phase.

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SOCIAL COGNITION IN PRIMARY PROGRESSIVE APHASIA

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Objectives: Decline of Theory of Mind (ToM) abilities in the behavioural variant of frontotemporal dementia (bvFTD) is a well-established finding, but far less is known about social cognition abilities in the semantic (svPPA) and the non-fluent (nfvPPA) variants of primary progressive aphasia. Aim of this study is to investigate cognitive and affective ToM and their neural correlates in PPA variants, comparing them with bvFTD.

Materials: We recruited 24 PPA (12 svPPA, 12 nfvPPA) and 29 age-, sex-, and education-matched bvFTD patients at initial stages of disease and diagnosed according to current established criteria. Patients underwent neuropsychological assessment including the Story-based Empathy Task (SET), a non-verbal ToM test assessing abilities of intention attribution (IA) and emotion attribution (EA).

Methods: Differences in SET global, IA, and EA raw scores, and distributions of pathological performances (based on Italian normative data) were compared across groups. Voxel-based morphometry (VBM) was used to compare grey matter (GM) density between patients and a group of 42 age-, sex, and education-matched healthy controls. Correlations between GM density and SET scores were performed.

Results: Global, IA, and EA performances, as well as distribution of pathological scores, did not differ across groups, even when bvFTD were compared with PPA patients combined in a single group (N=24). VBM analyses revealed a pattern of GM volume reduction correlating with SET scores that overlapped across patient groups. Specifically, both in bvFTD and PPA patients IA performance was positively associated with GM volume in mid-frontal and cingulate areas, while EA performance was positively correlated to GM density in temporal and orbitofrontal regions.

Discussion: We observed no differences between bvFTD, svPPA, and nfvPPA in cognitive and affective ToM tasks. The association between SET performances and GM volume reflects the areas known to be involved in cognitive and affective ToM tasks. Such association is present not only in bvFTD but also in PPA patients. These areas might be particularly vulnerable also in PPA patients, making them more prone to the development of social cognition deficits even from early stages.

Conclusions: These findings offer new potential behavioral markers for early diagnosis of FTLD conditions.

Supported by: Italian Ministry of Health (GR-2013-02357415); European Research Council (StG-2016_714388_NeuroTRACK); Foundation Research on Alzheimer Disease.

NEUROPSYCHOLOGICAL AND BEHAVIORAL CORRELATES OF FATIGUE AFTER ANEURYSMAL SUBARACHNOID HEMORRAGE

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Background and aims: Fatigue is a common consequence of aneurysmal subarachnoid hemorrhage (aSAH) and is reported by patients as one of their most disabling symptoms [1]. It can be detected in the subacute phase following the aSAH, but there is some evidence that relevant fatigue can last longly (up to years) after the hemorrhage. The aim of the present study was to assess the possible neuropsychological correlates of fatigue in subjects with aSAH.

Materials and methods: Subjects who underwent surgical or endovascular embolization of cerebral aneurysms after aSAH were assessed using a comprehensive neuropsychological battery including tests assessing memory, language, attention, executive functions and visuo-spatial abilities. Anxious and depressive symptoms were assessed by the Hospital Anxiety and Depression Scale (HADS). Fatigue was assessed using the Dutch Multifactor Fatigue Scale (DMFS) that explores the following domains: Impact of fatigue (IF), Mental fatigue (MF), Signs and Direct consequences (SDC), Physical fatigue (PF) and Coping (COP) with fatigue. The sample was stratified in two subgroups according to the interval from aSAH (<= 2 years [EARLY] and > 2 years [LATE]).

Results: The sample was composed by 31 subjects (19 women) with a mean age of 57 years (SD=9.2). the mean interval between aSAH and the assessment was 2.6 years. The DMFS (total score and subscores) showed a significant correlation with the HADS anxiety and depression scores and with scores in tests assessing executive functions (Trail Making and verbal fluency). Mental Fatigue was significantly higher in LATE subjects (24.7±4.92 vs 19.0±5.84; p=0.014). In the EARLY subjects, IF, MF, SDC, COP and total DMFS were all significantly correlated with HADS anxiety and depression scores ($p<0.001$ for all of them). As for LATE subjects, there was significant correlation between score obtained on the Trial Making test A, B and B-A and IF (p=0.008, p=0.008 and p=0.011 respectively); MF (p=0.002, p=0.002 and p=0.003 respectively); SDC (p=0.009; p=0.004; p=0.006); COP (p=0.037; p=0.018;p=0.022), and total DMFS (p=0.003; p=0.003; p=0.006).

Discussion: Our data confirm that fatigue is common among subjects who experience aSAH, and that it can be detected also years after the event, with increasing levels of mental fatigue. The clinical correlates of fatigue seem to vary in time, with psychological factors being prominent

in the first period, and cognitive executive being relevant at some distance from the event. This observation suggests that preventive and therapeutic approaches to fatigue may vary according to the time interval after aSAH.

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COGNITIVE ESTIMATION TASK AND MULTIPLE SCLEROSIS: AN EXPLORATORY ANALYSIS

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Introduction: Cognitive estimation can be defined as the ability to make predictions and provide answers to questions that are not immediate or unknown based on previous knowledge. It is daily used to estimate time, speed, distance, weight, dimensions. Cognitive Estimation Task (CET) requires to respond to questions that are not immediately answerable, but can be adequately guessed using general knowledge. It is thought to be a measure of frontal lobes functioning. Estimation difficulties have been identified in people suffering from a variety of psychiatric conditions, traumatic brain injury and stroke. Despite the occurrence of executive functions deficits, this ability appears to be understudied in MS patients. The study aims to explore the cognitive estimation ability in MS patients as well as the potential utility of CET in this clinical population.

Materials and methods: 123 MS patients (mean age 44.1 ± 11.7, education 13.2 ± 3,8, EDSS 2,4 ± 1.6, disease duration 13.7 ± 9.2) underwent neuropsychological assessment with Symbol Digit Modalities Test (SDMT) and CET (ref). Pearson correlation and regression analysis were used to explore the study's hypothesis, also examining demographic and clinical data.

Results: 61 patients (49.6%) presented with deficit score in the absolute error score, while 50 patients (40.7%) presented with a deficit score in the bizarreness index. A correlation of the two indices with age and education was reported by Pearson test. A relationship of the CET scores with age and education, as well as with lower SDMT performance was reported using linear regression analysis.

Discussion and conclusions: Half of the MS patients included in the study had impaired executive functioning as measured by CET. This impairment correlates with speed of processing information, age and education while it appears to be independent of the EDSS disability assessment. Further studies are needed to better understand the features of these correlations.

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PERCEPTION OF LANGUAGE DIFFICULTY IN MULTIPLE SCLEROSIS: RELATIONSHIP WITH MS FEATURES AND NEUROPSYCHOLOGICAL PERFORMANCE

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Introduction and objectives: Notoriously, Multiple Sclerosis (MS) can impair several cognitive domains, including sustained attention, information processing speed, memory, and executive functions. MS patients may also experience language difficulties in everyday life (i.e., verbal fluency, lexical access, language comprehension, pragmatics). Language difficulties have been described frequently associated with other cognitive deficits. Based on these findings, the present study aims to investigate the patients' self-perceived language difficulty, assessed by the SMAC questionnaire and its relationships with the neuropsychological performance, in particular with WLG.

Materials and methods: Neuropsychological evaluation was performed by using the Brief Repeatable Battery of Neuropsychological Tests (BRB-NT) and the questionnaire Sclerosi Multipla Autovalutazione Cognitiva (SMAC); patients who had at least 2 tests with z score below 2 standard deviations were considered cognitively impaired (CI). Pearson correlation and regression analysis were used to explore the study's hypothesis, also examining demographic and clinical data.

Results: 169 MS patients (female 136; 80.5%; mean age 45.41 ± 11.65 ys, education 12.67 ± 3.5 ys) were included, of these 78 (46.2%) presented with cognitive impairment (CI). MS duration and EDSS were 12.89 ± 9.6 and 2.53 ± 1.72 ys. Independent T-test shows a significant difference of WLG z between CI and not CI patients ($p<0.001$). A correlation between WLG and SMAC ($p=0.024$) was reported by Pearson test. The relationship of SMAC with WLG is confirmed by linear regression analysis ($p=0.048$), after controlling for other demographic and clinical data; an association of SMAC with female gender ($p=0.006$) is also observed.

Discussion and conclusions: The SMAC questionnaire is a useful tool for understanding the presence of language deficits perceived by patients. Although the questionnaire cannot replace a neuropsychological evaluation, it can assist the clinician in selecting the most appropriate tests to better evaluate language deficits.

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DISENTANGLING EXECUTIVE DYSFUNCTION FROM SLOW PROCESSING SPEED DUE TO MOTOR DISABILITY IN AMYOTROPHIC LATERAL SCLEROSIS: ITALIAN NORMATIVE VALUES OF VERBAL FLUENCY INDICES

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Objectives: In amyotrophic lateral sclerosis (ALS), verbal fluency index (Vfi=60 seconds-seconds to read aloud words/correct words generated) has been proposed to investigate fluency accounting for motor impairment. This study has three aims: 1) to provide Vfi reference values from a cohort of Italian healthy controls (HC); 2) to compare the ability of Vfi reference values (vs standard word fluency test [wFT] cut-offs) in distinguishing ALS patients with and without executive dysfunction; to investigate the association between wFT and Vfi values, separately, with brain features of ALS patients.

Materials: We included 180 HC and 158 ALS who underwent a neuropsychological assessment, including wFT and Vfi, and an MRI scan.

Method: HC were split into four sub-groups according to sex and education (N=37 females, education>13; N=76 females, education<13; N=27 males, education>13; N=40 males, education<13). For each HC sub-group, we defined the 95th percentile of Vfi as the cut-off. In ALS cohort, based on Vfi and standard wFT cut-offs, the distribution of 'abnormal' cases was compared using Chi-squared tests. In ALS patients, cortical and subcortical gray matter (GM) volumes were obtained, based on the Automated Anatomical Labeling atlas, and main white matter (WM) tracts were reconstructed using probtrackx in FSL. Using partial correlations in patients, we assessed the association between wFT and Vfi values, separately, with GM volumes and WM tract integrity, accounting for age, sex and education.

Results: Applying Vfi and wFT cut-offs, 13% of ALS cases had abnormal wFT, while only 9% showed altered Vfis ($p<0.001$). In ALS, poor wFT scores were associated with WM alterations of callosal fibers linking pre-motor and supplementary motor area (SMA), right uncinate fasciculus, bilateral cingulate bundle and bilateral superior longitudinal fasciculi. Higher Vfi scores (reflecting a poor performance) were associated with WM alterations of callosal fibers linking SMA, left cingulate bundle and inferior longitudinal fasciculus (ILF). In ALS cases, no associations were found between any fluency score and GM volumes.

Discussion: Compared to standard wFT, Vfis are critical to disentangle motor and cognitive deficits in ALS. In ALS patients, abnormal Vfis were associated with damage to WM tracts specifically involved in lexical processing and verbal fluency performance, such as callosal fibers linking to SMA and left ILF.

Conclusions: Our study provides Italian normative values of the spoken Vfi, which can be applied for detecting cognitive impairment in ALS.

Funding. Italian Ministry of Health (RF-2010-2313220; RF-2011-02351193; GR-2013-02357415); European Research Council (StG-2016_714388_NeuroTRACK); Foundation Research on Alzheimer Disease.

REPEATABLE BATTERY FOR THE ASSESSMENT OF NEUROPSYCHOLOGICAL STATUS (RBANS): ITALIAN NORMATIVE DATA FOR OLDER ADULTS

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Aims: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is widely used for detecting cognitive impairment in different neuropsychiatric conditions. It is more and more applied for measuring cognitive functioning in older individuals, being potentially suitable in Alzheimer's disease (AD) prevention studies [1.] Our intent was to overcome limitations of the original Italian validation [2] as for older ages (>60 yrs), ie, under-representation of older classes, no correction for education and lack of normative data for Subtests.

Materials: A consecutive series of healthy volunteers aged 60-79 years (N=173) classified as cognitively normal on the basis of a brief cognitive and functional assessment, recruited at Center for Memory Disturbances, University of Perugia. Method: We used a regression-based model to assess the effect of age, education, and gender on RBANS Subtests, Indexes and Total scores and to develop residual scores then converted to percentiles. The obtained norms were compared with the Italian original normative data by means of Wilcoxon rank-sum test.

Results: Multiple linear regression analyses showed that age and educational level influenced performances on most RBANS scores. We developed percentiles distribution, derived from the linear equations, and a free-to-use Excel to calculate subject's percentiles scores. When compared with original normative values, our percentiles distribution of Indexes and Total scores did not reveal significant differences ($p>.05$).

Discussion: Our study further improves the robustness of RBANS for the assessment of cognitive functioning in older adults. Obtained normative values are not in disagreement with the existing data. The possibility to correct for Subtests could make RBANS a more precise measure for capturing subtle cognitive deficits in prevention studies.

Conclusions: Considering the evidences of AD biomarkers positivity in subjects with subtle cognitive decline [3], the identification of neuropsychological measures sensitive enough to detect subtle cognitive changes is crucial in order to rule out an underlying AD pathology. Our results encourage to consider RBANS as a suitable tool for detecting and monitoring subtle cognitive deficits in prevention trials.

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POST-STROKE QUALITY OF LIFE AND COGNITIVE FUNCTIONING: A LONGITUDINAL STUDY

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Objectives: Stroke causes severe long-term disabilities with a significant reduction in quality of life (QoL). Our aim was to explore the predictive value of cognitive screening in the acute phase of stroke on QoL after discharge.

Materials: 3–10 days after stroke patients underwent the OCS, providing a five domain-specific cognitive profile. The National Institute of Health and Stroke Scale (NIHSS) estimated the stroke severity. QoL was evaluated by the Stroke Impact Scale 3.0 (SIS), a self-reported questionnaire with a 4-factor structure: Physical, cognitive, emotional, and social participation dimensions.

Methods: This is a longitudinal study. At baseline, stroke patients (both ischemic and hemorrhagic) were consecutively enrolled. Exclusion criteria: Pre-morbid cognitive decay, difficulties with Italian language, visual impairment or other preexisting conditions affecting cognitive status. OCS was considered not applicable when patients failed the preliminary subtests. At follow-up (FU), patients were invited to participate in an online survey exploring QoL. The correlation between OCS (total score) and QoL was explored by multivariate linear regression analyses.

Results: Between October 2019 and September 2021, 124 patients admitted to the Stroke Unit of Poliambulanza Foundation of Brescia underwent OCS. Eighty-two patients completed the online survey on QoL. Mean time of FU (months) was 11.75 (SD 7.52). Characteristics of the final sample: 54 (65.9%) male, mean age (years) 62.29 (SD 13.99), mean initial NIHSS score 2.84 (SD 3.91), 75 patients (91.5%) had an ischemic stroke and 47 (57.3%) a left side brain lesion. At baseline, age (B -.05; 95% CI -.08; -.01, p= .022) and NIHSS score (B -.17; 95% CI -.31; -.03; p= .019) were negatively associated to OCS total performance. At FU, patients showed the following scores on SIS factors (range 0-100, higher score means a better QoL): physical (M 79.55; SD 17.12), cognitive (M 88.08; SD 13.17), emotional (M 75.86; SD 16.98), and social participation (M 84.30; SD 20.14). Baseline OCS was positively associated with physical (B 1.46, 95% CI .03-2.90; p= .045), emotional (B 1.50, 95% CI -.29-3.04; p= .054), and social participation (B 1.71, 95% CI .01-3.40; p= .048) QoL dimensions, after adjusting for age and NIHSS score.

Discussion: At our online survey all dimensions of QoL resulted impacted by stroke. Cognitive screening in the acute phase of stroke was significantly associated to QoL after discharge.

Conclusions: OCS in acute stroke setting seems to be an independent predictor of QoL and could help clinicians in the long-term management of patients.

FTI: A NEUROPSYCHOLOGICAL MARKER TO DISCRIMINATE DIFFERENT CORTICAL FORMS OF DEMENTIA

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Objectives: Verbal fluency depends on the linguistic ability to retrieve lexical information (mainly ascribable to the temporal cortex) and on the attentive-executive ability to select several appropriate words (mainly ascribable to the prefrontal cortex). The former ability is especially crucial for semantic fluency, while the latter for phonemic fluency. Therefore, a deficit in phonemic fluency points towards a prefrontal dysfunction, while a deficit in semantic fluency points towards a temporal one. We evaluated whether FTI (Fluency Type Index)^1, a quantitative comparison of performance in the two fluency tasks, functions as a viable parameter to discriminate FTD (Fronto-Temporal Dementia) from AD (Alzheimer's Disease). Since Tau/Aβ is used with the same purpose, we expected a correlation between FTI and Tau/Aβ in demented patients. nFTI = (aCF - aLF)/(aCF + aLF) where aCF represents the adjusted Categorial Fluency and aLF represents the adjusted Letter Fluency.

Materials and methods: We tested the performance in phonemic and semantic fluency tasks of NC (Normal Controls; n=117) and of patients examined at the UVA of Policlinico Maggiore Hospital, already diagnosed with AD (n=85), bvFTD (behavioral variant FTD; n=48), or aMCI (amnestic Mild Cognitive Impairment; n=97).

Results: The rate of FTI>0 (suggesting a prefrontal impairment) is higher in FTD, while the rate of FTI<0 (suggesting a temporal impairment) is higher in AD ($\chi 2=22.6$; df=1; $p<0.001$). FTI significantly correlates with Tau/Aβ (F=3.76; df=1.156; $p<0.05$).

Discussion and conclusions: Similarly to Tau/Aβ, FTI functions as a (neuropsychological) marker of dementia, capable of distinguishing AD from other neurodegenerative causes of dementia.

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FIST PALM TEST (FIPAT): A QUIK BEDSIDE TEST TO REVEAL COGNITIVE DYSFUNCTION IN PARKINSON'S DISEASE

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Introduction: The FiPaT is a non-verbal test to screen for global cognitive status, attention, and executive functions, and to predict the Mild Cognitive Impairment (MCI). Four types of errors are possible at FiPaT: Topography, Perseverance, Attention and Planning. The maximum score of FiPaT is equivalent to the worst performance [1]. The aims of this study are to investigate: (I) differences between patients with Parkinson's disease (PD) and healthy controls (HC) on the FiPaT; (II) the relationship between FiPaT and cognitive and motor symptoms in PD.

Methods: One hundred and two subjects (51 PD and 51 HC) matched for age and educational, underwent a comprehensive neuropsychological battery and FiPaT. PD patients underwent an UPDRS-III and divided into: normal cognition (PD-NC) or PD-MCI, presence or absence of FiPaT errors, postural instability gait difficulty (PIGD) or tremor dominant (TD) phenotypes, presence or absence of freezing of gait (FOG). The Mann Whitney's U test and contingency tables, were used to measure FiPaT errors between PD and HC, between sub-groups of PD and neuropsychological differences between PD with and without FiPaT errors. A binary logistic regression analysis, with Bootstrap method, was used to investigate the role of FiPaT and of specific errors in identifying MCI in PD patients.

Results: The PD patients performed worse than HC on FiPaT (p = 0.006).The percentage of errors in topography, perseveration and planning is significantly higher in PD than in HC (p<0.05). While no difference was found between HC and PD-NC, PD-MCI performed significantly worse on FiPaT than PD-NC (p=0.002). As compared with PD patients with normal FiPat, PD patients with altered FiPaT performed worse on neuropsychological tests measuring memory, visuospatial and executive skills, but not ideomotor apraxia. Riguarding UPDRS-III motor score no difference was found between two groups. The FiPaT predicted the presence of MCI in PD with a variance of 24% (p=0.023). Topographic and attentional errors predicted the presence of MCI in PD, with a variance of 31% (p<0.021 e p<0.013 respectively). There were not significant differences on FiPaT between motor PD sub-groups but the TD subgroup showed more planning errors than the PIGD (p = 0.014). Patients with FOG had significantly higher percentage of attention errors at FiPat than patients without FOG (p = 0.023).

Discussion: The FiPaT is a bedside test to evaluate cognitive dysfunction in PD. Worse performance on FiPaT is associated with worse cognitive performance in PD. The different motor symptoms of PD are associated with different errors in the FiPaT.

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COGNITIVE RESERVE PREDICTS THE BASAL GANGLIA VOLUME IN THE EARLY PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) is hallmarked by a loss of dopaminergic tone in the Basal Ganglia (BG) leading to motor disorders and also non-motor disturbances for dysfunctional circuitry between the striatum and prefrontal cortex (PFC) [1]. Recently enormous progress has been made in understanding which factors may contribute to differential susceptibility to the effects of pathology mitigating disease-related neural decline. Cognitive Reserve (CR), the processing resources accumulated throughout the lifespan being engaged in mentally-stimulating activities [2], may play a substantial protective role. We tested the hypothesis that CR predicts the BG and PFC atrophy in PD at the early stage of the disease.

Materials and Methods: Sixty-five participants were enrolled, 45 early PD patients (mean age 69.19±7.87 years; 25 males; mean disease duration 4.22±3.10 years) and 20 age-gender-matched healthy controls (HC). All participants completed a standardised tool assessing CR, the Cognitive Reserve Index questionnaire (CRIq) [3], to quantify CR by three indices (CRI-Education, CRI-Working Activity, CRI-Leisure Time), and a structural MRI examination (3T Siemens PRISMA scanner). T1-3D (MPRAGE) images were analyzed using Freesurfer software (v.6.0) to extract brain parcellation and segmentation according to Desikan's atlas. Morphometrical indices for BG (bilateral volume of the putamen, caudate, pallidum) and PFC (bilateral volume of middle frontal and inferior frontal gyri) were computed. Significant differences between HC and PD groups were tested by direct comparisons (ANCOVA covarying for age and sex) on BG and PFC volumes normalized for the estimated Total Intracranial Volume (TIV). Then, two multiple regression analyses were performed to identify potential predictors (age, sex, TIV, disease duration, CRI-Education, CRI-Working Activity, CRI-Leisure Time) on the structural integrity in the two main regions of interest (model 1: BG volume, model 2: PFC volume).

Results: No differences were detected between PD and HC individuals on CRIq subscores. Regarding neural structural integrity, PD presented significantly reduced volumes of normalized BG (p=0.047) and PFC (p=0.002) compared to HC. The first regression analysis (R2=0.749) revealed that BG volume was significantly predicted by CRI-Education (p=0.037) as well as age (p<0.001), sex (p=0.020), and TIV (p<0.001). Instead, the second regression model (R2=0.841) on PFC volume showed that age (p<0.001) and TIV (p<0.001) were significant predictors.

Conclusions: Cognitive Reserve, especially the education accrued over the lifespan, has a protective role on the structural integrity of BG, the initial target of neural insults related to PD neurodegeneration.

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THEORY OF MIND IN BASAL GANGLIA PATHOLOGY: AFFECTIVE AND COGNITIVE COMPONENTS IN PARKINSON'S DISEASE AND HUNTINGTON'S DISEASE

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Aims: Within social cognition domain, Theory of Mind (ToM) is the ability to predict others' behavior by inference of their mental states. The affective component (Aff-ToM) is responsible for understanding others' emotions, while the cognitive component (Cogn-ToM) is related to the knowledge of others' mental states, beliefs, thoughts, and intentions. Several brain regions are involved in the ToM network, with the basal ganglia involved in both cognitive and affective components [1]. There is a growing interest in the investigation of ToM in basal ganglia pathologies, such as Huntington's disease (HD) [2] and Parkinson's

disease (PD) [3]. We examined affective and cognitive components of ToM in HD and PD patients compared to healthy controls (HC).

Materials and Methods: All 63 participants (mean age±SD: HD (n=20) 55.65±12.86; PD (n=21) 72.00±5.98; HC (n=22) 61.82±12.25); were evaluated using the computerized "Yoni task" which assesses affective and cognitive ToM abilities. This task also contains control items (Phys) balanced for the level of difficulty (1st and 2nd order). Only patients with mild-moderate cognitive impairment (MoCA: HD 17.58 ±5.90; PD 20.19±4.00) were included. Between groups, differences were tested with ANCOVAs inserting age and education as covariates. Repeated-Measures ANOVAs were performed in each group to explore differences across the different ToM dimensions.

Results: Compared to HC, HD patients performed worse on both the Aff-ToM and Cog-ToM (1st and 2nd order), whereas PD scored lower than HC only on 2nd order Cog-ToM. No between-group differences were observed on control items (Phys) compared to the level of difficulty. Within groups comparisons showed differences only on 2nd order items: for HC the accuracy in both Aff-ToM and Cog-ToM items was poorer than in the control items (Cog-ToM=Aff-ToM).

Conclusions: The good performance in control items confirms a specific deficit for ToM in clinical groups. In both groups, the affective component is more preserved than the cognitive component. Consistently with previous reports in the early stages only the cognitive component of ToM is impaired in PD [2], while in HD also the affective component is impaired although with a lower level of severity. ToM is impaired in basal ganglia pathology, but the affective component would appear to be less sensitive than the cognitive component to damage of the striatum and corticostriatal circuits.

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TIME-VARYING FUNCTIONAL CONNECTIVITY OF THE HIPPOCAMPUS IS ASSOCIATED WITH COGNITIVE PERFORMANCE IN MULTIPLE SCLEROSIS PATIENTS

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Objectives: The hippocampus has a key role in cognition and mood regulation. In multiple sclerosis (MS), cognitive impairment is related with hippocampal damage. Hippocampal time-varying (TV) functional connectivity (FC) in MS is yet to be completely investigated. We aimed to explore hippocampal static FC (sFC) and TVFC in patients with MS and assess their association with cognitive performances.

Materials: 3D T1-weighted and resting state (RS) functional MRI scans were acquired at 3.0 T from 108 right-handed MS patients and 63 right-handed healthy controls (HC). Subjects underwent a neuropsychological evaluation comprising the Brief Repeatable Battery of Neuropsychological Tests.

Method: Sliding-window correlation analysis using the left (L) and right (R) hippocampus as seed regions assessed TVFC, which was quantified by the standard deviation of connectivity across windows. Mean connectivity indicated sFC.

Results: Compared to HC, MS patients had decreased sFC between the L hippocampus and temporo-parietal regions, and increased sFC between L and R hippocampus and thalamus, precuneus and superior frontal regions. TVFC was decreased in MS patients vs HC between L hippocampus and temporo-parietal regions. Conversely, TVFC was increased in MS patients vs HC between L and R hippocampus and L pre- and postcentral gyri, cuneus, orbitofrontal cortex and inferior temporal gyrus (ITG). In MS patients, better global cognition correlated with higher TVFC between L hippocampus and L pre- and postcentral gyri (r=range 0.21-0.28; p=range 0.04-0.006). Better verbal memory correlated with higher TVFC between L hippocampus and L precentral gyrus (r=0.21, p=0.03), and better visuospatial memory correlated with higher TVFC between L and R hippocampus and L cuneus, pre- and postcentral gyri and ITG (r=range 0.19-0.23, p=range 0.02-0.04). Better information processing speed correlated with higher TVFC between L hippocampus and L postcentral gyrus (r=0.21, p=0.03) and with higher sFC between R hippocampus and L superior frontal cortex (r=0.21, p=0.03). Finally, better attention scores correlated with higher TVFC between L hippocampus and L temporal cortex (r=0.24, p=0.01) and with higher sFC between R hippocampus and L superior frontal cortex (r=0.20, p=0.05).

Discussion: Increased hippocampal TVFC and sFC contributed to explain better cognitive performances in MS. A peculiar association between higher hippocampal TVFC and better memory scores was detected.

Conclusions: Altered TVFC and sFC of the L and the R hippocampus seem to contribute maintaining good cognitive performances in MS patients.

NEUROPSYCHOLOGICAL PROFILE IN PATIENTS WITH TEMPORAL LOBE EPILEPSY PLUS PSYCHOGENIC NON EPILEPTIC SEIZURES

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Aims: Psychogenic non-epileptic seizures (PNES) consist of paroxysmal behavior resembling epileptic seizures, without ictal epileptiform activity. [1] PNES may occur in individuals with epilepsy and intellectual disability represents a prominent risk factor for this association [2]. The aim of this study was to characterize the neuropsychological profile of subjects with concomitant PNES and temporal lobe epilepsy (TLE+PNES), compared to subjects with only PNES or TLE.

Materials: Seventy-six individuals were consecutively enrolled in our clinic and included: 28/76 (37%) individuals TLE only (mean age: 37.82+9.31); 26/76 (34%) TLE+PNES (mean age: 40.04+13.59) and 22/76 (29%) PNES only (mean age: 40.00+13.00). All subjects did not have intellectual disability, according to the DSM-5.[3]

Methods: All individuals underwent a detailed clinical, video-EEG, neuroimaging, and neuropsychological assessment including evaluation of verbal memory (immediate and recall), visuo-spatial functions, language, and executive abilities. The neuropsychiatric examination included the following tests: Beck Depression Inventory (BDI-2); State-Trait Anxiety Inventory (STAI); Dissociative Experience Scale (DES); Toronto Alexithymia Scale (TAS-20); Traumatic Experience Checklist (TEC). The ANCOVA and the post hoc analysis were used to compare neuropsychological results of all our three groups. Association between variables was quantified through Pearson's correlation coefficient.

Results: Individuals with TLE+PNES had similar psychological constructs to patients with PNES but one. Indeed, they had high levels of depression, anxiety and alessithymic trait, but none of them experienced any trauma event (emotional abuse, emotional neglect, sexual abuse, sexual harassment, physical abuse), while these occurred in 18/22 with PNES only. Individuals with TLE+PNES obtained a significant lower score on WEIGL test, testing for executive abilities, compared to patents with PNES only (p=0.002). The other neuropsychological tests showed no statistical differences among the three groups.

Discussion: Our study gives evidence that patients with TLE+PNES and normal intellectual ability share similar psychopathological constructs to patients with PNES only, except for the absence of traumatic experience. Moreover, individuals with TLE+PNES have reduced executive skills compared to those with PNES, regardless of psychopathologic scores, age at onset, education, anti-seizure and psychiatric medications.

Conclusions: Our study allows to speculate that epilepsy itself may represent the stressful factor for the occurrence of PNES in patients with epilepsy and normal intellectual ability.

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THE ROLE OF COGNITIVE RESERVE ON ALEXITHYMIA IN SUBJECTS WITH SCI IN RELATION TO THE PERIOD OF HOSPITALISATION BEFORE AND DURING COVID-19 PANDEMIC

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Objectives: Spinal cord injury (SCI) is damage to a segment of the spinal cord that causes partial or complete loss of function below the injury site. Cognitive Reserve (CR) can be a protective factor on emotional dysregulation of the patient with SCI. CR is understood as the adaptability of cognitive processes that explains the differential susceptibility to brain aging, pathology or insult. This research aims to explore the impact of the CR on alexithymia levels in patients with SCI, differentiated according to the period of hospitalization (before and after the lockdown imposed by the Covid-19 pandemic).

Materials and methods: 94 patients with SCI (21 females and 73 males; mean age 46.14 ± 15.56) were recruited at the IRCCS Santa Lucia Foundation and were administered the Toronto Alexithymia Scale 20. 47 patients were hospitalized pre-Covid-19 (9 females and 38 males; mean age 44,21 ±14,10) and 47 hospitalized post-Covid-19 (12 females and 35 males; mean age 48,06±16,82). Both samples were divided into two groups, according to their CR scores obtained by the years of formal education. The two groups were homogeneous in age, gender distribution, education and hospitalisation period. Within such a distribution, all individuals reporting a z score <0 were considered as belonging to the group of patients with low CR (Pre-group CRLOW=21; Pre-group CRLOW=20). Conversely, individuals with a z score >0 were considered as belonging to the group of patients with high CR (Post-group CRHIGH=26; Post-group CRHIGH=27). All groups were administered a battery of standardised psychodiagnostic tests to evaluate various psychological variables.

Results: In the pre-Covid-19 group there appears to be an effect of reserve on alexithymic dimension as subjects with low levels of cognitive reserve showed significantly higher levels of alexithymia (p=0.03) than subjects with high cognitive reserve. The results show that subjects with low cognitive reserve become significantly more alexithymic (p=0.001) than those with high cognitive reserve during hospitalization. Furthermore, in the post-Covid-19 group it is observed that subjects with low levels of cognitive reserve have higher alexithymia scores in the initial period of hospitalization (p=0.02) than subjects with high CR scores.

Discussion: These findings suggest a positive association between low CR levels and symptoms related to emotional dysregulation in individuals with SCI.

Conclusions: Hight level of CR could be a protective factor for emotion dysregulation in individuals with SCI in relation to the period of hospitalisation.

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HIPPOCAMPAL MICROSTRUCTURAL INTEGRITY AND SPEED OF INFORMATION PROCESSING IN MULTIPLE SCLEROSIS

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Objectives: The contribution of hippocampal atrophy to cognitive impairment has been widely described in multiple sclerosis (MS). However, less

is known about measures of microstructural damage, which could provide further insights on mechanisms of cognitive dysfunction. We investigated the association between hippocampal microstructural integrity and information processing speed deficit (IPS) in MS.

Materials: Fifty healthy controls (HC) and 117 MS patients underwent 3.0T MRI. Global and subregional hippocampal volumes were assessed with the cross-sectional pipeline of the Freesurfer 6.0. Measures of microstructural integrity were obtained using diffusion tensor imaging (i.e., fractional anisotropy [FA], mean diffusivity [MD]) and neurite orientation dispersion and density imaging (NODDI, i.e., neurite density index, orientation dispersion index [ODI]). Symbol Digit Modalities Test (SDMT) was administered to assess IPS, and z-scores were calculated according to normative data. Methods. Age- and sex-adjusted linear models were used for between-group comparisons, while hierarchical linear regression analysis was run to identify predictors of SDMT z-scores among clinical and MRI variables in MS patients.

Results: Compared to HC, MS patients showed an average volume reduction in the fimbria ($p<0.01$). The hippocampus of MS patients was characterized by reduced FA and increased MD and ODI compared to HC ($p<0.01$). Older age ($\Delta R2=0.19$; $p<0.001$), higher T2-lesion volume ($\Delta R2=0.06$; $p<0.01$) and higher MD of the fimbria ($\Delta R2=0.05$; $p=0.01$) were selected as significant predictors of slower IPS measured with SDMT (Adjusted-R2=0.27).

Discussion: The results showed that for the SDMT, age, T2-lesion volume and MD of the fimbria were able to explain 27% of the variance.

Conclusions: The integrity of the fimbria appears to be a critical anatomical correlate of information processing speed performance in MS.

VISUOSPATIAL DEFICITS ARE SPECIFIC FOR PISA SYNDROME BUT NOT FOR CAMPTOCORMIA IN PARKINSON DISEASE

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Objectives: Pisa syndrome (PS) and camptocormia (CC) are frequent postural abnormalities (PA) associated with Parkinson disease (PD). The pathophysiology of these PA still remains largely unclear. Prior studies, involving small patient groups, have suggested that PS and CC may be associated with cognitive alterations involving visuospatial and attentive functions. The aim of our study is to evaluate the potential contribution of cognitive deficits in determining PA in patients with PD.

Materials: All patients underwent an extensive clinical and neuropsychological assessment, evaluating five cognitive domains: memory, attention, executive functions, visuospatial abilities, language. Z-scores of each test were used to estimate a cognitive domain score, which was compared for PS+ vs. PS- and CC+ vs. CC- using the Mann-Whitney test.

Method: We performed a multicenter, case-control study to analyze the cognitive profile of PD patients with either Pisa syndrome or camptocormia as compared to matched PD patients without PA. Seven Italian and 1 German centers specialized for movement disorders participated in the study. A total of 114 PD patients were enrolled: 32 with Pisa syndrome (PS+), 25 with camptocormia (CC+), 32 without PA who were matched for gender, age, education, PD duration, and PD stage with PS+ (PS-), and 25 without PA who were matched for gender, age, education, PD duration, and PD stage with CC+ (CC-).

Results: All groups were comparable for the main demographic and clinical features. PS+ showed significantly worse visuospatial performances than PS- (Z-score PS+ -1±1.1; PS- 0.5±0.9; p:0.025), while CC+ did not show any significant differences when compared to CC-. The global cognitive score, assessed by the Montreal Cognitive Assessment (MoCA), did not differ significantly between groups, nor did the scores regarding the other cognitive domains.

Discussion: Our results confirm, with an adequate sample size and methodology, preliminary data on the association of worse visuospatial abilities in PD patients with PS compared with matched PD patients differing only for the absence of PA. On the contrary, we did not observe the same association for CC patients.

Conclusions: These results indicate different pathophysiological trajectories between PS and CC, with specific visuospatial deficits that are possibly implicated in the development of PS but not of CC.

THE RELATIONSHIP BETWEEN SOCIAL COGNITION AND EXECUTIVE FUNCTIONS IN AMYOTROPHIC LATERAL SCLEROSIS: A CENTRE-BASED STUDY

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Objective: The aim of the present study was to explore the correlation between Facial Emotion Recognition (FER) and Theory of Mind (ToM) with Executive Functions in a cohort of ALS patients.

Background: In the last decade Social Cognition (SC) has been intensively investigated in neurodegenerative disorders, included ALS [1]. Impairment in SC subdomains were reported in ALS and SC deficits have been included in the revised Strong criteria [2]. However, to date, it is debated how executive functions relate to SC abilities and, specifically, to what extent a deficit in SC can be explained by a deficit in executive functions.

Methods: We enrolled 92 consecutive patients attending the Turin ALS Center with diagnosis of probable, probable laboratory supported or definite ALS. They underwent a Neuropsychological battery assessing the five fundamental cognitive domains, included executive functions and Social Cognition. Executive functions were assessed through the Letter Fluency test (FAS), Category Fluency test, Trail Making Test B-A (TMT B-A) and Frontal Assessment Battery. FER was assessed using the Ekman 60 Faces Test (EK-60F). Affective Theory of Mind was assessed though the Reading the Mind in the Eyes test-36 faces full version (RMET-36) and the Story-Based Empathy Task-Emotion Attribution. Cognitive ToM was assessed by Story-Based Empathy Task-Intention Attribution. Multiple linear regression analysis was conducted to correlate SC tests corrected scores with the Neuropsychological tests assessing executive functions.

Results: EK-60F did not show significant overall nor specific correlation (R2 adj 0.102, p 0.316) with tests assessing executive functions. RMET-36 showed an overall moderate significant correlation (R2 adj 0.353, $p<0.001$) with tests assessing executive functions and a significant specific correlation with FAS (p 0.025). SET-GS showed an overall weak significant correlation (R2 adj 0.282, $p<0.001$) with tests assessing executive functions and a specific correlation with TMT B-A (p 0.018).

Discussions: Taken together our results show that there is a different degree of correlation with executive functions based on the SC domain investigated. While FER is overall independent from executive functions, ToM show a partial correlation with executive functions and a specific correlation with TMT B-A, aimed at assessing mental flexibility and visual scanning, required for the execution of ToM tasks.

Conclusions: Our results show a differentiated pattern of correlation between SC abilities and executive functions, depending on the SC subdomain explored, in line with previous results [3]. This support the need of further studies on larger samples aimed at exploring neuropsychological determinants of SC abilities in ALS patients.

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PSYCHOLOGICAL IMPACT OF EXPOSURE TO THE COVID-19 HEALTH CRISIS IN HEALTHCARE WORKERS: THE ROLE OF COGNITIVE RESERVE AS A PROTECTIVE FACTOR

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Objectives: The COVID-19 health crisis is associated with emotional difficulties such as depression, anxiety, and reactive post-traumatic symptoms among healthcare professionals. This study aimed to investigate the effects of exposure to COVID-19 sanitary crisis on affective symptoms (anxiety, depression, post-traumatic stress) among health professionals and the role of CR, the ability to optimize or maximize performance through the differential recruitment of brain networks, as a protective factor capable of affecting the relationship between anxiety, depression and stress.

Methods: The sample is made up of 50 health workers (28 females and 22 males; mean age 50.74 ± 11.91) recruited at the Santa Lucia IRCCS Foundation. The sample was divided into two groups, based on the CR scores obtained in the years of formal education. Within such a distribution, all individuals reporting a z score <0 were considered as belonging to the group with low CR, conversely, individuals with a z-score> 0 were considered to belong to the high CR patient group. The sample was divided into two groups: CRLOW= 30 subjects; CRHIGH=20 subjects, according to CR scores based on the years of education. The two groups were homogeneous in age, gender distribution and educational level. The subjects were given an anonymous paper-pencil questionnaire, the DASS-21 Questionnaire (which provides dimensional measures of stress, anxiety and depression); aimed at investigating the stress caused by COVID-19. The same subjects were evaluated before and after the period of the health emergency.

Results: Results show few significant emotional difficulties. There are significant differences in anxiety levels (p=0.02), stress levels (p=0.03) and depression levels (p=0.01), all increasing in the post-covid period. CR has no effect on these dimensions.

Discussion: The impact of the pandemic on health workers was important on the psychological dimensions investigated, but the Cognitive Reserve does not seem to act on the emotional dimensions, so it is not enough to be protective.

Conclusions: Interventions to promote mental well-being in health care professionals exposed to COVID-19 need to be implemented immediately, promoting prevention and response strategies in terms of mental help and crisis management.

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THE IMPACT OF COVID-19 PANDEMIC ON PSYCHOPHYSICAL WELL-BEING IN PATIENTS WITH SPINAL CORD INJURY

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Objectives: The Covid-19 pandemic has had a huge worldwide impact in all medical sectors, including neurorehabilitation of patients admitted to spinal units following a spinal cord injury (SCI). People who suffer damage to the spinal cord are almost always faced with a condition of permanent disability that involves devastating and dramatic changes on a psychological status. The study aims to evaluate relations between psychological variables, evaluated before and during the Covid-19 pandemic.

Methods: Two groups of patients with SCI were recruited to the IRCCS Santa Lucia Foundation. The first group recruited before the pandemic event (Pre-Covid) was composed of 47 subjects (9 females and 38 males; mean age 44,21 ±14,10); the second group recruited after (Post-Covid) consisted of 47 subjects (12 females and 35 males; mean age 48,06±16,82). The two groups were homogeneous in terms of age, gender distribution and education. Both groups were administered the CBA STAI was used for assessing anxious states, the CBA-QD 8 for evaluating depressive symptoms and the CBA 5 for assessing extroversion. The Rosenberg Self-Assessment Scale was used to assess self-esteem. The motivational questionnaire was also used to measure motivation index and the Toronto Alexithymia Scale 20 (TAS-20) to measure alexithymia. The spinal cord independence measure (SCIM) was employed to evaluate the level of independence. Finally, the level of disease awareness and family support were also assessed.

Results: The Post-Covid group showed higher levels of anxiety upon entry (p=0.03) than those reported by the Pre-Covid group. The level of anxiety was seen to decrease during hospitalization. The Post-Covid group showed a significantly higher level of depression on entry (p=0.01) and on exit (p= 0.04) from hospitalization compared to the Pre-Covid group. This result is also related to the level of awareness experienced. Indeed, the subjects of the post-Covid group manifested a significantly higher level of awareness of the disease at entry (p=0.01)

than that shown in the other group. On the other hand, patients in the Pre-Covid group had significantly higher levels of disease awareness after hospitalization. Furthermore, it is highlighted that in the Pre-Covid group a higher level of family support was observed (p= 0.05).

Discussion: The results confirms that, following the pandemic break out, SCI patients have acquired a greater awareness of their condition and this correlates positively with the levels of anxiety and depression experienced.

Conclusion: Pandemic has had a significant impact on the psycho-physical status of people with SCI.

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APATHETIC FEATURES ACROSS NEURODEGENERATIVE MOTOR DISORDERS: A COMPARISON BETWEEN ALS, PARKINSON'S AND HUNTINGTON'S DISEASE

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Aims: Apathy is a behavioural feature common to several neurodegenerative conditions affecting cortical/subcortical frontal structures, whose assessment is clinically crucial as being a symptom that entails detrimental impacts on patients' prognosis [1]. However, across pyramidal (ALS) and either hypokinetic (Parkinson's disease, PD) or hyperkinetic (Huntington's disease, HD) extra-pyramidal disorders, the unraveling of its semiology is challenged by the confounding effect of motor disabilities, as well as by the different extent to which cortical-subcortical circuitries are involved [2]. This study thus aimed at 1) profiling apathy in ALS, PD and HD patients and 2) explore its association with disease-related variables.

Materials: Consecutive ALS (N=99), PD (N=73) and HD (N=25) patients matched for education underwent a motor-free assessment of apathy (Dimensional Apathy Scale, DAS) [3], global cognition (Edinburgh Cognitive and Behavioural ALS Screen, ECAS) and behaviour (Beaumont Behavioural Inventory, BBI), anxiety (State-Trait Anxiety Inventory-Y, STAI-Y1 and -Y2 for state- and trait-anxiety, respectively) and depression (Beck Depression Inventory, BDI). Functional outcome was assessed through disease-specific scales (ALS: ALS Functional Rating Scale-Revised; PD: Unified Parkinson's Disease Rating Scale-II and -III; HD: Unified Huntington's Disease Rating Scale-I, -IV, -V and -VI).

Methods: Between-group comparisons on DAS scores were implemented via linear models by covarying for age, sex, ECAS, BBI, STAI-Y1, STAI-Y2 and BDI scores. Bonferroni-corrected Spearman's correlations were run to examine the association between DAS-Total scores and disease-related variables separately for the three groups.

Results: HD scored higher than ALS patients on the DAS-Total (p=.005) and the DAS-Executive (p=.004), with no other comparisons yielding significance. The three groups were comparable on DAS-Emotional and DAS-Initiation scores. The DAS-Total was associated with STAIY-2 scores in ALS (rs=.45) and HD (rs=.59) patients, whereas, in PD ones, with the BBI (rs=.43) and the ECAS (rs=-.43). No associations were detected with functional measures.

Discussion: When compared to ALS patients, HD ones present with greater levels of apathy, which is likely of a dysexecutive nature. However, HD patients are comparable to PD ones as to such features. Emotional apathy and cognitive/behavioural initiation are not able to discriminate between ALS, PD and HD populations. Trait-anxiety contributes to apathy in ALS and HD patients, whereas, in PD ones, global cognitive efficiency and overall behavioural state does.

Conclusions: Partially different apathetic profiles may feature diverse neurodegenerative motor disorders. Moreover, different cognitive/behavioural underpinnings might account for apathy based on the clinical population.

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DETERMINANTS OF COUNTERFACTUAL THINKING IN ALS: AN EXPLORATIVE STUDY

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Aims: Counterfactual thinking (CFT) is defined as one's own ability to cognitively simulate alternatives to events that have occurred, this allowing individuals to regulate complex behaviours at both individual and social levels [1]. Despite having been shown that CFT can be altered in a variety of neurological and psychiatric conditions affecting frontal networks, and thus high-order executive processes and behavioural regulation [1,2], little is known on such an ability in the ALS population. However, assessing CFT in these patients may be prognostically relevant, given its likely link with functional independence, decision-making and adherence within care settings [1,2]. This study thus aimed at exploring the association between CFT measures and clinical variables in an ALS cohort.

Materials: Fifty-two consecutive ALS patients underwent two CFT measures, i.e. the Counterfactual Interference Test (CIT) [3] and the Spontaneous Counterfactual Generation Test (SCGT) [3], as well as an assessment of global cognitive efficiency (Edinburgh Cognitive and Behavioural ALS Screen, ECAS), social cognition (Story-Based Empathy Task, SET), overall behaviour (Beaumont Behavioural Inventory, BBI), apathy (Dimensional Apathy Scale, DAS), anxiety (State-Trait Anxiety Inventory-Y, STAI-Y1 and -Y2 for state- and trait-anxiety, respectively) and depression (Beck Depression Inventory, BDI). Functional outcome was assessed via the ALS Functional Rating Scale-Revised (ALSFRS-R).

Methods: Stepwise, multiple regression models were separately run on CFT and SCGT scores by entering age, education, sex, ALSFRS-R, disease duration, bulbar onset, presence of bulbar signs, ECAS-ALS-Specific, ECAS-ALS-Nonspecific, SET, BBI, DAS, STAI-Y1, STAI-Y2 and BDI scores as predictors.

Results: CIT scores were inversely predicted by the STAI-Y1 only (β=-.36; p=.022), whereas the only significant, positive predictor of the SCGT was the SET (β=.32; p=.04).

Discussion: When taking into account motor, cognitive, behavioural and psychological features, only state-anxiety and social-cognitive abilities appear to be predictive of CFT skills in ALS patients. More specifically, higher levels of state-anxiety negatively contributes to CFT abilities, whereas the latter increase with a higher level of social-cognitive functioning.

Conclusions: The present findings, albeit preliminary, support the notion of high-order, complex cognitive and behavioural processes being linked to CFT abilities in ALS patients, similarly to what has been found in other neurodegenerative conditions [1,2].

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MOTOR AND NON-MOTOR DETERMINANTS OF APATHETIC FEATURES IN ALS

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Aims: Among frontotemporal, dysexecutive features typical of ALS patients, apathy is the most common behavioural symptom (25-34%) [1], which allows per se to classify them as behaviourally impaired [2] and whose detrimental impact on their prognosis is thoroughly acknowledged [1]. As the underpinnings and clinical presentation of apathy in this population are still poorly understood, this study aimed at 1) profiling apathetic features and 2) identify their motor and non-motor determinants in ALS patients.

Materials: Ninety-nine consecutive ALS patients and 59 sex- and education-matched healthy controls (HCs) were compared on the Dimensional Apathy Scale (DAS) [3] and its Executive, Emotional and Initiation sub-scales. Patients further underwent motor (ALS Functional Rating Scale-Revised, ALSFRS-R), cognitive (Edinburgh Cognitive and Behavioural ALS Screen, ECAS) and behavioural assessment (Beaumont Behavioural Inventory, BBI; State-Trait Anxiety Inventory-Y, STAI-Y1 and -Y2 for state- and trait-anxiety, respectively; Beck Depression Inventory, BDI).

Methods: Between-group comparisons on DAS scores were implemented via linear models by covarying for age. Stepwise regressions were performed on DAS scores by entering as predictors disease duration, presence of bulbar signs, bulbar onset as well as ALSFRS-R, ECAS-Executive Function and -Fluency, BBI, STAI-Y1 and STAI-Y2 and BDI scores. Education was covaried within the latter analyses as having been shown to influence DAS scores [3].

Results: The two groups were comparable on the DAS-Total, with only its Initiation sub-scale being able to discriminate (p=.002) between patients (8.58±.43) and HCs (6.18±.61). DAS-total scores were predicted only by the STAIY-2 (β=.42; p<.001), the DAS-Emotional by disease duration (β=-.21; p=.046), STAI-Y1 (β=-.28; p=.009) and ECAS-Executive Function scores (β=.23; p=.033), the DAS-Executive by STAI-Y2 (β=.43; p<.001), ECAS-Executive Function (β=-.33; p<.001) and BDI scores (β=.2; p=.027), whereas the DAS-Initiation by ALSFRS-R (β=-.23; p=.017) and STAI-Y2 scores (β=.32; p<.001).

Discussion: Apathy in ALS patients is predominantly characterized by a diminished cognitive/behavioural initiation, being strongly determined by trait-anxiety levels and, to a lesser extent, by depressive symptoms and executive efficiency. Moreover, a more severe motor impairment appears to be linked to a decrease in cognitive/behavioural initiation. By contrast, a longer disease duration, a decreased executive efficiency and increased state-anxiety levels may be protective towards emotional apathy.

Conclusions: Apathetic features in ALS patients clinically present with a lack of cognitive/behavioural initiation and are underpinned by both motor (disease severity and duration) and non-motor determinants (executive functioning, anxiety and depression), which however contribute differently to each apathy domain.

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STRUCTURAL AND FUNCTIONAL MAGNETIC RESONANCE IMAGING CORRELATES OF FATIGUE AND DUAL-TASK PERFORMANCE IN PROGRESSIVE MULTIPLE SCLEROSIS

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Objectives: Damage of frontal cortico-subcortical networks contributes to fatigue and dual-task impairment in multiple sclerosis (MS). However, the mechanisms underlying these clinical deficits in progressive (P) MS still need to be fully explored. In this study, we investigated the associations between structural and functional MRI abnormalities of frontal cortico-subcortical circuits and fatigue and dual-task performance in PMS.

Material and Methods: Brain structural and functional MRI scans, Modified Fatigue Impact Scale (MFIS) and dual-task performances were obtained from 57 PMS patients with impaired processing speed from 4 centers and 10 healthy controls (HC). The associations of thalamic, caudate nucleus and dorsolateral prefrontal cortex (DLPFC) atrophy, microstructural abnormalities of their connecting tracts and their resting state effective connectivity (RS EC) with fatigue, single- and dual-task performances were investigated.

Results: Compared to HC, PMS patients had higher fatigue ($p \leq 0.027$) and worse dual-task performance ($p < 0.001$). Compared to non-fatigued (MFIS<38), PMS patients with fatigue (MFIS≥38) had lower RS EC from left-caudate nucleus to left-DLPFC ($p = 0.007$). In PMS, higher MFIS-physical and MFIS-psychosocial scores were predicted by lower RS EC from left-caudate nucleus to left-DLPFC ($R2 = 0.112$, $p = 0.027$) and higher RS EC from right-thalamus to right-DLPFC ($R2 = 0.102$, $p = 0.046$), respectively. Dual-task motor performances were predicted by lower RS EC from left-DLPFC to left-thalamus ($R2 \geq 0.137$, $p \leq 0.032$). Several structural MRI measures independently predicted dual-task correct response rates ($R2 = 0.307$, $p \leq 0.010$) and dual-task cognitive cost ($R2 = 0.188$, $p = 0.002$). Fatigue impact was not associated with single- and dual-task performances.

Discussion: Specific structural and functional MRI abnormalities were differently associated with fatigue impact and motor and cognitive performance of single- and dual-task. While fatigue was mainly associated with functional abnormalities within this network, worse cognitive dual-task performance was mainly explained by measures of structural damage involving this cortico-subcortical pathway.

Conclusions: Frontal cortico-subcortical structural and functional MRI abnormalities differently contribute to fatigue impact and single- and dual-task performance in PMS.

Funding. This study was funded by a grant from the Multiple Sclerosis Society of Canada (grant no. #EGID3185) and the National MS Society.

SEMANTIC VERBAL FLUENCY AS A SCREENING TEST IN EARLY STAGE OF ALZHEIMER'S DISEASE

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Objectives: The NeuroArtP3 (NET-2018-12366666) is a multicenter project, funded by the Italian Ministry of Health, aiming at harmonizing clinical data coming from the centers involved. Clinical diagnosis of dementia requires a time consuming psychometric testing which is difficult to incorporate into routine medical-practice. Screening instruments, as the Mini Mental State Examination (MMSE), have been developed as a brief global cognitive instrument to assist physicians in the detection of cognitive decline [1], whereas verbal fluency, memory and spatial abilities are the most common cognitive functions assessed during the concomitant neuropsychological assessment. In this study we want to investigate which neuropsychological test can be likely to serve as a screening test for the diagnosis of patients at a mild stage, since an early identification of patients with mild cognitive impairment (MCI) may lead to interventions in the early stages of the disease.

Methods: A population of 26 MCI patients (14 females, mean age 70.42 y.o., ±8.5, education 10.54 y.o., ±4.39, mean disease onset 5.35 y.o., ±1.87) underwent a cognitive assessment at baseline with the MMSE, the verbal fluency tasks (phonological and semantic fluency with three categories per each task), the memory (digit forward) and the spatial (Corsi block-tapping) tests. Patients were also evaluated annually for further three years follow-up undergoing FDG-PET imaging exam and were finally diagnosed with Alzheimer dementia (AD).

Results: By spearman correlation analysis, only the performance at the semantic fluency task revealed a significant correlation with the MMSE scores (multiple comparisons correction was applied). This correlation

was significant with patients presenting with mild symptoms (MMSE mean score 24.23, ±2.81; semantic fluency mean score 25.30, ±12.11) at baseline.

Conclusions: These results indicate that verbal fluency might be a significant predictor of diagnostic classification for AD [2]. Particularly semantic fluency might serve as a three minute test for the investigation of early symptoms of dementia in time-restricted clinical settings [3]. Future studies should investigate whether the same predictive ability of semantic fluency persists also in more moderate to severe disease stages.

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COGNITIVE PERFORMANCE IN ADOLESCENTS WITH MULTIPLE SCLEROSIS: THE ROLE OF THE TREATMENT

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Objectives: Multiple Sclerosis (MS) is a disease usually diagnosed in young and middle-aged adults. Although MS is a rare condition in pediatric age, an increasing rate of patients are diagnosed under the age of 18. The therapeutic options include oral, self-injected and intravenous agents (some of them still not approved in pediatric age). Cognitive decline is a common features of MS. It involves verbal and visuo-spatial memory, processing speed, attention and executive functions. Impairment in multiple cognitive skills has been described also in pediatric age, with possible impact on academic, familiar, and social functioning. Data on the role of the different therapeutic approaches on cognitive ability in pediatric age are sparse. We evaluated: 1) the impact of treatment received on patients' cognitive performance in one year follow up; 2) the association between cognitive profile, fatigue, psychological symptoms, and treatment received.

Materials: The cognitive profile was assessed by Rao's Brief Repeatable Battery (SDMT, CLRT, LTS, SPART, PASAT and LWG subtests). The Fatigue Severity Scale (FSS), Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 Questionnaire (GAD-7) were used to explore fatigue, depression and anxiety.

Methods: Twenty-nine adolescents with MS were included (9 boys, 20 girls; mean onset age=13.9 ± 2.1). Fourteen patients received infusion treatment (n= 10 Natalizumab; 3 Ocrelizumab; 1 Rituximab) and 15 received non-infusion treatment (n= 1 Glatiramer Acetate; 6 Interferon beta 1a; 2 Dimethyl Fumarate; 6 Fingolimod). Every patient underwent a baseline evaluation (T1) and the second evaluation (T2).

Results: Our data evidenced a general improvement in several subtests of the Rao battery (p= <0.05). Twenty-two patients (76%) obtained higher scores in processing speed (SDMT) in T2 compared with T1 (p= 0.06). Moreover, our data showed an improvement in short-term verbal memory (SRT- LTS, p= 0.02), short-term spatial memory (SRT, p= 0.00) and executive functions (LWG, p< 0.00). A positive association between the levels of fatigue and SDMT in T2 was found (p= 0.02). A large percentage of patients showed depression (62%) and anxiety symptoms (76%) in the second evaluation. Among our patients, no differences emerged in Rao subtests, anxiety, depression and fatigue levels between the first and second evaluations (p= >0.05).

Discussion and conclusions: Our study demonstrates a positive influence of medical treatment on cognitive performance in pediatric MS. Given the impact that MS can have on emotional development, a special attention should be paid to young patients' psychological symptoms.

REGIONAL DISTRIBUTION OF WHITE MATTER LESIONS AND MICROSTRUCTURAL ABNORMALITIES BUT NOT GRAY MATTER ATROPHY CONTRIBUTE TO EXPLAIN SEX-RELATED DIFFERENCES IN COGNITIVE PERFORMANCES IN MULTIPLE SCLEROSIS

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Objectives: Sex may influence cognitive performances in patients with multiple sclerosis (PwMS). However, the substrates of sex-related cognitive differences in PwMS still need to be fully investigated. To explore whether differences in the regional distribution of focal white matter (WM) lesions, WM microstructural abnormalities and gray matter (GM) atrophy may explain sex-related differences of cognitive performances in PwMS.

Material and Methods: Brain 3.0 T MRI scan and Rao's battery were acquired for 287 PwMS (women=173) and 172 healthy controls (HC) (women=92). Using voxel-wise analyses, we investigated sex-related differences in regional T2-hyperintense WM lesions, WM fractional anisotropy (FA) abnormalities and GM volumes between PwMS and HC and their associations with cognitive performances (p<0.05, family-wise error [FWE]).

Results: Verbal memory was significantly worse in male vs female PwMS (p<0.001), whereas verbal fluency was worse in female vs male PwMS (p=0.001). In both female and male PwMS, a higher prevalence of T2-hyperintense WM lesions in cognitively-relevant WM tracts was significantly associated with worse cognitive performances. Such associations were significantly stronger in female vs male PwMS in left anterior thalamic radiation and superior longitudinal fasciculus for global cognition and attention. Female vs male PwMS showed significantly lower FA in most of WM tracts, with a larger effect of MS in females on lowering FA values in the majority of WM tracts. In both female and male PwMS, worse cognitive performances were associated with lower FA values in the majority of WM tracts. Such associations were significantly stronger in female vs male PwMS in many several cognitively-relevant WM tracts for global cognition and verbal memory. A significantly lower GM

volume in bilateral frontal orbital cortex and left anterior cingulate cortex was found in male vs female PwMS. In both female and male PwMS, a significantly lower GM volume in several cortico-subcortical brain regions was associated with worse cognitive performances, without between-groups differences.

Discussion: Sex influences the patterns of WM FA abnormalities and the associations between regional T2-hyperintense WM lesions, WM FA abnormalities and cognitive performances. These sex-related differences may explain diverse cognitive profile in female and male PwMS.

Conclusions: The application of MRI sequences, sensitive and specific to the different pathological substrates of the disease, may contribute to explain the different clinical manifestation of MS between female and male patients.

NEUROREHABILITATION AND NEUROTRAUMATOLOGY

THE INSULA MODULATES THE EFFECTS OF AEROBIC TRAINING ON CARDIOVASCULAR FUNCTION AND AMBULATION IN MULTIPLE SCLEROSIS

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Objectives: Aim of this study was to understand the effects of aerobic training (AT), focusing on the role of insula (differentiating in right and left) in establishing cardiovascular fitness (CF) and AT responses in patients with multiple sclerosis (MS).

Materials: 61 MS patients were enrolled and randomized in two groups (MS-A and MS-C) to perform 24 training sessions of 30-40 minutes for 2-3 times per week.

Methods: MS-A performed moderate AT, while MS-C underwent non-specific motor training. All patients had a baseline and follow-up evaluation after the training period, including assessment of maximal peak of oxygen consumption (VO2max), heart rate reserve (HRR), 6-minute walk test (6MWT) and a MRI scan to quantify lesion volumes (LV), global and regional brain atrophy. Two age- and sex-matched healthy control (HC) groups were enrolled to have reference data for the analysis of CF and brain volumetric data. In addition, MS subjects were divided based on the baseline presence (MS-WL) or absence (MS-WOL) of insular lesions.

Results: At baseline, MS patients showed impaired values of VO2max, HRR and 6MWT ($p<0.001$) and a widespread pattern of atrophy compared to HC, including bilateral insula. Compared to MS-WL, MS-WOL tends to have higher values of VO2max ($p=0.066$) and longer distance of 6MWT ($p=0.05$). In MS, higher left insula LV correlated to higher HRR ($R=0.27$, $p<0.05$). After training, MS-A experienced an improvement in 6MWT compared to MS-C, independently from the presence of focal T2 lesions in the insula. Within MS-A, MS-WOL experienced more improvement in the 6MWT distance ($p<0.05$) compared to MS-WL. At follow-up, MS-C showed a reduction of left anterior insula volume compared to baseline ($p<0.001$). In MS-A, increase of the left anterior insula volume correlated to 6MWT improvement ($R=0.65$, $p<0.001$).

Discussion: Previous literature found different cardiovascular system response to exercise in MS [1] and a crucial role of insula on CF [2,3], as confirmed by baseline results of this study. Follow-up results sustain that AT improves CF and walking capacity in MS patients, but the presence of lesions within the insula is a key element to consider in the evaluation of the effect of AT.

Conclusions: AT improves CF and walking capacity in MS. It showed a neuroprotective effect, especially for the left insula that has a stronger relationship with CF, compared to the contralateral region.

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FUNCTIONAL OUTCOME AND DEATH THREE YEARS AFTER DISCHARGE FROM AN INTENSIVE REHABILITATION HOSPITAL IN MODERATE SEVERE STROKE PATIENTS

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Background: Long-term outcomes after moderate severe stroke are hardly known. Our aim was to describe functional outcome three years after discharge from an intensive stroke rehabilitation hospital.

Methods: This study was a single-center, prospective observational study. All patients (aged> 18 years old) discharged from January 2018 to June 2019 from IRCCS Fondazione Don Carlo Gnocchi in Florence, with a diagnosis of stroke were contacted by telephone 3 years after stroke. Study outcome was the modified Rankin Scale (mRS).

Results: Among 201 patients, we obtained telephone information for 116 (mean age 73.7±13.7, 49% male). Forty-two (36%) patients died, fifty-six (48%) had a mRS score 3 to 5, eighteen (16%) a mRS score 0 to 2. From multivariate logistic regression models, predictors of death were: older age, (OR= 1.075, CI- 95%: 1.021-1.132, $p<0.006$), clinical severity (intensive vs sub-intensive neurological rehabilitation unit OR= 0.185, CI-95%: 0.056-0.612, $p<0.006$), poorer functional improvement during rehab-stay (OR= 0.424, CI-95%:0.185-0.974, $p<0.043$) and presence of neglect at the time of index-stroke (OR= 0.216, CI-95%:0.061-0.767, $p<0.018$). From multivariate linear regression models, age (beta=0.232, $p=0.004$) pre-stroke functional status (beta=0.162, $p=0.004$), functional status at discharge (beta=0.324, $p=0.001$), and neglect (beta=0.228, $p=0.004$) were predictors of long-term functional status (mRS score).

Conclusions: Our results confirm that stroke is a severe disease with high mortality and poor functional status in the long-term despite intensive acute neurological rehabilitation. The presence of neglect is a strong predictor of functional long-term outcome. Improving knowledge about long-term outcomes may enable to identify a tailored rehabilitative approach after stroke.

UTILITY OF OPTIC NERVE ULTRASOUND IN PATIENTS WITH PERSISTENT VEGETATIVE STATE

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Objectives: Verify whether ultra-sonographic retro bulbar optic nerve sheath diameter (ONSD) measurement may be useful in supporting neurological evaluation in comatose patients, outside intensive care.

Materials: 32 patients in a persistent vegetative state, secondary to severe acquired brain injury. All patients underwent craniotomy and subsequent repositioning of the skullcap. These patients were examined through neurological and sonographic evaluation by the same operators.

Methods: In the intensive rehabilitation unit for 16 weeks, we performed daily neurological evaluation associated with weekly optic nerve ultrasound for 32 patients to estimate intracranial pressure (ICP) [1]. ONSD was performed by measuring the transverse diameter at about 3 mm from the nerve papilla with linear probe [1]. Radiological and neurophysiological examinations were performed at the beginning and rapidly repeated once worsening was identified.

Results: During the follow-up of the 32 patients, 27 patients showed a clinical stability or a progressive improvement (84.7% of all). These patients showed a mean optic nerve thickness of 4.56 ± 0.9 mm in OD and 4.67 ± 1.0 mm in OS. Over the weeks 5 patients (15.6% of all) show worsening of neurological picture. ONSD was increased in 4 of these patients (80% of patients worsened; 12.5% of all). An increase in mean optic nerve diameter of 2.32 ± 0.34 mm in OD and 2.25 ± 0.31 mm in OS was observed (initial values 4.24 ± 0.7 mm in OD and 4.31 ± 0.6 mm in OS).

Discussion: In all patients, the neurological evaluation was shown to be able to discriminate an objective deterioration. Measurement of the ONSD with an increase of more than 1.8 mm of starting value suggested an increase in ICP in 4 of 5 patients, subsequently confirmed by other methodic. The only patient in which there has not been an increase in ONSD was suffering from a slow and progressive hypertensive pneumocephalus, probably for valve effect with slow adaptation to the high ICP [2].

Conclusions: The ultrasonography evaluation of ONSD allows to acquire positive predictive values of an increase in the ICP. In patients with persistent vegetative state, it can be a useful data to suppose further examinations [3]. The goal is to identify complications of surgical procedures and exclude a recurrence of tumor or intracerebral hemorrhage. Since it represents a simple and low-cost method, it should be ensured for patients in a persistent vegetative state in association with neurological evaluation and JFK Coma Recovery Scale-Revised compilation.

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EFFECTIVENESS OF A NEW WEARABLE CUEING SYSTEM (Q-WALK) IN IMPROVING GAIT AND BALANCE IN PATIENTS AFFECTED BY PARKINSON'S DISEASE

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Objective: Gait and balance disorders represent one of the most disabling features of Parkinson's disease (PD). Cueing has proven to be an effective rehabilitative approach in PD. This study aimed at investigating the effectiveness of gait rehabilitation performed by means of a new wearable visual cueing system (Q-Walk) compared to traditional visual cues (stripes on the floor) in PD subjects.

Materials and Methods: Inclusion criteria for the study were: absence of cognitive impairment (Mini-Mental State Examination ≥ 24); Hoehn & Yahr stage II-IV; mild to severe gait disturbance with score ≥2 in the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) III; stable drug therapy for at least 3 weeks. At the enrollment (T0), all subjects underwent a clinical/functional evaluation and the instrumental gait and postural analysis; then they were randomly assigned to the Study Group (SG) or Control Group (CG). Rehabilitation program consisted in 10 consecutive individual sessions (5 sessions/week for 2 consecutive weeks). Each session included 60 minutes of conventional physiotherapy plus 30 minutes of gait training by Q-Walk (SG) or by visual cues on the floor (CG). Follow-up visits were scheduled at the end of the treatment (T1) and after 3 months (T2).

Results: Twenty-six subjects were enrolled in the study, 13 in each group. The within-groups analysis showed a significant improvement in clinical and functional status at the end of the rehabilitation treatment and at follow-up in both groups. At the between-group comparison, clinical scales and gait parameters were not statistically different at T1 and T2, while in SG a significant reduction of the center of pressure was detected at T2 as well as a reduction of postural asymmetry both at T1 and T2. In the satisfaction questionnaire regarding the use of the Q-Walk system, 84.6% of the subjects found the tool easy to use and 76.9% defined the training motivating. Furthermore, most patients (92.3%) rated that they could also use the instrument at home.

Discussion: Data showed that the Q-Walk cueing system was not inferior to traditional visual cues in improving kinematic gait parameters and was significantly more effective in improving balance control in PD, being a simple, motivating and easily usable tool, suitable for home use.

Conclusion: Wearable devices, such as Q-Walk system, allow both continuity of care in the long term and generalizability of learning to the "real" world, favoring independence and participation.

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THE EFFICACY OF A REHABILITATION TREATMENT FOR THE MANAGEMENT OF FATIGUE IN INDIVIDUALS WITH MULTIPLE SCLEROSIS: OUTCOME RESEARCH

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Purpose: 50 to 90% of people with Multiple Sclerosis (MS) experience fatigue in their lifetime and 80% described it as the most disabling symptom, [1,2] fatigue, in fact, is one of the main causes of impairment of independence in all daily activities [3]. In the literature, several randomized controlled trials [6-9] have demonstrated the effectiveness of fatigue management programs on reducing the impact of fatigue in daily life and on improving the Quality of Life (QoL). However, none of these studies were based on the benefit for social participation. Social participation and effective management of the environment are two fundamental dimensions of evaluation and directly influence the functioning of the person. For this reason, the objective of this outcome research was to evaluate the effectiveness of a rehabilitation intervention based on the management of fatigue in people with MS, evaluating its impact on the improvement of QoL, the management of architectural barriers and social integration.

Methods and Materials: The intervention was administered as an outpatient program at the Policlinic Umberto I (Rome). Adult individuals with confirmed diagnosis of MS according to McDonald criteria were included, Expanded Disability Status Scale (EDSS) < 5,5, Fatigue Severity Scale (FSS) ≥ 4, Mini Mental State Examination (MMSE) > 21 and absence of psychiatric comorbidities. The intervention was based on a five-week program and follow-up was performed 3 and 6 months after the end of administration. The impact of fatigue was measured using the Fatigue Impact Scale (FIS), the environmental impact was measured using the Craig Hospital Inventory of Environmental Factors scale (CHIEF), the QoL was evaluated with the Multiple Sclerosis Quality of Life 54 Questionnaire (MSQol-54), the level of social integration was assessed through the Community Integration Questionnaire (CIQ-R), finally the impact on social participation and autonomy was also measured with the Impact on Participation and Autonomy (IPA) To identify user priorities and measure changes in perception regarding satisfaction and performance during the intervention, the Canadian Occupational Performance Measure (COPM) was used.

Results: For the following study 15 people were recruited, pre- and post-treatment evaluations showed statistically significant data for all outcomes with a $p < 0.05$.

Discussion and Conclusion: This study has shown that the rehabilitation intervention based on the management of fatigue in people with MS is effective in improving QoL, the management of architectural barriers and social integration.

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THE EFFICACY OF A PROGRAMMABLE KEYBOARD ON THE FUNCTION OF THE UPPER LIMBS AND ON THE ABILITY TO PERFORM THE ACTIVITIES OF DAILY LIVING IN A PERSON WITH HEMIPLEGIA: CASE REPORT

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Purpose: Clinical trials examining rehabilitation software and devices in individuals with hemiplegia are few, finding that these types of robotic rehabilitation are more effective in subjects with mild rather than moderate or severe hemiplegia. [1-3] A case report is proposed with the aim of demonstrating the rehabilitative effectiveness of a "Click4all" ® programmable keyboard designed to improve the performance of daily life activities with PC, TABLET AND SMATRTPHONE. The project aims to investigate the effects of this tool on the function of the upper limbs and on the ability to perform the activities of daily living (ADL) in a person with hemiplegia.

Methods and Materials: The person recruited for this case-report is a 31 years-old man, in 2017 he underwent an operation to remove the prefrontal cortical dysplasia that precisely causes epileptic seizures. Following this intervention he develops a left hemiplegia. The upper limb shows asymmetry of the shoulder on the frontal plane arm extended along the trunk and thumb slightly adducted. The user was assessed three times with the following tools: the Matching Person and Technology (MPT), The Survey of Technology Use (SOTU); the Assistive Technology Device Predisposition Assessment (ATD PA), and the Quebec User Assessment of Satisfaction with Assistive Technology (QUEST). After the first evaluation, the person was trained to use click all at home and started to use it at home 30 minutes 1 time per day for a period of 2 months. After one month he was evaluated again.

Results: Through the use of the MPT rating scale (ADT PA) the person reported satisfaction with respect to the results achieved in a variety of functional areas. Moreover, the average score on the QUEST ranging from 4.62 and 4.25 showing that the user is "very satisfied" with the aid. Finally, from the analysis of the data identified through the patient's evaluation of adherence and performance through Click4all, it can be seen how the patient has improved over time the usability not only of the instrument but also of its residual functions in the plegic limb.

Discussion and Conclusion: In this study it was showed the use of a Click4all programmable keyboard, to create a system in the form of both rehabilitation and autonomy aid. In fact, our results highlight not only a good degree of independence in the hemiplegic subject but also a highdegree of degree of psycho-social well-being.

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COMBINING NON-INVASIVE BRAIN STIMULATION (NIBS) WITH SPEECH THERAPY FOR THE TREATMENT OF NEUROGENIC DYSPHAGIA: NEUROPHYSIOLOGICAL OUTCOME IN PARKINSON'S DISEASE (PD)

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Introduction: Currently, there is a growing interest in the modulation of cortical excitability to improve swallowing function in patients with neurogenic dysphagia (ND). The focus has been shifting from pure biomechanical aspects of the swallowing act to the sensory-motor integration processes that occur in the CNS, fundamental for the correct execution of an effective swallowing act. Among new therapeutic perspectives, the use of transcranial Direct Current Stimulation (tDCS). Moreover, in the literature there are few works about the use of MEPs for studying dysphagic patients. Our primary aim was to evaluate neurophysiological effects of a combined speech therapy and tDCS approach in patients with ND.

Materials: Six patients (mean age ±SD = 68.5 ± 8.4 years) with neurogenic dysphagia were enrolled; five of them were diagnosed as having idiopathic Parkinson's Disease (PD), and the remaining one was diagnosed as probable Multiple System Atrophy (MSA, female, 69 years). PD patients had a disease course of 3-15 years (range).

Methods: Participants underwent anodal tDCS (anode on Cz, cathode over the right shoulder; 20' duration, 2.0 mA intensity for two consecutive weeks) combined with speech therapy (45', after tDCS, 6 consecutive weeks). They were evaluated before treatment (T0), at the end of the first two weeks (T1), after the whole treatment (T2, at 6 weeks), and 6 weeks after the end (T3). We assessed changes in Motor Evoked Potential (MEP) amplitudes and Total Motor Conduction Time (TMCT). MEPs were elicited by transcranial magnetic stimulation (TMS) of the scalp, at the level of Cz, and recorded from the transverse muscle of tongue. Bayesian one-way repeated measures analysis of variance was used to compare all data.

Results: The model comparison carried out with Bayesian Repeated Measures ANOVA revealed no evidence supporting either amplitude changes between each time point (BF10 = 0.288) or TMCT changes along time (BF10 = 0.390). Statistical analysis within sub-groups (post-hoc analysis) also revealed no evidence for either amplitude or TMCT changes between each time point.

However, we observed a general increasing trend of both MEPs amplitudes (mean ± SD at T0: 2.55 ± 1.34 mV; mean ± SD at T3: 3.08 ± 0.71 mV) and TMCT (mean ± SD at T0: 7.19 ± 0.41 ms; mean ± SD at T3: 8.15 ± 1.89 ms).

Discussion: Our findings suggest that combined tDCS and speech treatment improves swallowing, likely modulating the conduction along the corticobulbar tract as revealed by TMS measures.

PREVALENCE OF ICH AFTER MILD TRAUMATIC BRAIN INJURY IN PATIENTS UNDER TREATMENT WITH DOAC

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Aims: Assessing the risk of intracranial haemorrhage (ICH) in patients with a mild traumatic brain injury (MTBI) who are taking DOACs is challenging. Currently, extensive use of CT is routine in the emergency department (ED). The aim of this study is to investigate whether the clinical and laboratory characteristics presented at the ED evaluation can also estimate the risk of post-traumatic ICH in DOACs-treated patients with MTBI.

Methods: A retrospective observational study was conducted in three EDs in Italy from 1 January 2016 to 15 March 2020. All patients treated with DOACs who were evaluated for an MTBI in the ED were enrolled. The primary outcome of the study was the presence of post-traumatic ICH in the head CT performed in the ED.

Results: 930 patients on DOACs with MTBI were enrolled. Of these, 6.8% (63/930) presented a post-traumatic ICH, while 1.5% (14/930) were treated with surgery or died as a result of the ICH. None of the laboratory factors were associated with an increased risk of ICH. On multivariate analysis, previous neurosurgical intervention, major trauma dynamic, post-traumatic loss of consciousness, post-traumatic amnesia, a GCS score of 14 and evidence of trauma above the clavicles were associated with a higher risk of post-traumatic ICH. The net clinical benefit provided by risk factor assessment appears superior to the strategy of performing CT on all DOAC-treated patients.

Conclusions: Assessment of the clinical characteristics presented at ED admission can help identify DOACs-treated patients with MTBI who are at risk of ICH.

THE ROLE OF THE SERUM BIOMARKERS NF-L AND GFAP IN PREDICTING ISCHEMIC STROKE PATIENTS' OUTCOME

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Objectives: The aim of this study was to evaluate the correlation between serum concentrations of biomarkers derived from damaged neuronal and glial cells (Neurofilament-Light-Chain – NfL; Glial-Fibrillary-Acidic-Protein - GFAP) with the neurological deficit, functional outcome and performances in rehabilitation scales of ischemic stroke patients during 3-months of follow-up. This study is part of a broader project, and neuroregeneration biomarkers will be subsequently assessed as well.

Materials and Methods: For this longitudinal, prospective, multicentric, observational study, inclusion criteria were: patients >18y, onset

symptoms <24h, NIHSS >1. Exclusion criteria were: previous clinically symptomatic ischemic and/or hemorrhagic stroke, previous traumatic head injuries, other active central or peripheral nervous system disease, life expectancy <12 months, pregnancy. Patients were treated according to standard of care; those requiring intensive neurorehabilitation were discharged at a specialized unit. The time-points of evaluation were: within 24h from symptoms onset (D1) and after 7 (D7), 30 (M1) and 90 days (M3) from stroke. For each time-point, anamnestic information, diagnostics and treatments were recorded; stroke severity and functional outcome were evaluated respectively by NIHSS and mRS; the TCT, FAC and FIM neurorehabilitation scales were assessed; the NfL and GFAP serum concentrations were quantified by Single Molecule Array (SiMoA®).

Results: At present, 36 patients have been enrolled (20 women, mean age 75.11 [±11.80]); 41.7% had a minor, 47.2% a moderate and 11.1% a severe stroke. Median value of NfL=31.87 pg/mL, GFAP=601.29 pg/mL. Respect to D1, NfL increased at D7 (p<10^-5) and M1 (p<10^-4), subsequently returning at baseline at M3. GFAP was higher in D1, showing a decreasing trend in D7 which afterwards became significant at M1 (p<10^-4) and M3 (p<10^-4). The following prospective correlations were found between biomarker concentrations measured at their peak and scores of clinical/rehabilitation scales: D7-NfL significantly correlated with NIHSS, TCT, FAC, FIM (total, motor and cognitive) scales evaluated at M1 and M3, while mRS only at M1. D1-GFAP correlated similarly with the exception of TCT, significant only at M1.

Discussion: These preliminary results show a specific temporal profile of NfL and GFAP after acute ischemic stroke and a significant correlation between these biomarkers and the assessed clinical/rehabilitation outcomes. Of note, significant associations were maintained with both motor and cognitive FIM subscales, giving insights for the evaluation of post-stroke cognitive decline.

Conclusions: When completed, this study will provide a panel of biomarkers to prospectively correlate patients' outcome with both the ischemic injury and the neuroregeneration processes occurring at molecular level.

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REHABILITATION TREATMENT OF MICROGRAPHS IN INDIVIDUALS WITH PARKINSON'S DISEASE: OUTCOME RESEARCH

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Purposes: Micrography is one of the most common effects of Parkinson's disease and can be defined as "an impairment of the fine motor skills of the hand which mainly occur with a progressive or stable reduction in the writing width [1,2]". The exact prevalence of micrography is not yet clearly defined in the literature, ranging from 9 to 72% incidence (3-6); despite this, it is globally recognized as one of the first symptoms of Parkinson's disease, which can be used as a reliable criterion for early diagnosis. The aim of this study is to evaluate the effectiveness of a rehabilitation treatment for the improvement of micrography in individuals with Parkinson's disease through outcome research.

Methods and Materials: The program will be administered on an outpatient basis at the Policlinico Umberto I (Rome), where a minimum of 10 patients with a diagnosis of Parkinson's disease and a Hoehn & Yahr scale score from 1 to 3 will be recruited. The intervention will last 9 weeks (two weekly treatments) and the sample will be evaluated in three times: pre-treatment (t0), post-treatment (t1) and 1 month after the end of treatment (t2). For the evaluation of the intervention, the following will be used as outcome measures: the Jebsen Tajlor Hand Function test, Parkinson Disease Questionnaire-39 and the measurement of the size of the letters.

Results: 15 patients, who met the inclusion requirements, were recruited. The pre and post treatment evaluations showed statistically significant data for all the outcome measures used with a $p < 0.05$. Significant data were also obtained in the evaluation of the size of the handwriting for all follow-ups.

Discussion and Conclusions: Our study has shown that rehabilitation treatment for micrography in Parkinson's disease is effective in reducing writing times and improving letter size.

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ASSESSMENT OF MANUAL DEXTERITY USING A SMARTPHONE IN SUBJECTS WITH PARKINSONS'S DISEASE

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Objectives: People with Parkinson's disease (PD) often complain difficulties in activities involving precise, ample, and rapid hand movements such as the use of a smartphone. The aim of the study was to assess hand dexterity abilities using a smartphone in PD relative to healthy controls using customized tests and software.

Materials: Ten PD and 15 age/sex-matched healthy controls underwent hand dexterity assessments.

Methods: We assessed hand function using Manual Ability Measure (MAM-36) and the Purdue Pegboard Test (PPT). To obtain objective data on movement speed and amplitude, we developed tests involving the most commonly used gesture when using a smartphone (i.e. tap, swipe, slide). These tests were performed on the touchscreen of a smartphone and consisted in: a) alternatively tap with the thumb on two rectangles (TAP); b) perform swipe gestures to browse pages (SWIPE); c) perform thumb movements to link dots of a grid according to a defined path (Swipe-Slide Pattern - SSP).

Results: Relative to healthy controls, PD showed worse performance in the PPT, lower score in the MAM-36, reduced movement amplitude and speed in TAP, SWIPE and SSP tests and a reduced number of correct sequences in SWIPE and SSP tests ($p<0.05$). Moreover, a higher number of correct gestures during the SWIPE test correlated with a better motor performance assessed with the UPDRS-III both on and off medication ($r>0.66$; $p<0.05$).

Discussion: As expected, PD showed reduced hand dexterity abilities. Interestingly hand dexterity objective outcome measures obtained with the smartphone correlated with the motor performance assessed with clinical scales.

Conclusions: This study showed that technological devices can be used to assess dexterity in PD providing objective and task-specific outcome measures of hand dexterity rehabilitation in PD.

Funding: Italian Ministry of Health grant GR-2018-12366005.

EEG-ECG BASED MACHINE LEARNING MODELS FOR THE ASSESSMENT OF PATIENTS WITH A DISORDER OF CONSCIOUSNESS

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Objectives: Clinical responsiveness of patients with a Disorder of Consciousness (DoC) correlates to sympathetic/parasympathetic homeostatic balance [1]. The latter can be evaluated via proxies of autonomic function as Heart Rate Variability (HRV) [2]. For this reason, we investigated if HRV-derived metrics may improve the diagnosis of consciousness with respect to known electroencephalographic biomarkers.

Materials and Methods: A prospective observational study was performed enrolling consecutively adults with a DoC admitted to intensive rehabilitation unit of the IRCCS-Fondazione Don Gnocchi from 01-06-2020 to 01-01-2022. Patients with pacemakers were excluded. Consciousness state was assessed using a repeated administration of the Coma Recovery Scale-Revised (CRS-R). Resting state polygraphy (Electroencephalography/Electrocadiography (EEG-ECG) recording were performed and background frequency, anteroposterior gradient and presence of cortical reactivity were labeled by expert neurophysiologists. RR-intervals were analyzed by calculating: the square root of the mean of the sum of successive RR differences between adjacent intervals, their median absolute deviation and the proportion of RR-intervals absolute differences bigger than 20ms. Machine learning methods (decision-trees) were studied and cross-validated (5-fold) in discriminating consciousness states at admission Unresponsiveness Wakefulness State / Minimal Conscious State (UWS/MCS). One tree was trained using only EEG descriptors and the other adding HRV-related metrics. Results were compared by McNemar change test.

Results: Eighty-two patients (Male: 46) were included with median age of 67 years [IQR=20] and median time post-onset of 51 days [IQR=21] of which 22 traumatic, 6 anoxic, 14 ischemic, and 40 hemorrhagic patients. Fifty-one (62.2%) of patients were diagnosed with MCS (median CRS-R score =12, [IQR=7]). Higher HRV values were found to be associated to better consciousness levels ($p<0.005$). Adding such metrics to EEG descriptors significantly increased the diagnostic accuracies of decision trees ($p=0.008$) from 75.6% to 85.4%.

Discussion: Recent guidelines for the diagnosis of consciousness emphasized the combination of clinical and instrumental assessments to reduce the misdiagnosis risk [3]. In this analysis, we provided evidence of how quantitative analysis of heart rate in patients with a DoC may improve consciousness state assessment.

Conclusions: In addition with latest recommendations, HRV might be integrated within multimodal bedside, low-cost, non-invasive diagnosis pipelines improving the accuracy of consciousness diagnosis.

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HOW CONSCIOUSNESS LEVEL INFLUENCES THE TRACHEAL CANNULA WEANING IN PATIENTS WITH DISORDERS OF CONSCIOUSNESS: PRELIMINARY DATA

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Objectives: Weaning from the tracheal tube is a rehabilitation milestone during inpatient rehabilitation for severe Acquired Brain Injury (sABI) patients with prolonged Disorder of Consciousness (DoCs) since it facilitates communication, minimizes the infection risk, and reduces the nursing burden allowing a return to home [1,2]. Consciousness level has been suggested to be related to decannulation in retrospective studies [3]. The present work aimed to investigate the relationship between consciousness level and weaning from the tracheal tube in patients with DoC prospectively enrolled in an Intensive Rehabilitation Unit (IRU).

Materials and Methods: All sABI patients admitted to the IRU of the IRCCS Don Gnocchi Foundation of Florence, from 24.07.2019 to 09.03.2022 were included. Inclusion criteria were diagnosis of a DoC, age 18+, and presence of tracheostomy at admission. Within seven days from admission, skilled specialists in Neurology and speech therapists assessed patients' consciousness stratifying them into Unresponsivness Wakefulness State (UWS), Minimal Conscious State (MCS) minus or plus (MCS- / MCS+) using a repeated administration of the Coma Recovery Scale-Revised (CRS-R). The weaning from the cannula was performed according to an internal protocol described in a previous work. A repeated administration of the CRS-R was performed during the week before decannulation. Categorical and dichotomous variables were summarized using frequencies and percentages, continuous variables using median and interquartile range [IQR] due to the non-normality of the

distributions checked using Shapiro-Wilk's test. Software used: SPSS v27 (IBM, Armonk, NY).

Results: One hundred and twenty-eight patients were enrolled (females 50 (39.1%); median age 68 years [IQR: 20 years]; etiology: hemorrhagic (46.0%), traumatic (23.8%), ischemic (16.7%), anoxic (10.3%), infective or other (3.2%); median time from event 39 days [IQR: 23 days]; median CRS-R at admission 9 [IQR: 7]). After a median time from admission of 43 [IQR: 61 days]; 69 (53.9%) patients admitted with the following consciousness states: 38 (55.1%) MCS+; 16 (23.2%) MCS-; 15 (21.7%) UWS) were decannulated. During the week before decannulation, the assessment of consciousness has the following distribution: 54 (78.3%) Emergent from MCS, 7 (10.1%) MCS+, 4 (5.8%) MCS-, and 4 (5.8%) UWS.

Conclusions: This prospective study suggests that patients with higher consciousness states are more likely to achieve tracheal cannula weaning.

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A COMPARISON BETWEEN THE AMERICAN, EUROPEAN AND UK GUIDELINES ON THE USE OF INSTRUMENTAL TOOLS FOR PATIENTS WITH DISORDERS OF CONSCIOUSNESS

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Objective: The use of instrumental tools to improve the diagnostic accuracy and the prognostic soundness in patients with Disorders of Consciousness (DOC) is still debated. We aimed to shed light on such heterogeneity.

Materials: We compared the recommendations of the three most recent international guidelines on DOC, namely the American Academy of Neurology (AAN) [1], the European Academy of Neurology (EAN) [2], and the UK Royal College of Physicians (RCP) [3].

Method: We listed the guidelines' recommendations distinguishing between the diagnostic and prognostic tools use. Then, we compared the guidelines focusing on the methodologies adopted to retrieve and grade the evidence and to build recommendations.

Results: The main difference between the three guidelines is represented by the adopted methodology. Specifically, while both AAN and EAN adopted the traditional GRADE system to grade the evidence, the RCP adopted the National Service Framework for long-term conditions typology which allowed to include also the opinions and the experience of service users and caregivers. Furthermore, there is a difference concerning the adopted inclusion criteria during the review process, so determining the inclusion of some evidence over the others, and producing heterogeneity among the evidence on which the recommendations were built. While the RCP guidelines produced a single recommendation for both diagnostic and prognostic use of the instrumental tools, both AAN and EAN produced several recommendations. However, the EAN only considers the diagnostic application of the instrumental tools (12 recommendations) whilst the AAN clearly divided the diagnostic (1 recommendation) and prognostic (5 recommendations) recommendations. With the exception of an EAN recommendation on the use of standard EEG (receiving a strong recommendation), the three guidelines are consistent in one important respect: Most of the evidence falls in the low evaluation category with a consequent weakness of the recommendations.

Discussion: The adoption of different methodologies highlights the risk to produce recommendations that do not derive from all the existing evidence on the topic and that are missing solid evidence-based roots. Even the different National Health Systems provide a further possible explanation for guidelines' discrepancies, influencing their more or less positive attitude on the use of instrumental tools in the DOC patients' clinical routine.

Conclusion: There is an urgent need to align the recommendations development' methodology and to provide a common and practical framework for clinicians who have to choose the most informative instrumental tool, case-by-case, depending on the patients' features and the health system.

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COGNITIVE OUTCOMES IN PATIENTS TREATED WITH POST-OPERATIVE ELECTRICAL STIMULATION AFTER CORONARY ARTERY BYPASS GRAFT (CABG)

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Objectives: Mechanisms of neurocognitive injury, such as postoperative sequelae of cardiac surgery, are not fully understood. Postoperative bed rest and systemic inflammation induced by surgical stress lead to skeletal

muscle impairment. In addition to the critical role of skeletal muscle function for physical mobility, increasing attention has recently been paid to the endocrine function of skeletal muscle as an important secretor of circulating factors involved in cognitive health (myokines). In the light of evidence supporting a link between muscle vitality and cognitive function, there is a need to preserve skeletal muscle trophism and strength during hospitalization for surgery, and this could be crucial to preserve cognition postoperatively.

Materials and Methods: We performed a single-center, pilot, randomized, two-arm, controlled trial to test our central hypothesis that initiating an early rehabilitation protocol, through neuromuscular electrical stimulation (NMES) + usual care (UC) versus UC alone, preserves skeletal muscle mass in CABG patients and promotes the secretion of neuroprotective myokines in the bloodstream (i.e., Klotho and brain-derived neurotrophic factor). Primary outcome variables included: circulating Klotho, fibroblast growth factor 23 (FGF-23), Interleukin 6 (IL-6), and brain-derived neurotrophic factor (BDNF) values. Secondary outcomes variable included physical and cognitive function: muscle strength measured using a hand-held dynamometer, repeatable battery for the assessment of neuropsychological status (RBANS), and mini-mental state examination (MMSE) test scores.

Results: The analysis only included patients who completed the entire protocol (55 patients; NMES group: 23; UC group: 32). No statistically significant differences were found between the two groups in biomarkers levels assessed three months after hospital discharge, nor in cognitive assessment and muscle strength performance. We then divided our patients in two groups (responders and non-responders) based on Klotho's increase three months after hospital discharge compared to baseline values, regardless of the type of physical therapy. We found better performances in delayed memory tasks in the responders group.

Discussion: While we cannot confirm the addition of NMES as offering an added benefit for postoperative rehabilitation to prevent postoperative cognitive impairment when compared to UC alone, our work does demonstrate a link between increased Klotho protein levels and improved memory test performance. These findings suggest that the Klotho myokine could exert a neuroprotective role for individuals post-CABG.

Conclusions: There is the need to understand the mechanisms that link Klotho levels with postoperative neuroprotection and, more interestingly, comprehend why some individuals are responders while others are not.

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PROSPECTIVE, BLINDED, RANDOMIZED, CROSSOVER-PILOT STUDY OF TRUNK CONTROL REHABILITATION IN STROKE PATIENTS USING THE LOKOMAT GAIT ORTHOSIS

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Objective: Treadmill training with partial body support has been suggested as a useful strategy for early rehabilitation after stroke. This prospective, blinded, randomized controlled pilot study realized in the department of Moriggia Pelascini's Neurehabilitation Hospital, tests the potential efficacy of using an electromechanical-driven gait orthosis (Lokomat) for trunk control rehabilitation training.

Methods: 20 patients with acute cerebral lesion are randomized into two treatment groups F/F+Lk or F+Lk/F (F+Lk= 2 weeks, 5 days a week of Lokomat verticalization training and treatment with physiotherapist; F=2 weeks, 5 days a week of conventional physical therapy with physiotherapist without Lokomat training). The outcome measures Trunk Control Test, Trunk Impairment Scale, Postural Assessment Scale for Stroke Patients, Balance Subscale of Fugl-Meyer are tested after 2 and 4 weeks of treatment by two different blinded physiotherapists.

Results: Group F/F+LK show a significative increase of all values of rating scales when patients start Lokomat training. Group F+LK/F perform highly after 2 weeks of treatment when they make Lokomat training and they maintain the results after other 2 weeks of conventional therapy. Mann-Whitney test demonstrates that groups are homogeneous at first evaluation (TCT p=0.82/PASS p=0.22/ TIS p=0.33/FUGL MEYER p=0.85). Then, within group comparisons of treatment effects relative to baseline and the various phases are carried out with Wilcoxon Test. For group F/F+LK there are these statistically significant results: TCT 2 weeks-TCT 4 weeks: W=0 and critical value at p<= 0.05 is 5; PASS 2 weeks-PASS 4 weeks W=0 and critical value at p<=0.05 is 5, TIS 2 weeks-TIS 4 weeks W=0 at p <=0.05 is 5; FUGL MEYER 2 weeks-4 weeks W value=0. For group F+LK/F there are these statistically significant results: TCT baseline-TCT 2 weeks W=0 critical value at p>00.05 is 5; PASS baseline-PASS 2 weeks W=0; TIS baseline-TIS 2 weeks W=0 at p <=0.05 is 5; FUGL MEYER baseline-2 weeks W=0. Spearman's rho coefficient measure the statistically significant inter reliability between Physiotherapist A and B for all rating scales (TCT r=1; PASS r=0.98; TIS r=1; FUGL MEYER subscale r =0.98).

Discussion: Dynamic stability of the trunk requires flexibility, muscle strength, neuronal control and proprioception. The use of Lokomat at early seems to be the best rehabilitative strategy, because it allows to work on all of these elements.

Conclusion: This preliminary study could be suggest that the most efficient trunk rehabilitation treatment in stroke acute patients includes a sequence of early Lokomat training.

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POST STROKE DEPRESSION: A RETROSPECTIVE OBSERVATIONAL STUDY IN AN ITALIAN REHABILITATION WARD

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Introduction: Post-stroke depression (PSD) is commonly seen in the first year after acute stroke, while the characteristic of PSD in the early post-stroke phases are less known.

Materials: Neurological signs, anamnestic data and neuroradiological reports of every patient were prospectively recorded in an ad-hoc e-chart. The Italian version of the Beckpression Inventory (BDI II) was used to assess the severity of depression. The Montreal Cognitive Assessment (MoCA) was used to quantitatively assess patients' cognitive status.

Method: This survey is a 36-month retrospective observational study. Assessments were performed at the entry the hospital. We set a BDI II > 9 as a cut off for the presence of depressive symptoms. Patients underwent inclusion (compliance with the WHO criteria for stroke and capability to understand the scales administered) and exclusion criteria (motory/fluent aphasia, cognitive impairment expressed as a MOCA < 12, neurosensorial or linguistic impairment, illiteracy) before the administration of both MOCA and BDI II scale.

Results: We recruited 402 patients (mean age 71.31 y; M/F 247/155) which undertaked a rehabilitation after first ever stroke (ischemic/haemorrhagic: 80%/20%); among them, 304 underwent MOCA evaluation (mean value 16.38). After that, 124 patients were excluded and the remaining 180 were administered the BDI II scale (mean BDI II score 8.5). Based on BDI score (minor than 9) the prevalence of depressive symptoms in the cohort was 55%; among patients with depressive symptoms, the mean age was 71.3 y (vs 70.9 on the other group) and there was a predominance of female sex (56% vs 44%) and patients which had suffered from an ischemic stroke (79% vs 21% of hemorrhagic); there was no difference considering the site of the stroke. We also separated, among the patient which underwent BDI scale, one group who were already in antidepressant therapy (22% vs 78%). Notably, the mean BDI II in the first group was 10.12 and mean BDI was 7.98 in the second one.

Discussion: Depression symptoms in the early post-stroke phase is more common among elderly, females, patient who had suffered by an ischemic stroke and patient which were already on antidepressant therapy.

Conclusions: The presence of PSD is a common event in patients after the first stroke and it should be considered carefully in planning a rehabilitation program and post-stroke clinical outcomes.

EMOTIONAL TRAINING AFTER FACIAL NERVE PALSY: FROM THEORY TO PRACTICE

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Background: Facial expressions can be either voluntary or emotionally controlled. According to the Component Theory of facial expressions, the upper and lower face motor control is behaviorally independent in adults. In addition, the right and the left face may also exhibit partially independent motor control. Spontaneous facial expressions are organized predominantly across the horizontal facial axis and secondarily across the vertical axis. Two neural networks for laughter have been recently described in a tractography study. One network is involved in producing emotional laughter (the pregenual anterior cingulate, ventral temporal pole and ventral striatum/nucleus accumbens), while the second one in non-emotional and conversational laughter (frontal operculum and primary motor cortex M1). Smile production and recognition of others' smiles are encoded in the pregenual anterior cingulate cortex. Unlike hand mirror neurons (MNs), mouth MNs do not receive their visual input from parietal regions. Facial visual input could reach mouth MNs through the ventrolateral prefrontal cortex. Other strong connections derive from limbic structures involved in encoding emotional facial expressions and motivational processing. The mirror mechanism linked to the face motor control is connected with limbic structures, involved in communication and emotions.

Discussion: Peripheral paralysis of the facial nerve compromises facial motility, resulting in alterations in facial expressions, particularly in representing emotionality and non-verbal communication. The primary therapeutic goal of rehabilitation treatment should be to recover expressive gestures, characterized by a biological function and facial expressions for non-verbal communication. A rehabilitation protocol could be based on neurocognitive exercises with an emotional component (Emotional training) to recover spontaneous and emotional expressive movements. The patient is asked to reproduce the movements to express different emotions by showing drawings or photos of faces, by reproducing the examiner's expression or by imaging a situation that evoked a specific emotion. The different sensory channels can be used: visual (viewing photos or videos that arouse a particular emotion), auditory (listening to emotionally significant music), tactile (touching surfaces that evoke a pleasant feeling) and gustatory (tasting some favorite foods). Even functional exercises, such as producing movements with the mouth (e.g. blowing) or the other parts of the face, can be proposed in contexts with emotional connotations (e.g. imagine blowing candles at a birthday party).

Conclusion: After a facial paralysis, once voluntary contraction appeared, neuromotor treatment should be integrated with emotional training which is a promising rehabilitation proposal that radically changes rehabilitation intervention.

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ACTION OBSERVATION THERAPY IN ACQUIRED BRAIN INJURY

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Introduction: Action Observation Therapy (AOT) is a rehabilitative technique based on the mirror neuron system: the observation of a specific action activates the same brain areas that are engaged in that motor function, stimulating the injured ones by promoting neuronal plasticity and reorganization of the primary motor cortex. Very little data in the literature regarding the possible efficacy of AOT in patients with Severe Acquired Brain Injury (ABI), so this study aims to evaluate the application and efficacy of rehabilitation treatment with AOT in patients with ABI.

Materials and methods: Ten patients with ABI were enrolled. The patients underwent rehabilitation treatment with AOT once a day, for 5 days a week, for 3 consecutive weeks. A video that repeatedly played a simple movement of daily life for 5 consecutive minutes was shown. After 1 minute of rest, the patient was asked to try to perform the newly observed movement for at least 2 minutes and maximum for 5 minutes.

This cycle was repeated 3 times, for 35 minutes per session. Patients were evaluated: a) T0 baseline; b) T1, after 7 sessions; c) T2, the end of treatment. Were assessed: motor performance (Motricity Index Uppel Limb, MI-UL), spasticity (Modified Ashworth Scale, MAS), cognitive level (Level of Cognitive Functioning, LCF), disability (Disability Rating Scale, DRS) and electrodermal activity of the skin (EDA) as indirect measures of the Autonomic Nervous System (ANS).

Results: Comparison of scores at T0, T1 and T2 was performed by means of Friedman's non parametric test. 10 patients, 8 males and 2 females, with mean age (standard deviation, SD) of 50.60 (22.23) years and education of 12.4 (4.67) years were enrolled. At T0, the group had a mean score at DRS of 14 (4.32), LCF of 5.1 (1.37), MI-UL R (right) of 53.3 (10.94), MI-UL L (left) of 51.4 (24.25), MAS R of 0.9 (0.87), MAS L 1.1 (0.87). At T2, significant improvement was observed in DRS ($p<0.001$), LCF ($p<0.001$), MI-UL R ($p<0.001$) and MI-UL L ($p<0.001$) scores, no significant difference was observed in MAS score for both limbs between T0 and T2. Electrodermal activity (EDA) increased significantly during AOT, with lower values at baseline and after treatment recorded at T0 ($p<0.001$), T1 ($p<0.001$) and T2 ($p<0.001$).

Conclusions: An analysis of preliminary data shows that AOT is effective in patients with ABI. Changes in EDA indicates an increase in SNA activity during and after AOT treatment at each evaluation time, probably related to an increase in nervous system involvement.

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ABNORMAL THALAMIC FUNCTIONAL CONNECTIVITY CORRELATES WITH CARDIORESPIRATORY FITNESS AND PHYSICAL ACTIVITY IN PROGRESSIVE MULTIPLE SCLEROSIS

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Objectives: Patients with progressive multiple sclerosis (PMS) have insufficient levels of physical activity (PA) and cardiorespiratory fitness (CRF), which showed some associations with measures of structural MRI damage. Functional MRI (fMRI) correlates of reduced PA/fitness have never been explored in patients with PMS. Given the role of thalamus in motor planning, sensory processing and cognition, abnormal thalamic resting state (RS) functional connectivity (FC) might explain PA/fitness levels in these patients. Our aim was to assess thalamic structural and functional MRI alterations and investigate their correlations with PA/CRF levels in PMS patients.

Materials: Seven-day accelerometry and cardiopulmonary exercise testing with analysis of expired gases were used to assess PA/CRF levels in 91 PMS patients. They also underwent, together with 37 matched healthy controls (HC), a structural and RS fMRI acquisition at 3.0T, which was used to derive whole-brain and thalamic atrophy, as well as thalamic RS FC.

Methods: Between-group comparisons of MRI measures and their correlations with PA/CRF variables were assessed.

Results: PMS patients had significant whole-brain and subcortical atrophy compared to HC (all $p<0.001$). Patients also showed decreased intra- and inter-thalamic RS FC, decreased RS FC of the thalamus with caudate nucleus, cerebellum and bilateral anterior cingulate cortex (ACC), and increased thalamic RS FC with the bilateral hippocampus and some occipital regions. Lower CRF levels correlated with lower normalized white matter volume (r=range 0.28;0.31, p=range 0.003;0.01), with decreased thalamic RS FC with the left ACC (r=range 0.22;0.28, p=range 0.01;0.04), and with increased thalamic RS FC with the left hippocampus, left calcarine cortex, and right lingual gyrus (r=range -0.26;-0.21, p=range 0.01;0.04). Lower PA correlated with decreased inter-thalamic RS FC (r=0.27, p=0.02), and with increased thalamic RS FC with the right hippocampus (r=-0.3, p=0.01) and left lingual gyrus (r=-0.23, p=0.04).

Discussion: Structural MRI analysis showed that only white matter atrophy correlated with CRF. Conversely, abnormal RS FC in the thalamic network showed multiple maladaptive associations with PA and fitness status in PMS. Despite previous findings linking atrophy to PA/CRF levels in patients with lower disability, our results show that functional changes, rather than structural abnormalities, might be more informative in PMS patients with moderate-to-severe disability.

Conclusions: Given its extensive correlation with PA and CRF, thalamic RS FC might be used as an outcome to monitor physical impairment and efficacy of rehabilitative and disease-modifying treatments in PMS patients.

Funding. Funded by a grant from the Multiple Sclerosis Society of Canada (grant no. #EGID3185) and the National MS Society.

USING HOME-BASED EXERGAMES TO IMPROVE COGNITIVE FUNCTION IN MULTIPLE SCLEROSIS: A MULTICENTER, RANDOMIZED, SINGLE-BLIND NON- INFERIORITY TRIAL (THE EXTREMUS STUDY)

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Introduction: Motor and cognitive dysfunctions are common and disabling symptoms in multiple sclerosis (MS) across all disease stage. Exergaming is an emerging tool in neurorehabilitation that incorporates goal-based training and gross motor exercise, thus having the potential for improving both cognitive and automatic components of motor control by exploiting adaptive plasticity.

Objectives: We tested the hypotheses that: (i) home-based exergaming (Wii balance board) has similar efficacy to working memory-based exercises (COGNI-TRAcK) on information processing speed, and (ii) superior efficacy on motor outcomes, as compared to a placebo-analogue intervention.

Methods: This was a multicenter, randomized, sham-controlled, single-blind, parallel arm study (ClinicalTrials.gov registration: NCT04169750). Patients with impaired Symbol Digit Modalities Test (SDMT), i.e. <5th percentile of normative value, were randomized in a 1:1:1 ratio to an 8-week home-based training (five 30-min sessions per week) with commercial exergames (intervention of interest), or adaptive COGNI-TRAcK (reference comparator), or sham COGNI-TRAcK (placebo- analogue intervention). The primary endpoint was the change at the SDMT; secondary endpoints included the Stroop test and other tests included in the Brief International Cognitive Assessment for MS, as well as motor assessments, including the 2-minute waking test (2MWT) and timed-up-and go test (TUG). Additional endpoints were changes in patient-reported outcomes (PROs), i.e. the 29-item Multiple Sclerosis Impact Scale (MSIS-29) and 21-item Modified Fatigue Impact Scale (MFIS-21). All endpoints were analyzed according to the intention-to-treat principle using analyses of covariance (ANCOVA), with the 8-week value as dependent variable, baseline value as covariate, and arm as random factor. Effect size (ESs), expressed as Cohen's d, were also estimated; d=0.2, d=0.5, and d=0.8, were considered small, medium, and large ES, respectively.

Results: Out of 95 screened for eligibility, 62 patients (38 women, 24 men) were randomized to exergames (n=20), adaptive COGNI-TRAcK (n=23), sham COGNI-TRAcK (n=20). Their mean age was 49.7±11.8 years, their disease duration was 14.7±9.2 years, and their median EDSS was 4.5 (range: 1.5 to 6.5). Their disease courses were: relaping-remitting (n=43), secondary progressive (n=14), primary progressive (n=5). Baseline characteristics were comparable across the three arms (p-values>0.25). At 8-week visit, SDMT score improved with exergames [mean change: +4.1 points] and adaptive COGNI-TRAcK [mean change: +4.1 points] versus sham COGNI-TRAcK [mean change: +0.5 points] (p<0.035 for both comparisons). A clinically meaningful improvement of ≥4 SDMT points was observed only in 4 (21%) patients with sham COGNI-TRAcK versus 9 (45%) with exergames (p=0.087) and 11 (49%) with adaptive COGNI-TRAcK (p=0.052). The Stroop test improved only with exergames versus sham COGNI-TRAcK (p=0.039), whereas there was no between-arm difference in the California Verbal Learning Test and revised Brief Visuospatial Memory Test. Only the exergaming arm showed improvements in 2MWT (+7.9 meters) and TUG (-1.1 sec) versus sham COGNI-TRAcK (p=0.035, and p=0.052, respectively). PROs improved only with exergames versus versus sham COGNI-TRAcK: the mean change in MSIS were -9.8 versus -0.6 (p=0.050), and the mean change in MFIS were -4.6 and 2.9 (p=0.037), respectively. All effect size were small (d<0.1). Lastly, we found strong correlations between changes at SDMT and 2MWT (rho=0.59, p=0.010) and between changes at Stroop and TUG (rho=0.61, p=0.004) in the exergaming group, suggesting that improvement in cognitive and motor functions were related each other.

Conclusions: This study provides class II evidence for the efficacy of home-based exergames as a single comprehensive approach to address MS-related cognitive and motor issues. Our study raises the hypothesis is that exergames may induce functional or structural plasticity in brain networks subserving both motor and cognitive functions.

Disclosure: This study was supported by FISM — Fondazione Italiana Sclerosi Multipla — cod. 2017/R/22 and financed or co-financed with the '5 per mille' public funding.

ACTION OBSERVATION AND MOTOR IMAGERY IMPROVE MOTOR IMAGERY ABILITIES IN PATIENTS WITH PARKINSON'S DISEASE – A FUNCTIONAL MRI STUDY

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Objectives: Motor imagery (MI) is a recognized motor learning skill that could be impaired in patients with Parkinson's disease (PD). The aim of the study was to assess MI ability changes and brain functional reorganization after 6 weeks of action observation training (AOT) and MI associated with increasingly difficult gait/balance exercises in PD patients with postural instability and gait disorders (PD-PIGD) relative to gait/balance training alone.

Materials: Twenty-two PD-PIGD patients were randomized into 2 groups: the DUAL-TASK+AOT-MI and DUAL-TASK. A group of 24 healthy controls was also included.

Methods: DUAL-TASK+AOT-MI group performed 6 weeks of gait/balance exercises including dual-tasks combined with AOT and MI; DUAL-TASK group performed the same exercises combined with watching landscape videos. MI was assessed using the Kinaesthetic and Visual Imagery Questionnaire (KVIQ). All the subjects performed brain MRI including a MI fMRI-task: subjects were asked to watch first-person perspective videos representing challenge gait/balance tasks, identify themselves in the proposed environment and mentally simulate to move themselves in each condition.

Results: At baseline, during MI task, PD-PIGD showed reduced activity of pre/post-central gyri, temporal areas, motor and cognitive cerebellar areas and an increased activity of the parahippocampal gyri relative to controls. After training DUAL-TASK+AOT-MI group showed

improvement in the KVIQ score together with increased activity of cerebellar lobule IX, anterior cingulate and fronto-temporal areas and a reduced recruitment of cerebellar lobule VI and crus I. The KVIQ improvements correlated with the increased activity of cerebellar lobule IX and anterior cingulate, and with the reduced activity of crus I.

Discussion: PD-PIGD patients showed an altered recruitment of brain areas belonging to the mirror neuron system and related to sensorimotor functions.

Conclusions: A motor learning training including AOT and MI can improve MI abilities in PD-PIGD patients, promoting the functional plasticity of brain areas involved in MI processes and gait/balance control.

EARLY REHABILITATION PROGRAM AFTER STROKE AT THE STROKE UNIT OF NEUROLOGY OF THE ASL OF TERAMO

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Despite current rehabilitation strategies, stroke remains a major cause of disability. Studies report that there is the potential for an improved neuroplasticity window early after stroke, during which the brain's dynamic response to injury is increased and rehabilitation could be particularly effective. According to the AA. based on their experience, the early rehabilitation management of the stroke patient is an important aspect of the care pathway that allows a decrease in the incidence of disability and residual deficits for this type of pathology. at the Stroke Unit of Neurology of the ASL of Teramo is based on an individual project to be formulated under the responsibility of the physiatrist specialist in collaboration with the neurologist. The patient admitted to the stroke unit begins physiotherapy and / or speech therapy within 48 hours of admission to the ward. In fact, rehabilitation, in patients for whom there is an indication, must already be started during the hospital stay in the Stroke Unite, and then take place in the post-acute event rehabilitation wards. The AA. showed in patients with an early post-stroke rehabilitation program, in a considerably shorter time, an improvement in general physical and psychological conditions, a reduction in residual deficits and, last but not least, in hospitalization times.

THE EFFECTS OF EXERCISE ON NEUROPSYCHIATRIC DISORDERS AND INSTRUMENTAL ACTIVITIES IN PATIENTS WITH ALZHEIMER'S DISEASE

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In the elderly population there is a high incidence of neuropsychiatric disorders and this is associated with frequent problems of physical comorbidity, social isolation and consequent high levels of disability. Numerous evidences and even some works by the same AA. testify how the performance of physical activity can lead to an improvement in psychopathological conditions, even if the mechanisms by which this occurs are not fully known. The A.A. structured a program of aerobic exercises (flexibility, strength and agility) and functional balance exercises in order to analyze the influence of a six-month exercise program on neuropsychiatric disorders and on the performance of instrumental activities in elderly patients with Alzheimer's disease (TO). The study aims to include 20 patients with AD in the mild to moderate stages of the Clinical Dementia Rating (CDR) divided into two groups: the experimental group, consisting of 10 patients. who will participate in the six-month exercise program, and the control group, consisting of 10 patients paz. remaining and with the same characteristics that will not take part in any exercise program during the same period. All participants will be assessed using the Mini-Mental State Exam for global cognitive function, the Neuropsychiatric Inventory Questionnaire for neuropsychiatric disorders and ADL and IADL for the degree of functional impairment. The interventions will be aerobic exercises (flexibility, strength and agility) and functional balance exercises were conducted over six months for 60 minutes three times a week. The AA. with their work they want to further demonstrate as already done in previous works that aerobic exercise is associated with a reduction in neuropsychiatric symptoms and all this also contributes to mitigating the burden of caregivers.

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TECHNOLOGICAL ASSESSMENT OF HANDWRITING AND FINGER TAPPING IN SUBJECTS WITH PARKINSON'S DISEASE

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Objectives: People with Parkinson's disease (PD) often complain difficulties in repetitive hand movements and handwriting. Micrographia, defined as a reduction of handwriting speed and amplitude, is a common sign of PD. The aim of the study was to assess handwriting and finger tapping abilities in PD relative to healthy controls using new technological devices and software.

Materials: Ten PD and 15 age/sex-matched healthy controls underwent handwriting and finger tapping assessments.

Methods: Three electromagnetic sensors placed on first and second fingertips and on the back of the right hand were used to evaluate finger tapping amplitude and speed. We developed handwriting tests consisting

of pre-writing tasks such as drawing repetitive cursive loops as ample and fast as possible and colouring a figure as much as possible in a given time. Handwriting tests were performed on the touchscreen of a tablet using a touch stylus pen.

Results: Relative to healthy controls, PD patients showed reduced handwriting amplitude and speed ($p<0.05$). During finger tapping, patients with PD showed decreased movement amplitude and speed and a higher tendency to reduce them during the repetition of movements compared to healthy controls ($p<0.05$). The ability to colour the figure and to perform ample and rapid finger movements correlated with a better performance at the UPDRS-III both on and off medication ($r>0.65$; $p<0.05$).

Discussion: As expected, patients showed reduced handwriting and tapping abilities relative to healthy controls. Interestingly, handwriting and finger tapping outcomes obtained through technological devices correlated with the motor performance assessed with clinical scales.

Conclusions: This study showed that technological devices with customized software can provide quantitative measures of handwriting and bradykinesia that can be used in future studies to assess the effect of hand abilities rehabilitation in PD.

Funding: Italian Ministry of Health grant GR-2018-12366005

BASIC NEUROSCIENCE

COMBINED RNA INTERFERENCE AND GENE REPLACEMENT THERAPY TARGETING MFN2 FOR THE TREATMENT OF CHARCOT-MARIE-TOOTH TYPE 2A

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Introduction and Aims: Mitofusin-2 (MFN2) is an outer mitochondrial membrane protein essential for mitochondrial networking in most cells. Autosomal dominant mutations in the MFN2 gene cause Charcot-Marie-Tooth type 2A disease (CMT2A), a severe and disabling sensory-motor neuropathy that impacts the entire nervous system. Here we propose a novel potential therapeutic approach combining RNA interference (RNAi) and gene therapy, whereby mutant and wild-type MFN2 mRNA are inhibited by RNA interference (RNAi), while the wild-type protein is restored by overexpressing cDNA encoding functional MFN2 modified to be resistant to RNAi.

Materials and Methods: After obtaining induced pluripotent stem cells (iPSCs) from somatic cells of CMT2A patients, we targeted the MFN2 mutant allele with specific short hairpin RNAs (shRNAs) and simultaneously introduced a mutagenized MFN2 gene resistant to shRNA activity and encoding the native protein. We then differentiated iPSCs into spinal motor neurons (MNs) and analyzed the sub-cellular parameters previously found to be altered in CMT2A in vitro model [1] to assess the impact of our therapy. We then evaluated this strategy in vivo in the MitoCharc1 CMT2A transgenic mouse model after cerebrospinal fluid (CSF) delivery of the constructs into newborn mice using adeno-associated virus 9 (AAV9).

Results: This approach significantly rescues the CMT2A MN phenotype in vitro, stabilizing the altered axonal mitochondrial distribution and correcting abnormal mitophagic processes. This strategy also allows proper MFN2 molecular correction in CMT2A MitoCharc1 mice.

Conclusions: Overall, our results led to a significant level of rescue of disease phenotype in CMT2A MNs, suggesting that RNAi/gene therapy combined approach might represent a promising therapeutic strategy for the broad spectrum of human diseases associated with MFN2 mutations.

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BRAIN CONNECTIVITY IN STROKE: THE CHALLENGE OF A COMPREHENSIVE MULTI-MODAL APPROACH

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Rationale: Clinicians commonly assume that deficits in patients with brain lesions are directly related to structural damage. This principle is a cornerstone of clinical practice and relies on the framework that different aspects of cognition are represented in well-defined parts of the brain. In opposition to this "localizationist" theory, recent advances suggest a more "connectionist" approach (Ref1). Lesions disconnect communicating parts of neuronal networks supporting task performance. The observation that lesions can cause remote functional changes provides a better understanding of brain-behaviour relationships and opens the possibility to address novel interventions focusing on unaffected areas of the brain. A fundamental contribution for the understanding of functional organization following stroke comes from brain imaging techniques and, only recently, the study of eye movement dynamics (Ref2). In particular, functional magnetic resonance imaging (fMRI) or high-density electroencephalography (EEG) can be used to estimate functional connectivity based on the statistical dependence of signals recorded across the brain (Ref3). No routinely performed methodology exists to study how synchronization in brain networks is altered following stroke. To address this issue, we designed a protocol to study brain connectivity following stroke through different neurophysiological modalities. The main aim of this design is to effectively compare different brain signals (i.e. hemodynamic, metabolic and electrical) for the detection of neural changes occurring after focal brain lesions.

Methods: We enrolled patients with an ischemic stroke admitted to the Padua University Hospital. All patients were tested with a comprehensive neurobehavioral assessment (including motor and cognitive functions) in the acute phase (<10 days after onset) by a neuropsychologist and speech therapist. During hospitalization we obtained functional MRI, hdEEG and eye-tracking data for each patient. We enrolled healthy participants matched for age, sex and education level. Each control was tested with a

neurobehavioral assessment and underwent fMRI, hdEEG and eye-tracking data collection. At 3-months post stroke each patient repeated the neurobehavioral assessment and underwent a control fMRI, hdEEG and eye-tracking examination.

Discussion: The primary outcome will be to develop a better understanding of how brain damage alters neural activity in connected regions of the brain. This data will provide neural markers with diagnostic and prognostic value in stroke. The detection of hdEEG resting state networks could define the complementary value of this technique in comparison to other techniques such as fMRI. Our chronic follow-up data will address the recovery of different neurophysiological modalities and their relationship with behavioral correlates in stroke and healthy volunteers.

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VALIDATING VISUAL EVOKED POTENTIALS AS A PRE–CLINICAL, QUANTITATIVE BIOMARKER FOR REMYELINATION EFFICACY

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Objective/Background: By utilizing tools that allow us to control and induce remyelination, to evaluate whether VEP actually measures myelin restoration. We completed the first positive double-blind placebo-controlled human trial for a remyelinating therapy in MS using VEP as an outcome [1]. We unequivocally demonstrated improvement in longstanding latency delay on VEP for patients during the period on treatment despite the chronicity of injury. A full understanding of visual system injury in animals could enhance the ready and robust adaptation of these techniques for additional human clinical trials - and the appropriate interpretation of trial results.

Materials/Methods: We obtained VEP from C57BL/6J mice using an Espion Diagnosys system (Diagnosys LLC, Littleton, MA). We induced EAE with MOG35-55 in female 8-week-old mice using adjuvant-injected mice as controls. Toxic demyelination was induced with 5 weeks of cuprizone diet. IHC for CASPR was performed on optic nerve sections. Electron microscopy of mice optic nerves was performed. We assessed VEPs comparing Myrf (flox/flox) versus NG2-creER; Myrf (flox/flox) following the administration of tamoxifen, in adult animals 2 weeks after cuprizone-induced demyelination.

Results: Prolongation of VEP latency precedes clinical onset of disease in EAE. N1 delay increase till day 18, with a consequent conduction improvement. Quantification of optic nerve IHC for CASPR in EAE mice mirrors the VEP delay, showing the histopathologic substrate of N1 delay. Clemastine is effective in improving VEP in EAE 7days post-immunization($p=0.0002$), maintaining its effect at day 21 ($p=0.018$) and day 28 ($p=0.03$). Cuprizone diet also provokes N1 latency delay ($p=0.003$). Clemastine is effective in enhancing remyelination, more quickly than expected after suspending the toxic demyelinating diet ($p=0.03$). Optic nerve EM showed reduced unmyelinated axons and increased remyelinating axons in mice treated with Clemastine. CASPR staining of optic nerves shows a higher number of paranodes in treated mice. Clemastine does not improve VEP latency following demyelinating injury when administered to NG2-creER; Myrf (flox/flox) mice.

Discussion: VEP latency correlates with quantitative measures of myelin from histopathology in mouse models of both inflammatory and chemical visual pathway demyelination. Furthermore, VEP latency delay improves after treatment with a tool remyelinating compound in both models, mirroring quantitative/qualitative myelin assessment, and does not improve in a transgenic animal incapable of forming new myelin.

Conclusions: Using the capacity for therapeutic enhancement and biological loss of function we demonstrate conclusively that VEP measures myelin status and is thereby a validated tool for preclinical verification of remyelination.

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PROPOSAL OF A PROTOCOL FOR THE ASSESSMENT OF UNILATERAL SPATIAL NEGLECT IN ACUTE PHASE

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Aim: Unilateral spatial neglect is a neuropsychological syndrome characterized by inability to attend people, objects and representations located in a visual hemifield, generally the contralesional, and to act in that side of space. Several clinical guidelines for management of patient affected by stroke recommend a timely and complete assessment of neglect as an essential part of the planification of clinical care post stroke. According to guidelines and considering the wide variety of assessment tools for neglect, in this trial, we developed a single standard protocol for the acute phase, easy to administer and able to quantify reliably patient's difficulties limiting them to the portion of space concerned.

Materials and methods: The protocol was composed of 2 standardized tests for the assessment of personal neglect, 11 tests for peri-personal neglect, 2 for extra-personal neglect and 2 for representational imagery neglect. It was administered to 12 patients with at least one lesion in the right brain. Additionally, the protocol evaluated the level of awareness of motor difficulties in the limbs and the right-left orientation by using a clinical questionnaire and a standardized test respectively.

Results: The assessment found that personal neglect was observed in a percentage of the sample ranging from 58.30% to 75%, peri-personal neglect was found to be between 66.70% and 100%, while extra-personal neglect was found to be between 41.70% and 58.30% of the sample. The same study established that representational neglect was detected in a sample percentage between 75% and 91.70% and, finally, 25% of the sample showed additional pathological performance to the right-orientation test right-left of Benton, 75% a poor or absent awareness of the deficit in the upper limb and the whole sample affected by motor deficiency in the lower limb was anosognosic. However, the reported percentages are affected by the level of attention and impairment of the clinical condition which sometimes made it impossible to administer the tests.

Discussions: The subsequent statistical analysis showed numerous correlations between the tests. Particularly, the Line Bisection test correlates significantly with the totality of the tests used and therefore appears to be indicated as a first approach test.

Conclusions: In conclusion, the protocol was found to identify the presence of neglect and the related disorders in acute phase in the study population considering different sensory modalities, the various neglect subtypes and the three dimensions of the space within which the disorder may occur: horizontal (right - left), vertical (high - low) and radial (near - far).

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SYNTAXIN-1A AND SNAP-25 EXPRESSION LEVEL IS INCREASED IN THE BLOOD SAMPLES OF ISCHEMIC STROKE PATIENTS

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Objectives: The interest for the discovery of blood biomarkers for several neurological disorders, including Ischemic Stroke (IS), is growing and their identification in blood samples would be revolutionary allowing a fast and better pathology prediction or outcome and to collect information on patient recovery. The increased permeability of the blood-brain barrier, following a brain infarct, allows the detection of brain proteins in the blood flow.

Materials: In this work, we analyzed the expression levels of two synaptic proteins Syntaxin (STX)-1a and Synaptosomal Associated Protein, 25 kDa (SNAP-25), in Peripheral Blood Mononuclear Cell (PBMC), serum and in Neuronal Derived Extracellular vesicles (NDEs) of IS patients, age and sex matched healthy control (HC) and younger HC (Y-HC).

Method: Blood samples were collected from both non ischemic and ischemic age-matched patients. Blood was treated to isolate PBMC, Serum that was frozen until use. The Serum was later used to isolate Neuronal derived exosomes (NDE). The PBMC, Serum and NDE fraction were then used for western blot analyses or immunofluorescence.

Results: Interestingly, we identified STX-1a protein in the cytoplasm of PBMC and both STX-1a and SNAP-25 expression levels were significantly augmented in all IS patient's blood fractions compared to control subjects. In addition, STX-1a blood levels correlated with the IS clinical scales National Institutes of Health Stroke Scale (NIH-SS) and the modified Barthel Index (BI).

Discussion: These results prompted us to speculate that STX-1a and SNAP-25 hematic fluctuations depict the brain damage after an ischemic attack and that their hematic detection could represent a novel and accessible IS biomarkers.

Conclusions: Our results are showing that presynaptic proteins could represent a peripheral marker for this pathology and that could be also associated to the progression of ischemic clinical manifestations.

CSF LIPOPROTEINS INHIBIT THE AGGREGATION OF A-SYNUCLEIN IN SEED AMPLIFICATION ASSAYS BY INTERACTING WITH OLIGOMERIC SPECIES

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Objective: Aggregation of α-synuclein (α-syn) is a prominent feature of Parkinson's disease (PD) and other synucleinopathies. The extracellular spreading of misfolded α-syn significantly contributes to the cell-to-cell propagation of the α-syn misfolding pathology in a prion-like fashion. Seed amplification assay (SAA) is a technique based on the amplification of a small amount of prone-to-aggregation prion-like protein present in a biological fluid by recruiting recombinant monomers that are provided in the reaction mixture, through cycles of incubation and sonication/shaking [1]. Currently, α-syn SAAs using cerebrospinal fluid (CSF) represent a promising diagnostic tools for synucleinopathies. However, CSF contains several compounds that interfere with the aggregation of α-syn [2,3], potentially impairing α-syn SAAs and preventing seed quantification. The aim of this study was to characterize the interaction between CSF constituents and α-syn in order to improve the development of the SAAs as diagnostic tools for synucleinopathies.

Materials and methods: A multi-technique integrative approach including SAA, mass spectrometry (MS), solution nuclear magnetic resonance spectroscopy (NMR), dot-blot assays and transmission electron microscopy (TEM), was applied in order to characterize the inhibitory effect of CSF on in vitro α-syn aggregation.

Results: We initially confirmed that human CSF inhibits α-syn aggregation in SAAs in different experimental conditions. After the fractionation of human CSF, we noticed that CSF fractions of different molecular weight (MW) differently modulated α-syn aggregation. The strongest inhibitory effect on α-syn aggregation was observed for the CSF fraction relative to high MW compounds (>100 kDa) and lipoproteins were identified as the main drivers of this effect. We evaluated direct interaction between lipoproteins and α-syn and observed lipoprotein-α-syn complexes by TEM. Direct interaction between lipoproteins and monomeric α-syn was not detected by solution NMR, suggesting interaction between lipoproteins and oligomeric/proto-fibrillary α-syn intermediates instead. Lastly, we found significantly slower amplification of α-syn seeds in PD CSF when lipoproteins were added to the reaction mix of a highly accurate diagnostic SAA.

Discussion: We described a drastic reduction of α-syn aggregation in the presence of human CSF by SAAs. CSF lipoproteins are the main

responsible of this inhibitory effect. This interaction may be relevant in diagnostic SAA protocols and it does not involve α-syn in its monomeric state.

Conclusion: The identification of endogenous compounds able to modulate α-syn aggregation may improve the development of SAAs by identifying possible confounders to be controlled, with profound implications in current efforts to establish molecular diagnosis as gold standard for synucleinopathies.

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THE SYNARMOTIC NEURON. A CANDIDATE PROJECTIVE NEURON TYPE OF THE CEREBELLAR CORTEX

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Previous studies on the granular layer of the cerebellar cortex revealed a wide distribution of a population of less known large neuron types, called 'non-traditional large neurons', which are distributed in three different zones of the granular layer. These neuronal types are mainly involved in the formation of local circuits inside the cerebellar cortex. A subpopulation of these neuron types is represented by the synarmotic neuron, which, on the other hand, may rather play a projective role within the cerebellar circuitry. The synarmotic neuron cell bodies map within the internal zone of the inner granular layer or in the subjacent white substance. In addition, their axons cross the granular layer and run within the subcortical white substance. Therefore, together with the Purkinje neuron, the traditional projective neuron type of the cerebellar cortex, the synarmotic neuron, is candidate to represent the second cerebellar projective neuron type. Chemical neuroanatomy studies indicated a predominant inhibitory GABAergic nature of such neuron, suggesting that it may mediate an inhibitory GABAergic output of cerebellar cortex within cortico-cortical interconnections or in projections towards intrinsic cerebellar nuclei. On this basis, the present study mainly focuses on morphofunctional and neurochemical data of such neuron type and, explores the potential involvement of such a neuron in some forms of cerebellar ataxias.

IL-17-DEPENDENT MODULATION OF THE BASAL GANGLIA NETWORK: IMPLICATIONS FOR MULTIPLE SCLEROSIS

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Introduction: The basal ganglia (BG) network exerts a key role in integrating cortical inputs and underlies motor learning and the regulation of behavior, emotional responses, and cognitive functions. Little is known on how immune cells and soluble immune mediators influence BG activity [1]. Interleukin-17A (IL-17A) is under the spotlight because of its emerging role as neuromodulator of cortical synaptic transmission and plasticity in both physiological and pathological conditions, including multiple sclerosis (MS) [2,3].

Aim: To investigate if the IL-17 axis is involved in the regulation of synaptic plasticity in the nucleus striatum, the gateway to the BG.

Methods: Electrophysiological recordings were performed in the striatum of wild-type (WT) mice, mice affected by experimental autoimmune encephalomyelitis (EAE), and mice lacking IL-17A or its receptor (IL-17RA). IL-17RA expression patterns were assessed through immunehistochemistry. Glutamatergic NMDA receptor (NMDAR) subunit composition was assessed through western blot in post-synaptic fractions.

Results: The IL-17 axis contributes to the physiological expression of long-term potentiation (LTP) in medium spiny neurons (MSNs). Indeed, LTP induction was impaired in mice lacking IL-17A or IL-17RA ($p<0.05$). This effect might rely on an alteration of glutamatergic transmission, since synaptic expression of NMDAR subunit GluN2B is reduced in mice lacking the cytokine ($p<0.05$). However, the exposure to high IL-17A concentrations impairs LTP induction ($p<0.05$), mimicking EAE-related LTP loss ($p<0.05$), through a modulation of NMDAR currents ($p<0.05$). These results highlighted a dual effect of this cytokine on synaptic plasticity. Immuno-histochemistry showed that striatal projecting neurons and interneurons highly express IL-17RA, suggesting a direct neuronal effect of the cytokine as shown in other brain areas [2].

Conclusions: The IL-17 axis emerges as a key neuromodulator in the BG circuit, with potential implications for neuroinflammatory disorders such as MS.

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MODULATION OF AMPA GLUTAMATE RECEPTORS AS A STRATEGY TO COUNTERACT HIPPOCAMPAL HYPER-EXCITABILITY AND COGNITIVE DEFICITS IN CEREBRAL AMYLOIDOSIS

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Background: Pathological accumulation of Aβ oligomers has been linked to neuronal networks hyperexcitability [1,2], which could be underpinned by glutamatergic AMPA receptors (AMPARs) dysfunction [3].

Aim: We aimed to investigate whether the modulation of AMPARs was able to counteract the alteration of hippocampal epileptic threshold and of synaptic plasticity linked to Aβ oligomers accumulation, being this glutamate receptor a valuable specific therapeutic target.

Methods: Field-excitatory postsynaptic potentials (fEPSPs) were recorded from hippocampal dentate gyrus (DG) in a mouse model of Aβ oligomers-induced neurotoxicity. We induced epileptic-like activity in vitro with bath-application of either bicuculline or 4-aminopirydine (4-AP). Long-term potentiation (LTP) was induced by high frequency stimulation. Seizure susceptibility to bicuculline and 4-AP was also evaluated in an in vivo mouse model of amyloidosis obtained by stereotaxic injection of Aβ oligomers in the DG. Injected mice were also challenged to hippocampal based behavior and cognition with the Morris water maze, passive avoidance and novel object recognition tasks, to assess possible cognitive deficits associated with oligomers accumulation. Forced swimming test and elevated plus maze were used to assess depression and anxiety-like behaviors, respectively.

Results: Aβ-induced in vitro hyperexcitability was counteracted by AMPARs non-competitive antagonism which, per se, did not affect physiological synaptic transmission. Moreover, the reduced in vivo epileptic threshold found in Aβ oligomers-injected mice was restored by AMPARs antagonism, together with a recovery of hippocampal LTP impairment and significantly improved hippocampal-based cognitive performances.

Conclusions: Targeting glutamate AMPARs might be a valuable strategy to reduce both hippocampal networks hyperexcitability and synaptic plasticity deficits induced by Aβ oligomers accumulation, with potential implications for patients with amyloid-linked cognitive impairment and seizures.

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WHAT PUPIL SIZE AND EYE MOVEMENTS TELL US OF VIGILANCE AND SPATIAL ATTENTION

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Introduction: Pseudo-neglect is defined as a leftward visuospatial asymmetry producing an overestimation of the magnitude of the left side of a stimulus. According to the activation-orientation theory, pseudo-neglect depends on stronger leftward spatial bias generated by the right hemisphere, as compared to the rightward spatial bias of the left hemisphere [1]. Since the right hemisphere appears to be dominant also for non-spatial functions, it has been hypothesized that pseudo-neglect depends on the interaction between spatial and non-spatial (i.e., vigilance, arousal, sustained attention) mechanisms in the right hemisphere [2]. In the present study we hypothesized that alertness exerts a modulation on spatial allocation of attention, and we aimed to (1) investigate pseudo-neglect during free-viewing of real-world scenes, and (2) study its relation with pupillary size, a physiological marker of vigilance [3].

Methods: We recorded eye movements in a sample of N=120 healthy subjects while they were freely observing a set of 185 images on a PC screen, by means of an eye-tracker (Eyelink 1000 Plus, SR research). The relation between vigilance and pseudo-neglect was investigated by means of two measures: a) the correlation between pupil diameter and laterality of fixations at image level; b) a linear mixed-effects to predict pupil diameter by using fixation duration, gaze position, time and image features (saliency, semantic information, and luminance) as predictors, and accounting for inter-subject variability.

Results: At the group level, the percentage of first leftwards fixation after scene comparison was 56% when considering a subset of photos with balanced salience lateralization. Most subjects (63%) globally showed a stronger tendency to fixate on the left portion of the scenes. Around 60% of participants showed a negative correlation between leftward first fixation and pupil size. The linear mixed-effects model demonstrated a moderate influence of pupil size on the direction of gaze.

Discussion: The greater tendency to generate saccades to the left following images onset, net of the influence of salience distribution in the pictures, and to visually explore the left hemi-space during the whole experiment suggest the presence of pseudo-neglect in free-viewing. Notably, this leftward asymmetry in orienting has been correlated with higher alertness as suggested by pupil behavior.

Conclusion: Vigilance as indexed by the pupil size might exert an influence on the spatial allocation of attention, and this interaction may account for pseudo-neglect, also during free-viewing.

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TREATMENT WITH ROS DETOXIFYING GOLD QUANTUM CLUSTERS ALLEVIATES THE PROGRESSIVE FUNCTIONAL DECLINE IN A MOUSE MODEL OF FRIEDREICH'S ATAXIA

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Friedreich's ataxia (FRDA) is caused by the reduced expression of the mitochondrial protein frataxin (FXN) due to an intronic GAA trinucleotide repeat expansion in the FXN gene. Although FRDA has no cure and few treatment options, there is research dedicated to finding an agent that can curb disease progression and address symptoms as neurobehavioral deficits, muscle endurance and heart contractile dysfunctions. Since oxidative stress and mitochondrial dysfunction are implicated in FRDA, we demonstrated the systemic delivery of catalysts activity of gold cluster superstructures (Au8-pXs) to improve cell response to mitochondrial reactive oxygen species (ROS) and thereby alleviate FRDA-related pathology in mesenchymal stem cells of FRDA patients. We also found that

systemic delivery of Au8-pXs induced significant amelioration of motor function and cardiac contractility of YG8sR mouse model that recapitulates the FRDA phenotypes. These effects were linked to long-term improvement of mitochondrial functions and antioxidant cell responses. We coupled these events with increased expression of frataxin, which is sustained by reduced autophagy. Overall, these results suggest a cascade of Au8-pXs-related signals that encourage further optimization of the use of Au8-pXs in experimental clinical strategies for the treatment of FRDA.

PAIN

SENSORY PHENOTYPING IN TRIGEMINAL NEURALGIA WITH AND WITHOUT CONCOMITANT CONTINUOUS PAIN: INSIGHTS INTO PATHOGENETIC MECHANISM

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Objectives: Trigeminal neuralgia (TN) is a disorder characterised by recurrent paroxysmal episodes of unilateral facial pain in the distribution of one or more branches of the fifth cranial nerve [1]. Beside this characteristic paroxysmal pain, about 50% of patients experience a concomitant continuous pain, which may be underlain by distinct pathogenetic mechanisms [2]. The aim of the present study is to investigate the sensory phenotype that characterises the presence of concomitant continuous pain in TN.

Materials and Methods: We enrolled 25 patients with clinically defined TN, including 13 patients (52%) with concomitant continuous pain and 12 patients with purely paroxysmal pain (48%). All of them underwent a Quantitative Sensory Testing (QST) following the standardised protocol of the German Research Network on Neuropathic Pain [3], on both sides of the face. We compared QST parameters with normative values and sensory phenotyping between affected and not affected sides in all patients and in each subgroup.

Results: In the preliminary analysis of 25 patients, the only parameter with a mean Z-score greater than 1.96 was Pressure Pain Threshold (PPT), on both sides (2.043±1.58 on the symptomatic side and 2.09 ±1.66 on the asymptomatic side). The comparative analysis between affected and non-affected side showed a significative difference in Cold Detection Threshold (CDT) and Mechanical Pain Threshold (MPT), both lower on the affected side (p=0.03). When the same analysis was conducted in the group with concomitant continuous pain, it approached statistical significance (p=0.04 for CDT and p=0.08 for MPT), while no differences were found in the group with purely paroxysmal pain (p=0.2).

Discussion and conclusions: We found that objective loss of sensory function characterizes the profile of the symptomatic side in patients with TN. These abnormalities may reflect small fibres axonal loss, possibly triggering the development of concomitant continuous pain in a subgroup of patients with TN.

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PAIN PERCEPTION IN PARKINSON'S DISEASE AND PARKINSONISMS. PRELIMINARY REPORT

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Background and aims: In Parkinson's disease (PD) and Multiple System Atrophy (MSA), pain is frequently reported as one of the non-motor symptoms of the disease. Conversely, in other neurodegenerative disorders including Progressive Supranuclear Paralysis (PSP) and Corticobasal degeneration (CBD), painful symptoms are rare and pain perception is increased. We aimed to evaluate and characterize the presence of pain, pain thresholds and sensory profile, and pain tolerance in PD, MSA, PSP, and CBD patients.

Methods: We enrolled consecutive patients with a probable diagnosis of the parkinsonian and cerebellar forms of MSA, PD, PSP, and CBD. Only patients with Hoehn & Yahr < 2 were included. Patients with cognitive impairment, other painful conditions, or significant comorbidities were excluded. All performed extensive clinical, neuroalgological examinations, including clinical scales, QoL score, pain questionnaires (DN4, NPSI), neuropsychological examination, and psychological scales. Quantitative sensory testing (QST) battery including 12 somatosensory parameters, was performed in all patients, bilaterally, in upper and lower limbs, in L-Dopa ON and OFF conditions. We tested for differences in pain and sensory thresholds and pain tolerance between groups, patient's the more affected side and association with neuropsychological tests.

Results: We included 18 MSA, 20 PD, 12 PSP, 11 CBD, and 25 healthy subjects (HS), sex, and age-matched. Ongoing or evoked painful symptoms were reported in 11 patients with MSA, in 12 patients with PD, and in 5 patients with CBD, none in the PSP group. The painful syndrome was classified as musculoskeletal in 11, peripheral neuropathic pain in 9, and central neuropathic pain in 7. Warm thresholds were higher in MSA and PSPS compared with PD and HS, and heat pain thresholds were higher in PSP, and lower in MSA. PSP and CBD reported errata perception of different sensory modalities and higher pain tolerance. Central sensitization phenomena were also prevalent in PD and MSA, compared with other groups. L-Dopa treatment improved pain and sensory perception only in the PD group. All patients were also evaluated with a test-retest QST paradigm to improve the data's reliability.

Conclusion: Sensory and painful processing assessed by QST battery showed the presence of significant and more severe abnormalities in the PSP group, that experience prevalent negative signs, and pain tolerance not related to cognitive impairment. MSA patients experienced prevalent positive signs with thermal allodynia and hyperalgesia, in particular on the worse motor side, according to the multisystemic pathophysiology of this neurodegenerative disorder.

AUTONOMIC DYSFUNCTION IN FIBROMYALGIA: NEW INSIGHTS FROM THE SKIN

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Objectives: Fibromyalgia is a well-recognized chronic widespread pain condition commonly associated with chronic fatigue, sleep disturbances, and mood disorders. Autonomic symptoms are also frequently reported [1]. The mechanisms underlying this pain condition are still a matter of debate. Small fibre pathology (SFP) is described in nearly half of patients with fibromyalgia [2], although its impact on the clinical picture is still controversial [3]. Our skin biopsy study aims at analyzing the cutaneous autonomic innervation in patients with fibromyalgia and to correlate it with autonomic symptoms.

Materials: We consecutively enrolled 42 patients with fibromyalgia, diagnosed according to 2016 Wolfe diagnostic criteria. Each patient underwent clinical evaluation with a standardized autonomic symptoms questionnaire (COMPASS-31) and skin biopsy with PGP9.5 immunostaining from distal calf and proximal thigh. IENFD, piloerector muscle nerve fibers density (PMNFD) quantification and sweat gland innervation semi-quantitative evaluation (GNFD) were performed on skin samples from patients and 32 healthy controls.

Method: Autonomic skin biopsy parameters were compared between patients with fibromyalgia and healthy controls. Patients with fibromyalgia were then divided in two subgroups according to IENFD (with and without SFP). We compared clinical and skin biopsy autonomic parameters between the two subgroups and each subgroup with healthy controls. Therefore, we correlate skin biopsy parameters with COMPASS-31 score.

Results: All patients with fibromyalgia complain of autonomic symptoms in COMPASS-31 questionnaire. PMNFD and GNFD were lower in fibromyalgia patients with-SFP compared to healthy controls (p=0,003). There were no differences in COMPASS-31 scores between patients with and without SFP (p=0,8168). Autonomic skin biopsy parameters in the SFP fibromyalgia group did not correlate with COMPASS-31 scores.

Discussion: Our study suggests that fibromyalgia patients with-SFP have a reduction of dermal autonomic fibres density. These alterations are not seen in the fibromyalgia subgroup without- SFP, reinforcing the concept of SFP in fibromyalgia. Nevertheless, fibromyalgia patients with alteration of autonomic small fibers did not report more autonomic symptoms respect to patients without-SFP, confirming the controversial impact of SFP on the fibromyalgia clinical picture.

Conclusions: Autonomic nerve fiber reduction is part of the SFP observed in nearly half of patients with fibromyalgia, but autonomic symptoms are independent from the pathological findings.

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COVID-19 VACCINE-INDUCED FIBROMYALGIA-LIKE SYNDROME

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Objectives: Since the introduction of COVID-19 vaccination, several vaccine-induced neurological complications have been reported [1]. Fibromyalgia is a well-recognized chronic widespread pain condition commonly associated with chronic fatigue, sleep disturbances, and mood disorders. Recent evidence demonstrates the role of autoimmunity in the pathophysiology of fibromyalgia [2] and associations have been described between various vaccinations and fibromyalgia [3]. We present a clinical series of 12 patients that experienced a fibromyalgia-like syndrome after the COVID-19 vaccination.

Materials: From January 2022 to June 2022, we prospectively screened 12 consecutive patients suffering from pain as long-term complication after COVID-19 vaccination, attending the Pain Centre at the Department of Human Neuroscience, Sapienza University of Rome. Inclusion criteria were age > 18 years and pain persisting from at least six months after vaccination.

Method: Each patient underwent neurological examination, standardized questionnaire exploring the characteristics of sensory symptoms, pain and autonomic symptoms (DN4, NPSI, COMPASS-31), a blood tests' screening for neuropathy, electroneurography (ENG), Quantitative Sensory Testing (QST) with the calculation of sensory profiles and skin biopsy. Intraepidermal (IENFD) and piloerector muscle nerve fibers density (PMNFD) quantification and sweat gland innervation semi-quantitative evaluation (GNFD) were performed on skin samples. Descriptive statistics were applied to summarize the variables.

Results: All patients received mRNA vaccine except for one that received adenovector-based vaccination. In the totality of patients, clinical examination yielded unremarkable findings and sensory profiling disclosed no sensory abnormalities. According to the NPSI questionnaire, pain was described as burning or electric shock like sensation in most patients. Pins and needles and tingling were frequently reported. All patients reported autonomic symptoms with orthostatic intolerance as the most represented. Although in all patients the DN4 questionnaire were compatible with a diagnosis of neuropathic pain (score ≥ 4), objective diagnostic tests did not disclose any somatosensory system damage. According the 2016 Wolfe diagnostic criteria, 8 patients met a definitive fibromyalgia diagnosis.

Discussion: Our study showed a peculiar widespread pain distribution, combined with chronic fatigue and cognitive symptoms, resembling a fibromyalgia syndrome. The temporal link, the exclusion of large and small-fiber damage by a comprehensive diagnostic work-up and the persistence of symptoms for several months, suggest that COVID-19 vaccination may have triggered an active pain-promoting process.

Conclusions: Our study shows that COVID-19 vaccination can act as a trigger for the development of a Fibromyalgia-like-syndrome.

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COMPARISON OF QUANTITATIVE SENSORY TESTING PROFILING BETWEEN FIBROMYALGIA PATIENTS WITH AND WITHOUT SMALL-FIBRE PATHOLOGY AND PATIENTS WITH SMALL-FIBRE NEUROPATHY

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Small fibre pathology is a common finding in patients with fibromyalgia (FMG). However the mechanisms underlying pain are still an issue of controversy. Some authors suggest that small-fibre pathology has a negligible impact on somatosensory system function in FMG. Quantitative sensory testing (QST) is a widely agreed technique for investigating small-fibre damage. The standardized protocol for QST of the German Network on Neuropathic Pain has been applied for defining sensory profiles. Different sensory profiles may be related to distinct pathophysiological mechanisms. In this clinical and psychophysical study, we aimed at verifying whether patients with fibromyalgia, with and without small-fibre pathology, and patients with pure small-fibre neuropathy share common sensory phenotypes. In 64 consecutive patients with fibromyalgia (20 with small-fibre pathology, 44 without) and 30 patients with pure small-fibre neuropathy associated with a definite aetiology (11 patients with amyloidosis, 8 with diabetes and 11 with systemic lupus), using an algorithm based on quantitative sensory testing variables, we grouped patients in different sensory phenotypes: sensory loss, thermal hyperalgesia, mechanical hyperalgesia, and healthy phenotypes. We found that the frequency of the different sensory phenotypes strikingly differed between patients with fibromyalgia and patients with small-fibre neuropathy. While in patients with fibromyalgia, with and without small-fibre pathology, healthy phenotype, and hyperalgesia phenotypes (both thermal and mechanical hyperalgesia) were similarly represented, in patients with small-fibre neuropathy the sensory loss and mechanical hyperalgesia phenotypes were the most frequent phenotypes. Our findings indicate that small-fibre damage shapes distinct sensory phenotypes in patients with fibromyalgia and in patients with small-fibre neuropathy. The lack of phenotype differences between patients with and without small-fibre pathology and the relatively high frequency of the healthy phenotype underlines the complex association between small-fibre pathology and pain in patients with fibromyalgia, in line with the hypothesis that small fibre pathology doesn't lead to functional sensory deficits in FMG.

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ON-LINE-BEHAVIOURAL-APPROACH (BEHOME) IN PATIENTS WITH CHRONIC NEUROPATHIC PAIN DURING COVID-19 EMERGENCY: EARLY RESULTS

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Objective: Patients with chronic neuropathic pain present severe disability and a low quality of life because pharmacological therapies are often inadequate and poorly tolerated. Recently, the literature shown how educational support and use of behavioral approaches can be helpful for this category of patients when combined with specific pharmacological prophylaxis. Mindfulness is considered an effective approach for helping patients to being more conscious about their condition, to enforce the ability to cope with pain and to manage their pain without or more less medications. Usually, the behavioral approach with mindfulness is delivered with weekly, face-to-face sessions. Due to COVID-19 the treatment protocol was changed, reducing face-to-face visits, taking advantage of technologies facilities. Aim of this study is to assess the feasibility and effectiveness of a specific protocol, designed during the COVID-19 emergency, consisting of a specific behavioral with mindfulness sessions program delivered by web modality.

Materials: Patients were enrolled after a clinical evaluation at the Besta Foundation. Pharmacological treatment and behavioral approach were proposed to patients

Methods: Mindfulness sessions were performed online by a specific web platform with one-hour-weekly groups sessions, leaded by mindfulness expert, alongside daily standardized mindfulness 12-minutes sessions on their smartphone; face-to-face visits every three months were scheduled up to one-year. We assessed: pain intensity and medication intake, catastrophizing (PCS), depression (BDI) and self-efficacy perception (GSE).

Results: 22 patients were enrolled. Mean age 45±14.4y; onset of disease 34±7.8y; age at pain chronification 40±15y. Three patients left the program, leaving19 patients at the 3-month follow up. Pain intensity and medication intake did not change significantly; questionnaire results: GSE (pretreatment 26±5.5 vs R 3 months 26.5±6.3), BDI (17±9 pretreatment vs 12±8.1 R 3 months), PCS (32 ±10.8 pretreatment vs 23 ±10.5 R 3 months).

Discussion: No changes in clinical indexes were reported at 3-months. GSE, PCS and BDI decreased, although not significantly. Although the small group of patients and the short-term follow-up adherence to treatment was high. Although not specifically assessed, patients reported higher ability to cope with pain and to tolerate drug-treatment.

Conclusion: Although we did not observe any clinical change up to now, the results confirm that this protocol supported by the use of technology is effective and feasible and allows more patients to access to behavioral approaches.

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MAGNETIC RESONANCE-GUIDED FOCUSED ULTRASOUND FOR NEUROPATHIC PAIN: A SYSTEMATIC REVIEW WITH CLINICAL CONSIDERATIONS

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Neuropathic pain (NP) is the result of dysfunction of nerve fibers which send incorrect signals to pain centers. The thalamus transfers nociceptive information from spinothalamic and spino-reticulo-thalamic pathways to large domains of the cortex [1]. Magnetic resonance-guided focused ultrasound (MRgFUS) is a combination of high intense focus ultrasound with MRI used to provoke microlesions in selected anatomical sites. To date, the FDA-approved neurological indications for MRgFUS are medically refractory essential tremor and Parkinson Disease-related tremor but this technique is under investigation in the setting of NP [2]. We aimed to systematically analyze the effectiveness and safety of MRgFUS in NP, in order to summarize the available evidence and identify eligibility criteria in clinical practice. Studies were identified on PubMed and Scopus from inception to April 2022. We considered clinical trials, observational studies, and case series published in research databases. We also searched ongoing studies on the clinicaltrials.gov. We retrieved three published observational studies and nine clinical trials. The population of the included studies was ranged from 8 to 46 patients with overall 66 patients included; mean duration of pain ranged from 1.5 to 21 years having NP or trigeminal neuralgia. The treatment target was the posterior part of the Central Lateral nucleus of thalamus (CLT); MRgFUS was performed bilaterally unless contraindicated or not tolerated. Outcome was assessed at 24-48 hours, three and twelve months after the procedure analyzing frequency of pain paroxysms and Visual Analogue Scale (VAS). Patients experienced pain relief at 1 year of follow-up with mean VAS reduction from 35 to 59 and from 28.5 to 80/100. In one case there was an intracerebral bleeding. All other adverse events were mild, transient and included vertigo (6%), paresthesias (2%), and dysesthesias/pain (5%). Regarding ongoing studies, we found 6 observational studies and 3 prospective, randomized, sham-controlled, crossover studies. In all those studies therapeutic target is the thalamus; inclusion criteria mostly require failure to >3 treatments and NP duration >6 months. Primary measures of outcome include accuracy of the technique and pain relief. The follow-up period ranges from one week to one year. Our systematic review showed a lack of high quality studies investigating MRgFUS for treatment of NP. Preliminary data from observational studies on a limited numbers of subjects indicate that targeting the thalamus is safe and effective for the control of NP. RCTs are ongoing and will provide more robust data to understand benefit and risk of this procedure.

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MULTIPLE SCLEROSIS

THE INFLUENCE OF COAGULATION BALANCE POLYMORPHISMS ON MULTIPLE SCLEROSIS ONSET CHARACTERISTICS AND CLINICAL COURSE

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Background and aims: Several hemostasis components, including platelets, the coagulation cascade, and the fibrinolysis system, are known to promote and sustain neuroinflammation in immune-mediated demyelinating diseases [1]. A disturbed hemostatic function in MS patients was also suggested from a genetic perspective, where the genetic tendency to hypercoagulability state might influence MS susceptibility [2]. Herein, we aimed to evaluate whether pro-hemostatic variants revealed to be over-represented in MS patients compared to healthy subjects (Beta-Fibrinogen 455G/A, GPIIIa P1A2, Factor V Leiden, Factor V H2R, and Prothrombin 20210G/A) [2], might influence the clinical and radiological characteristics at onset and the disease course of RRMS.

Methods: We retrospectively collected demographic, clinical (age at onset, EDSS at onset) and radiological data (spinal cord involvement, number of T2 lesions) at disease onset and 5-year follow-up clinical data (EDSS and number of relapses at 2- and 5-years follow-up). Patients were genotyped and a cumulative genetic risk score (CGRS) was built, including the 5 hemostatic risk alleles revealed to be over-represented in RRMS patients (Beta-Fibrinogen 455G/A, GPIIIa P1A2, Factor V Leiden, Factor V H2R, and Prothrombin 20210G/A). Influence of CGRS on clinical and radiological characteristics was analyzed by linear and logistic regression models, as appropriate. The regression models were adjusted according to age, gender, and number of disease-modifying therapies over the follow-up period.

Results: 236 RRMS patients were enrolled. Five years follow-up clinical data were available for 90 patients. In the linear regression, an increasing number of unfavorable alleles were associated with a lower age at onset (p=0,022) and a lower likelihood of spinal cord involvement at onset (p=0,009). Further, the presence of at least 3 risk alleles was associated with a higher number of relapses at 2 (p=0,004) and 5 years (p=0,014) follow-up.

Discussion: Previously, we have compared the frequency of single-nucleotide polymorphisms (SNPs), thought to be involved in fibrinogen-mediated hemostatic pathways, in patients with MS compared with healthy controls. We found that Beta-Fibrinogen 455G/A and Factor V H1299R polymorphisms may be associated with MS and that an increasing number of pro-thrombotic alleles might increase the likelihood of being in the MS group. [2]. Here, we found that a genetic unbalanced coagulation state might influence MS onset characteristics and disease activity.

Conclusions: Taken together, these data suggest that a genetic determined hypercoagulability state might influence MS onset characteristics and clinical course.

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THE COMBINED EFFECT OF COGNITIVE RESERVE AND BIOLOGICAL SEX ON COGNITIVE CHANGES IN PEOPLE WITH MULTIPLE SCLEROSIS: AN EXPLORATORY AND LONGITUDINAL STUDY

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Introduction and Aim: Longitudinal studies on the effect of cognitive reserve (CR) on neuropsychological performance in people with Multiple Sclerosis (pwMS) are inconsistent [1,2], and the interaction effect between sex and CR on cognition was not fully investigated. The aim of the study was to evaluate the effect of CR, sex, and their interaction on cognitive changes in a sample of newly diagnosed pwMS.

Materials and methods: 74 newly diagnosed pwMS (41 women, 33 men) according to 2018 McDonald criteria underwent a neurological and neuropsychological evaluation at baseline (T0; evaluation <12 months from diagnosis) and follow-up (T1; ≥ 1 year from T0). As for the cognitive assessment, the STROOP test was administered to assess performance on inhibitory control, whereas the Italian version of the Brief Repeatable Battery of Neuropsychological Tests was employed to evaluate levels of verbal and spatial memory (Selective Reminding Test [SRT-LTS, SRT-CLTR, SRT-D]) and Spatial Recall Test [SPART, SPART-D]), processing speed/attention (Symbol Digit Modalities Test [SDMT], Paced Auditory Serial Addition Test [PASAT]), and verbal fluency (Word List Generation [WLG]). CR was assessed by means of Cognitive Reserve Scale (Altieri et al., 2018). A MANOVA for repeated measures with correction for multiple comparison was performed. Within-subject factor was time (T0, T1), between-subject factors were CR (high, low) and sex (men, women), whereas the dependent variables were neuropsychological scores.

Results: T1 evaluation was performed after 20.2 ±4.9 months from T0. The MANOVA revealed a significant main effect of i) time on SRT-LTS, SRT-D, SPART, SPART-D, SDMT, PASAT 3", WLG, and STROOP scores (T1>T0), and ii) sex on SRT-CLTR, SRT-D scores (women>men). Moreover, the interaction effect between time, sex and CR was statistically significant on SPART (F (1,70)=4.253, p=.043), SPART-D (F(1,70)=7.913, p=.006), WLG (F(1,70)=3.975, p=.05), and STROOP (F(1,70)=4.689, p=.034) scores, with only men with high CR showing improvement at T1 evaluation.

Discussion: The present findings suggest that cognitive decline in MS might be reversible in the short term, probably due to some influencing factors (e.g. levels of depression or anxiety, coping strategies, use of DMTs) that deserve to be investigated in future studies. Moreover, only men with high CR showed an improvement on selected aspects of cognition at T1.

Conclusion: There is evidence of a combined role of CR and sex on cognitive changes in MS, especially on visuo-spatial memory and some executive functions.

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THE IMPACT OF BIOLOGICAL SEX AND COGNITIVE RESERVE ON COGNITION IN MULTIPLE SCLEROSIS

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Introduction and objective: Biological sex and cognitive reserve (CR) have showed an impact on cognitive performance in people with Multiple Sclerosis (pwMS) [1,2,3]. To date, no studies focused on the interaction effect between sex and CR on cognitive status in pwMS by employing a specific CR scale assessing multiple cognitively stimulating activities. The aims of the study were to assess, in pwMS, the possible presence of a combined effect of CR and biological sex on performance on several cognitive domains.

Materials and methods: 196 people with RRMS (117 women) were consecutively recruited at the MS Center of the I Division of Neurology at University of Campania. They underwent a neurological examination and the Expanded Disability Status Scale was calculated to evaluate the degree of physical disability. Moreover, each participant was administered i. the Stroop test to assess performance on inhibitory control, and ii. the Italian version of the Brief Repeatable Battery of Neuropsychological Tests to evaluate levels of verbal and spatial memory (Selective Reminding Test [SRT-LTS, SRT-CLTR, SRT-D]) and Spatial Recall Test [SPART, SPART-D]), processing speed/attention (Symbol Digit Modalities Test [SDMT], Paced Auditory Serial Addition Test [PASAT]), and verbal fluency (Word List Generation [WLG]). Levels of CR was assessed with a specific CR scale, the Cognitive Reserve Scale (I-CRS; Altieri et al., 2018); depression was evaluated by means of Beck Depression Inventory. T-test for independent samples was calculated to evaluate possible differences between clinical and socio-demographic variables among sexes; a MANOVA controlling for levels of depression served to evaluate the effects of CR and sex, and their possible interaction effect on cognitive performance. Bonferroni correction was applied.

Results: Men and women with MS did not differ for clinical and socio-demographic variables. The MANOVA revealed a significant main effect of CR on SRT-LTS (p=.010), SRT-CLTR (p<.001) and WLG (p=.042) scores (high CR>low CR), and a significant main effect of biological sex on PASAT 3'' (p=.025), PASAT 2'' (p= .005) (men>women), and on WLG (p=.004) scores (women>men). The interaction effect between sex and CR was not significant.

Discussion: The results revealed that the possible impact of CR on cognitive performance did not depend on being a man or a woman with MS.

Conclusions: Both sexes may equally benefit from specific tailored psychosocial neuropsychological rehabilitation programs to increase CR and cognitive performance.

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MATERNAL AND FETAL OUTCOMES AMONG PREGNANT MULTIPLE SCLEROSIS WOMEN WITH COVID-19 INFECTION

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Objectives: To evaluate maternal and fetal outcomes and their predictors in a population of pregnant women with MS diagnosed with COVID19 selected from two large national registries and compared with matched control pregnancies extracted from a historical Italian multicenter MS cohort.

Methods: Pregnant patients with Multiple Sclerosis (pwMS) who contracted SARS-CoV-2 infection after conception and were prospectively followed-up in Italian and Turkish MS Centers from 2020 to 2022 were included. Detailed information on pregnancy course and outcomes, as well as on possible confounders, were acquired through a structured interview. The control group was extracted from a previous Italian multicenter cohort (Amato 2008). The primary outcome measures were indices of maternal and severe neonatal/perinatal morbidity and mortality. Data on pregnancy outcomes were compared using logistic and linear multivariable regression analyses, when appropriate.

Results: Currently, clinical characteristics and data on COVID-19 outcome are available for 85 pregnant MS women with COVID-19 after conception (mean age 35.2 +/- 6.4 years, 83 relapsing remitting (RR) MS, mean disease duration 8.3 +/- 6.86 years, median EDSS 1.0 (IQR 1.0-2.5). As for COVID-19 course, 8 women (9.4%) were hospitalized; no one required transfer to intensive care unit (ICU); no deaths were recorded. The historical control group consists of 232 women with RRMS (mean age 34.6 +/- 3.1 years, mean disease duration 8.8 +/- 4.8 years, median EDSS 1.5 (IQR 1.0-2.0). The collection of information on maternal and fetal outcomes is ongoing.

Discussion: In the general population, pregnancy is associated with an increased risk for respiratory infections [1]. Data regarding pwMS have reported an increased risk of severe COVID19 in patients treated with antiCD20 or who received corticosteroid treatment close to COVID19 onset [2]. However, no studies so far have investigated maternal and fetal outcomes in pregnant women with MS who contracted COVID19 during gestation. In our study, a few patients (9.4%) required hospitalization, and no one was admitted to ICU. This finding is apparently not in line with previous studies on general population, which have shown a general increased risk for hospitalization and ICU in infected pregnant women, as well as for other adverse maternal and fetal outcomes [3]. No data are available so far on adverse pregnancy outcomes in our cohort.

Conclusion: Our preliminary data show no significant increase of severe COVID-19 in pwMS who contracted the infection during pregnancy. The analysis on pregnancy-related maternal and fetal outcomes is ongoing.

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FUNCTIONAL AND STRUCTURAL MRI CHANGES ASSOCIATED WITH COGNITIVE WORSENING IN MULTIPLE SCLEROSIS: A 3-YEAR LONGITUDINAL STUDY

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Objectives: Heterogeneous pathological processes may contribute to cognitive impairment in multiple sclerosis (MS); however, the association between brain structural and functional MRI changes and cognitive worsening in MS still need to be fully explored. We aimed to apply a multiparametric MRI approach to identify the mechanisms associated to cognitive worsening in MS patients.

Material: Brain dual-echo, 3D T1-weighted, diffusion-weighted imaging, and resting state (RS) functional MRI scans were acquired at baseline and after a median follow up of 3.4 years in 35 MS patients and 22 healthy controls (HC). Neuropsychological evaluation was performed at both timepoints using Rao's Brief Repeatable Battery (BRB).

Methods: Cognitive worsening was defined using reliable change index $\leq$ -1.25 on BRB. Associations between cognitive worsening and global and regional voxel-wise longitudinal changes in white matter (WM) microstructural damage, gray matter (GM) atrophy and RS functional connectivity (FC) were explored using tract-based spatial statistic (TBSS), tensor-based morphometry (TBM) and independent component analysis (ICA).

Results: Fifteen (43%) MS patients were cognitively impaired at baseline and 10 (29%) showed cognitive deterioration at follow-up. At baseline, compared to HC, MS patients showed widespread WM damage and GM atrophy, and decreased RS FC in some clusters of executive control (ECN) and working memory networks (WMN). At follow-up, annualized volume loss of caudate nucleus was significantly higher in MS patients with vs those without cognitive deterioration (-1.2% vs -0.2%, $p<0.05$), whereas no significant between-group differences in regional WM microstructural changes or GM atrophy were found. Compared to cognitively stable MS patients, those with cognitive deterioration showed decreased RS FC in the right hippocampus of right WMN and in right insula of default mode network. In the opposite comparison, an increased RS FC in the left insula of the ECN was found.

Discussion: While cognitively stable MS patients showed increased RS FC in the left insula, possibly reflecting a compensatory mechanism, cognitive deterioration at medium-term in MS patients was associated with decreased RS FC in several functional brain networks, with a more limited GM atrophy progression.

Conclusions: Our study suggests that, in MS patients already characterized by substantial structural damage, cognitive deterioration might be secondary to functional network collapse.

LOW POSITIVE PREDICTIVE VALUE OF MULTIPLE SCLEROSIS DIAGNOSTIC CRITERIA IN DEMYELINATING SYNDROMES WITH RED FLAGS OF BETTER EXPLANATION

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Introduction: Perivenular lesions (PVL) are a cardinal pathological feature of Multiple Sclerosis (MS), that brain MRI can non-invasively detect. In demyelinating syndromes, a frequency of PVL above 50% among all white matter lesions (50%-rule) is characteristic and specific of MS.

Objectives: To evaluate the positive predictive value of current MS diagnostic criteria in a group of atypical MS patients, considering the 50%-rule as the diagnostic gold standard of true MS cases.

Methods and materials: The frequency of PVL was tested in "MS-plus" patients, defined as fulfilling MS 2017 revised McDonald diagnostic criteria based on the dissemination in space (DIS) and in time (DIT) but also carrying red flags (clinical, laboratory or MRI features) suggesting the existence of a better explanation, but not formally allowing another diagnosis. MS-plus patients were compared with typical MS controls: Relapsing-remitting (RR) MS cases with typical demyelinating syndromes (Typical MS, n=28) and RR-MS-plus patients (MS-plus, n= 60), were included. The patients received one brain MRI scan with conventional and 3DFLAIR* scans for PVL analysis. The PVL frequency (PVL-f) and other conventional brain MRI characteristics were evaluated in each patient, who was then categorized according to the MS-specific PVL-f threshold of 50%.

Results: The Typical MS patients had a median PVL-f of 91% (range 67–100%) whereas the MS-plus patients of 55% (range 8–100%; p=0.001). Patients fulfilling the 50%-rule were 28/28 (100%) and 32/60 (53%) respectively in the two groups (p< 0,00001). Considering this MS-plus enriched MS population as a whole (n= 88), the patients fulfilling the 50% rule were n= 60 (68%). These frequencies represent the positive predictive values of the 50%-rule fulfillment when the diagnostic criteria for MS based on DIS/DIT are applied in each of these patient populations. The other conventional MRI measures examined did not improve the values of the DIS/DIT criteria.

Conclusions: Considering the 50% rule the "gold standard" for identification of true MS cases, the positive predictive value of the current MS diagnostic criteria in demyelinating syndromes with red flags of better explanation is low. In any MS population, this predictive value will depend on the prevalence of MS-plus cases.

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NON-RANDOM LOCALIZATION OF CORTICAL LESIONS IN FUNCTIONAL NETWORKS IS RELATED TO COGNITIVE AND PHYSICAL IMPAIRMENT IN MULTIPLE SCLEROSIS

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Aim: To characterize the localization and extent of cortical lesions (CLs) in multiple sclerosis (MS) across functional networks and their impact on cognition and physical disability.

Methods: 307 MS patients, pooled from the Verona (N=130; age 38.8±10.0 years, disease duration 5.7±5.4 years) and Amsterdam MS cohort (N=177; age 54.2±9.1 years, disease duration 16.7±5.7 years), underwent to a resting-state functional and structural MRI, including double inversion recovery (DIR). A subgroup of 266 underwent to neuropsychological testing (expanded BRB-N). Patients were categorized as cognitively preserved (CP; N=143) and impaired (CI; z−1.5 on ≥2 cognitive tests, N=123) compared to 48 matched healthy-controls for the Amsterdam cohort and to Italian literature-based normative for the Verona cohort. Moreover, they were grouped in early (N=150; < 16 years) and late (N=157; ≥ 16 years) MS using as cut-off the median value of disease duration from onset (16 years) and, in high (N=120) and low disability (N=187) using as cut-off the milestone EDSS 4.0. The Brainnetome atlas was used to parcellate the brain into 7 resting-state functional networks (RSNs): visual, sensorimotor (SMN), ventral attention (VAN), dorsal attention (DAN), default mode (DMN), frontoparietal (FPN) and limbic. Volume/fraction measures of CLs, manually segmented on DIR sequences, within each network were compared between groups.

Results: In the pooled MS dataset, largest lesion volumes were found in limbic (median [IQR] mm3; 61.3[4.0-223.8]), DMN (53.4[0.9-144.5]) and VAN (34.7[6.2-135.7]). Looking specifically at the CLs fraction within the networks, these regions remained the most affected with reverse order given the different volume of the RSNs (first VAN, following limbic network and DMN). This result was confirmed also looking separately at the two MS cohorts. In the pooled dataset, looking at CI versus CP, a higher total lesion volume and fraction (p<0.001) was seen in all networks, with reduced differences between networks in CI patients, with highest effect sizes in the DMN (Cohen's d=0.53; CP 34.9[0.0-93.6]; CI 76.0[19.1-238.6]), SMN (d=0.49; CP 14.9[0.0-75.1]; CI 54.7[4.0-144.0]) and FPN (d=0.50; CP 0.0[0.0-31.0]; CI 23.7[0.0-97.6]). When comparing subgroups based on disability or disease duration similar results were obtained, with significant higher (p<0.001) total lesion volume and fraction in each RSN in the more disabled group, but with smaller effect size (d<0.2) compared to cognitive groups.

Conclusions: Cortical lesions were not randomly distributed in MS, but preferentially affected the limbic network, DMN and VAN. Effects on clinical performance were especially seen for cognition, specifically when affecting DMN, FPN and SMN.

NATALIZUMAB VS OCRELIZUMAB: PRELIMINARY LONG-TERM RESULTS IN A REAL-WORLD SETTING

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Introduction and Aim: Both Natalizumab (NTZ) and Ocrelizumab (OCR) are high efficacy monoclonal disease modifying therapies (DMTs) for Relapsing Multiple Sclerosis (R-MS). The aim of our study was to compare long-term clinical effectiveness and treatment persistence of NTZ and OCR in a cohort of patients with MS (PwMS) treated in a real word setting.

Materials and Methods: 73 RMS subjects (38 in NTZ and 35 in OCR) with at least 1 relapse in the previous 2 years were recruited from 2011 to 2017 at S.Andrea MS Center, Rome. We collected demographic and clinical data through the study follow-up. Clinical outcomes were defined as time to first relapse and disability worsening, evaluated with between-group comparisons by Cox models (adjusted for baseline variables).

Results: There was no difference between groups in proportions of male patients (36.8% in NTZ group and 36.3% in OCR group, p=0.82), disease duration (SD) before treatment [NZT: 5.5 (5.7) years vs. OCR: 5.2 (5.0) years, p=0.81], median baseline EDSS score (2.0 in both groups; range 0-4.5 for NTZ vs. 0-5 for OCR, p=0.22). Mean age (SD) at onset was 24.9 (7.1) years for NTZ-treated vs. 30.4 (7.0) years for OCR-treated patients (p=0.001). Patients previously treated with one or more immunomodulatory agents were 23/38 (60.5%) for NTZ group and 23/35 (65.7%) for OCR group(p=0.65). The mean follow-up duration was 7.5 (2.3) years with NTZ and 5.9 (2.2) years for OCR. Five (13.2%) and 7 (20%) patients discontinued NTZ and OCR, respectively (p=0.43). Reasons for discontinuing NTZ were safety related to JVC+ (n=3) and patient's decision (n=2); reasons for discontinuing OCR were pregnancy desire (n=4), patient's decision (n=2), disease progression (n=1).The two groups did not differ in terms of both occurrence of relapses (NTZ: n=4 [10.5%] vs. OCR: n=2 [5.7%]; HR=0.59, p=0.54), and disability worsening (NTZ: n=4 [10.5%] versus OCR: n=2 [5.7%]; HR=0.71, p=0.68).

Discussion and Conclusions: The results of our case-control study showed no significant differences in effectiveness between the NTZ and OCR on a long-term follow-up, although suggested a preferred choice of neurologists to use Ocrelizumab in older PwMS. Study limitations were related to its observational design, small sample size and lack of reliable MRI data across treatment groups. Further research is warranted to confirm our findings on a larger scale.

IMPACT OF MULTIPLE SCLEROSIS ON DAILY AND WORK ACTIVITY: AN EXPLORATORY MONOCENTRIC STUDY

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Objectives: Multiple sclerosis (MS) mainly affects young people of working age [1]. Notoriously, MS related disability and several MS symptoms such as fatigue can affect the quality of life and work efficiency of people (pw) with MS [2], with impact on employment rate, reported around 59% in pwMS. Based on these bases, the aim of the study was to examine the employment status of MS patients, also exploring demographic and clinical variables associated to daily and working functioning.

Materials and Methods: MS patients according to the 2010 McDonald criteria were recruited [3]. A descriptive analysis of demographics, MS features and patients' working status was performed. Clinical differences between employed and unemployed MS patients were assessed by using independent t-test for quantitative variables and the Chi-Square test for qualitative variables. Impairment of daily and work functioning was assessed using the Work and Social Adjustment Scale (WSAS). Thus, Person correlation analysis was carried out to evaluate the relationships with clinical variables, in particular with the level of disability (EDSS score). Logistic regression was performed to evaluate the relationship of employment status with demographic and clinical features of MS patients.

Results: 207 patients were enrolled, of which 152 (73.4%) were female (mean age 40.9 ± 11.6 years, mean disease duration 14 ± 8.7 years, mean EDSS 2.4 ± 1.9). Ninety-four patients (45.4%) were employed, while 21 (10.1%) were unable to work. The level of disability with EDSS> 4 was found to have a negative impact on the daily activities, social, recreational and working functioning of the patients ($p < 0.001$). A relationship between the total WSAS score and the EDSS score was observed by using Person test ($r = 573$, $p < 0.001$). Logistic regression analysis showed an association of the employment status with the education ($p = 0.023$), while a negative association was found with the female gender ($p = 0.005$).

Conclusions: MS has a strong impact on employment status, demonstrated by the employment rate found in our study. The level of disability negative influence the daily activities, social life and work functioning of the employed subjects, for this reason specific job placement programs should be designed.

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HUMORAL AND T-CELL RESPONSE TO SARS-COV-2 MRNA VACCINE IN MULTIPLE SCLEROSIS PATIENTS TREATED WITH DISEASE MODIFYING THERAPIES

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Objective: Vaccination against SARS-CoV-2 is the main strategy to contain the pandemic. Disease-modifyng therapies (DMTs) may impact on vaccine responses in multiple sclerosis (MS). The aim is to study the humoral and T-cell response after SARS-CoV-2 mRNA vaccine in MS people treated with different DMTs.

Materials and Methods: 130 MS patients treated with different DMTs were recruited, blood samples for detection of SARS-CoV-2 antibodies were collected at T0, before the first dose of vaccine, at T1, before the

second dose, and T2 one month after. In a subgroup of 51 patients and 20 controls, samples were collected at T0 and T2 to test T-cell immune response to Spike antigen of SARS-CoV-2 by ELISPOT-IFNγ.

Results: All 130 patients had negative SARS-CoV-2 antibodies before vaccination, 66% showed IgG response to the first dose of vaccine (mean [SD], 757 [852] AU/mL), and 88,5 % after the second dose (7259,06 [7251]). The IgG response rate to vaccine was 100% (20/20) in healthy controls and MS patients treated with teriflunomide (5/5), dimethyl-fumarate (5/5) and natalizumab (9/9), while it was significantly lower in patients treated with fingolimod (76.2%, 16/21) and ocrelizumab (36.4%, 4/11). The IgG levels in fingolimod (552.3 [957.9]) and ocrelizumab (159.1 [301.2]) were also significantly lower than healthy controls (P<0.0001). We detected positive Spike–specific T-cell responses in 100% of vaccinated healthy controls and patients treated with teriflunomide, dimethyl-fumarate and natalizumab, in 90.5% (19/21) of patients treated with fingolimod, and 63.8% (7/11) of patients treated with ocrelizumab.

Discussion and Conclusions: The study confirm that the mRNA vaccine induce humoral specific responses in the majority in the majority of DMT-treated SM patients. It is noticeable the development of a T- cell–specific response to SARS-CoV-2 in patients treated with fingolimod and ocrelizumab, even with lower rates of humoral response. These findings encourage SARS-CoV-2 vaccination in all MS patients treated with DMTs.

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SAFETY AND TOLERABILITY OF CONVERSION TO SIPONIMOD WITH AND WITHOUT TITRATION IN PATIENTS WITH ADVANCING FORMS OF RELAPSING MULTIPLE SCLEROSIS: INTERIM RESULTS OF THE PHASE 3B EXCHANGE STUDY

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Objectives: Report interim analyses of EXCHANGE (NCT03623243). EXCHANGE is assessing conversion to siponimod with/without dose titration and completed 50% subject enrollment.

Materials: Analysis included patients aged 18-65 years with advancing forms of RMS, EDSS 2.0–6.5, and on continuous oral/injectable DMTs for ≥3 months at time of consent.

Methods: Patients previously on teriflunomide required 11-14 days' accelerated washout. Those converting from fingolimod immediately switched to siponimod 2 mg, without dose-titration. All other patients initiating siponimod were titrated from 0.25 to 2 mg over 6 days. Primary endpoint was incidence of AEs possibly related to siponimod treatment.

Results:163 patients (74.2% female; mean age 46.6 years; mean baseline EDSS 3.9) from 42 US centers were eligible for safety analysis (16.6% ongoing; 18.4% discontinued; 65.0% completed). At screening, 76.7% had RRMS, 20.2% SPMS, 2.5% PPMS, and 0.6% single demyelinating event. Most patients (54%) had no relapses in the year prior to screening. Most common prior DMTs were oral/injection therapies: 30.7% fingolimod, 27.6% glatiramer acetate/IFNβ, 20.9% dimethyl fumarate, and 17.2% teriflunomide. 31.3% of patients reported ≥1 AE possibly related to siponimod treatment. Most common AEs by preferred term were headache (8.0%), dizziness (4.3%), nausea (3.7%), bradycardia (3.1%), and fatigue (3.1%). There was no decrease in heart rate at 6-hours post-1st dose from baseline in the overall or any of the prior DMT groups. In the subgroup of fingolimod patients (n=7) who were switched to siponimod without dose titration, mean heart rate (SD) was 73.1 bpm (18.1) at 6 hours post 1st dose vs 68.4 bpm (10.8) at baseline.

Conclusions: Immediate conversion from other DMTs to siponimod had an acceptable safety/tolerability profile, with no unexpected findings. There was no evidence of a meaningful reduction in heart rate when initiating siponimod in the overall group or in subgroups stratified by prior DMTs, including subjects transitioning from fingolimod to siponimod without dose titration. EXCHANGE: ClinicalTrials.gov Identifier: NCT03623243; https://clinicaltrials.gov/ct2/show/NCT03623243

FUNCTIONAL NEUROLOGICAL DISORDER IN MULTIPLE SCLEROSIS

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Objective: There is increasing evidence that Functional Neurological Disorder (FND) can co-occur with other neurological diseases, but there are no available data in Multiple Sclerosis (MS). We aimed to: 1) evaluate the presence of FND in consecutive patients with MS during a one-year period; and 2) assess the clinical correlates of FND in MS.

Materials: To evaluate the frequency of FND in MS, consecutive patients attending the MS outpatient clinic on an elective basis or admitted to our center on an emergent basis were evaluated by the same neurologist with a significant expertise in both FND and MS.

Methods: The diagnosis of FND was based on the presence of positive signs (i.e., positive hoover sign, distractibility, etc). To explore the clinical correlates of FND, these patients were compared to a sample of consecutive MS patients without FND (ratio 1:2) matched for EDSS.

Results: Out of 21 emergent visits, 6 (26.5%) were identified as functional "relapses". Moreover, 12 patients out of 318 (3.77%) were found having functional signs on examination, yielding to a total of 5.47% having comorbid FND. The latter had longer disease duration, a higher number of therapeutic switches due to the presence of side effects, a higher rate of self-reported depression and anxiety (for all p<0.05; table 1). A logistic regression model with stepwise method revealed disease

duration (p<0.01), anxiety (p=0.01) and depression (p=0.01) to be independent predictors of FND, overall explaining a variance of about 73%.

Discussion: FND are much more common than currently appraised in MS, with an overall frequency of about 5%, that increases to up to 30% in our cohort of MS patients admitted on an emergent basis. Longer disease duration and presence of mood disorders are associated with the presence of FND.

Conclusion: It is crucial to identify FND in MS to avoid iatrogenic harm from unnecessary therapies. Future studies are needed to better characterize patients with FND and MS.

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DISABILITY ACCRUAL IS MAINLY DETERMINED BY PROGRESSION INDEPENDENT OF RELAPSE ACTIVITY IN A REAL-WORLD COHORT OF RELAPSING-ONSET MULTIPLE SCLEROSIS PATIENTS

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Aim: To assess whether relapse associated worsening (RAW) and progression independent of relapse activity (PIRA) events can coexist in a single patient in case of multiple confirmed disability accrual (CDA) events; to evaluate predictors of PIRA or RAW events.

Materials and Methods: Relapsing-onset multiple sclerosis (MS) patients with follow-up >/= 5 years (n=16,130) were extracted from the Italian MS Registry. CDA was defined by an increase in Expanded Disability Status Scale (EDSS) score confirmed at 6 months and classified per temporal association with relapses. Predictors of PIRA and RAW were assessed using logistic multivariable regression analyses.

Results: Over a follow-up of 11.8 + 5.4 years, a total of 16,731 CDA events occurred in 8,998 (55.8%) patients. Overall, PIRA (n=12,175) accounted for 72.3% of CDA events. Focusing on 4,217 patients with at least 2 CDA events, only 279 (6.6%) had exclusively RAWs, whereas 2,100 (49.8%) had exclusively PIRAs. In the remaining 1,838 (43.6%) patients RAW and PIRA were variably interwoven over time. PIRA accounted for 67.2% of first CDA (2,100 out of 4,217), 77.1% of 2nd-4th CDAs (5,507 out of 7,151) and 86.9% of CDAs from 5th onwards (506 out of 582). Having exclusively RAW events was associated with female sex (OR=1.5; 95%CI 1.1-2.0; p=0.010), younger baseline age (OR=1.5; 95%CI 1.1-2.0; p<0.001), lower baseline EDSS (OR=0.97; 95%CI 0.96-0.99; p<0.001), shorter follow-up duration (OR=0.88; 95%CI 0.86-0.91; p<0.001) and higher number of relapses over-time (OR=1.20; 95%CI 1.17-1.24; p<0.001).

Discussion: Disability worsening in MS may derive from RAW or PIRA. In our cohort, PIRA resulted to be more common than RAW on the whole follow-up considering all the CDA events. Moreover, when analyzing multiple CDAs separately in patients experiencing at least 2 CDA events, PIRA was more prevalent than RAW already from the first CDA, with an increasing proportion of subsequent events classified as PIRA. A minority of patients experienced exclusively RAW events, with female sex, younger age at baseline, lower disability burden and higher number of relapses over time associated with a 'pure' RAW disability worsening at multiple CDAs.

Conclusion: In a real-world relapsing-onset MS cohort, PIRA was the main determinant of disability accumulation. RAW events were relatively more represented in younger, less disabled, female patients, and in early CDA events. The analysis on multiple RAW-PIRA events and the risk of conversion to secondary progressive MS is ongoing.

MOTION CAPTURE ANALYSIS OF DOMINANT ARM TRAJECTORIES IN SUBCLINICAL PATIENTS WITH MULTIPLE SCLEROSIS VS HEALTHY CONTROLS: AN EXPLORATIVE STUDY

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Objectives: To examine differences in motion capture analysis parameters of dominant arm in early Relapsing-Remitting Multiple Sclerosis (RRMS) patients with no evident neurological deficits compared with healthy controls (HCs).

Materials: Motion capture analysis of the dominant upper limb was performed via the Smart DX motion capture system (BTS Bioengineering), synchronized with a grid of 8 proximity sensors (Witty Sem by Microgate). Each subject was equipped with 6 markers placed on the following anatomical landmarks: both the shoulders, C7, elbow, ulnar styloid and second metacarpal caput.

Methods: Patients were extracted from a prospective cohort included in the project NET-2018-12366666, funded by the Italian Minister of Health, and compared with age- and sex-matched HCs. Inclusion criteria were the following: diagnosis of RRMS; Expanded Disability Status Scale (EDSS) $\leq$ 1.5. Two tasks with increasing difficulty were administered: the first one was the achievement of 50 light stimuli (a green "F") in random sequential while the second included the addition of distractors (different green letters and numbers). The following parameters were analyzed for both tasks: time to complete the task, entropy, spectral arc length, speed metric and log dimensionless jerk (LDJ). The two tasks were compared within each group using a Wilcoxon signed-rank test. Interaction between within-subjects factor (task) and between-subjects factor (group) on the dependent variable was evaluated by a two-way mixed ANOVA. Significance threshold was set at $\alpha = 0.05$.

Results: Twenty RRMS patients and 22 HCs were included in the analysis. Wilcoxon test showed a significant difference between single and dual task for all the tested variables ($p<0.05$) in both groups. At the mixed-ANOVA analysis, LDJ (median [IQR] HCs: first task -6.08 [0.38], second task -6.89 [0.48]; RRMS: first task -6.75 [0.86], second task -7.09 [0.72]) was significantly different between the two groups ($p=0.016$) and between tasks ($p<0.001$).

Discussion: Motion capture analysis of upper limbs is a largely unexplored area in Multiple Sclerosis. In this explorative study, we have searched for useful parameters that can distinguish HCs from RRMS that did not exhibit noticeable disability on neurological examination. The LDJ parameter, a variable used to quantify the smoothness of movement, appeared significantly worse in RRMS compared with HCs, p.

Conclusion: Motion capture analysis of dominant arm movements in scaling difficulty conditions might be useful to detect subclinical deficits in RRMS patients. However, these preliminary results need to be validated on a larger, multicentric cohort.

DECIPHERING MULTIPLE SCLEROSIS ENDOPHENOTYPES THROUGH MENDELIAN DISORDERS: A NETWORK-BASED APPROACH

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Background and aims: Growing evidence indicates that complex diseases constitute phenotypical continuums with monogenic disorders. Cross-matching "simple" diseases, endophenotypes of multifactorial disorders and their susceptibility variants from GWAS could facilitate the understanding of shared physiopathology and relative biomarkers. Furthermore, analysis of functionally related genes and their products' interactome offers a basis to drug targets identification for both conditions (i.e., the Mendelian disease and the phenotypically- matched endophenotype of the complex disease). Here we apply such principles through reworking the latest GWAS for Multiple Sclerosis (MS), a common dysimmune and neurodegenerative disease of the central nervous system displaying extreme clinical heterogeneity.

Methods: MS-associated SNPs were derived from the latest GWAS. Enrichment testing of MS-associated variants with Mendelian disorder genes was performed through MendelVar algorithm, integrating disease knowledge from OMIM, DECIPHER, Orphanet and Genomics England databases. The output list of genes was used to construct the MS-mendelian network through STRING, analyzed in Cytoscape to define phenotypic modules via semantic classification. For each subnetwork, a pathway analysis was performed through WebGestalt. Finally, NeDReX algorithm was used to perform a network-based drug-repurposing screening.

Results: Starting from 618 genomic loci associated with MS, we confirmed a significant enrichment of monogenic diseases with either dominant or recessive inheritance ($p<0.001$). We defined a highly interconnected MS-Mendelian molecular network based on 353 genes and 566 related monogenic disorders, on which 5 MS intermediate phenotypes were mapped. Enriched subnetworks included: autoimmune disorders and immune deficiencies, whose genes pertained to IL4, IL6 and IL7 pathways; neurodegenerative ataxias, associated with genes involved in synaptic transmission and neurodevelopment; primary disorders of the visual system, such as retinitis pigmentosa and hereditary optic atrophy; metabolic and mitochondrial diseases, such as. Leigh's syndrome; axonopathies, including amyotrophic lateral sclerosis (ALS) and spastic paraplegias, deriving from genes relevant for ion channels and ubiquitination. The network-based drug targeting algorithms prioritized cross-phenotype molecules, such as tyrosine kinase inhibitors, and phenotype-specific drugs, such as promethazine for the neurodegenerative processes, bithionol for optic dysfunctions, zinc-based compounds for ataxias.

Discussion and conclusions: Our results underscore the existence of shared physiopathological aspects between MS and phenotypically-affine rare diseases. Our molecular map may be the basis for further investigations on endophenotype-specific biomarkers, helping portraying patient-specific disease profiles and possible combinatorial therapies. Also, this work supports smarter clinical trials designs enrolling subgroups of people with MS or matched Mendelian diseases, such as basket trials, searching for effective, quickly actionable and shareable cures.

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ASSOCIATION BETWEEN CEREBRAL BLOOD FLOW AND CLINICAL DISABILITY IN PROGRESSIVE MULTIPLE SCLEROSIS IN THE MS-OPT TRIAL BASELINE DATA

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Background: Evidence has emerged that changes in cerebral blood flow (CBF) can occur and contribute to the pathophysiology of progression in multiple sclerosis (MS). Indeed, hypoperfusion might indicate neuronal loss and decreased metabolic activity and it has been described in progressive MS (pMS).

Objectives: Simvastatin has been shown to reduce the development of brain atrophy in pMS, but its mechanisms of actions are still unclear. The MS-OPT Trial aimed to test the impact of Simvastatin on CBF in pMS.

Aim: To evaluate the correlation between the CBF in the brain white matter (WM) and grey matter (GM) and clinical outcomes in pMS.

Methods: Data were obtained from the baseline visits of the MS-OPT Trial, a randomised, placebo-controlled study of high dose Simvastatin treatment for pMS (NCT03896217). Forty patients, including 12 primary progressive MS (PP-MS) and 28 secondary progressive MS (SP-MS), aged 18–70 years, and presenting with an Expanded Disability Status Scale (EDSS) score 4.0-6.5 were randomly assigned (1:1) to simvastatin 80 mg or placebo for 16 weeks, stratified by sex, age, EDSS, and type of MS (PP-MS vs SP-MS). At baseline, clinical and radiological data, including pulsed arterial spin labeling (PASL) and pseudo-continuous arterial spin labeling (pCASL) brain imaging were obtained. The Statistical Parameter Mapping-based software package ExploreASL was used to obtain quantitative data on CBF in WM (WM-qCBF) and GM (GM-qCBF). Multiple regression models were applied to evaluate the association between qCBF and clinical outcomes.

Results: The mean WM-qCBF was 20.01±6.31 mL/100g/min and the mean GM-qCBF was 61.25±14.09 mL/100g/min. No differences were observed between PP-MS and SP-MS. We found that both qCBF correlated with the Timed 25-Foot Walk (T25FW) score (WM-qCBF: rho=-0.32, p=0.002; GM-qCBF: rho=-0.33, p=0.001) and the 9-Hole Peg Test (9HPT) score (WM-qCBF: rho=0.23, p=0.031; GM-qCBF: rho=0.25, p=0.018). The associations remained significant after adjusting for age, sex, and disease duration (WM: T25FW: coeff=-1.26, p=0.001, 95%CI=-2.002 – -0.523; 9HPT: coeff=0.04, p=0.034, 95%CI=0.004 – 0.085; GM: T25FW: coeff=-0.63, p=0.001, 95%CI=-0.980 – -0.284; 9HPT: coeff=0.02, p=0.048, 95%CI=0.001 – 0.039).

Discussion: Our results suggest that lower qCBF in WM and GM correlates with increased disability, as assessed by in upper and lower limbs.

Conclusion: In conclusion, our findings support the potential of perfusion magnetic resonance imaging in evaluating the disease course of patients with MS.

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MICROCHIMERISM IN MULTIPLE SCLEROSIS: THE IMPACT OF MICROCHIMERIC CELLS ON THE RADIOLOGICAL FEATURES IN WOMEN WITH MULTIPLE SCLEROSIS

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Background and aims: Multiple Sclerosis (MS) is a chronic autoimmune disorder characterized by inflammation and neurodegeneration. Persisting fetal microchimeric cells seem to contribute to autoimmune diseases pathogenesis. The aim of the study is to investigate the impact of microchimerism on the radiological features of MS.

Methods: We recruited 26 nulliparous MS patients (NPp) (age: 34.7 ± 8.8), 20 patients with at least one male son (XYp) (age: 40.4 ± 7.2 years; number of pregnancies: 2.75 ± 1.29), and 8 patients with only daughters (XXp) (age: 43.8 ± 12.6 years; number of pregnancies: 1.88 ± 1.46). Each patients underwent a magnetic resonance (MR) scan to acquire 3D-T2w FLAIR FatSat and 3D-T1w FSPGR. The Lesion Segmentation Tool toolbox and FreeSurfer software were used to obtain quantitative data on white matter, cortical, and subcortical areas. Demographic and clinical data were collected using medical records. Multiple regression models were applied to evaluate the association between microchimerism and radiological data.

Results: In the cortical areas, NLp had a lower thickness in the left paracentral cortex when compared with XXp (2.34 ± 0.16 vs 2.39 ± 0.17; p-value = 0.043) and XYp (2.34 ± 0.16 vs 2.46 ± 0.17; p-value: 0.004). The same group had a lower thickness in comparison to XXp in left precuneus (2.27 ± 0.11 vs 2.34 ± 0.16; p-value = 0.046) and right lateral occipital cortex (2.14 ± 0.11 vs 2.25 ± 0.08; p-value = 0.006) and a lower thickness in comparison to XYp in left precalcarine (1.64 ± 0.14 vs 1.72 ± 0.12; p-value = 0.041) and right paracentral areas (2.34 ± 0.17 vs 2.42 ± 0.14; p-value = 0.015). Comparing XXp and XYp, we found that XYp had a higher thickness in the left cuneus (1.80 ± 0.14 vs 1.93 ± 0.10; p-value = 0.042) and in the left pericalcarine cortex (1.59 ± 0.19 vs 1.72 ± 0.12; p-value = 0.032) and a lower thickness in right lateral occipital (2.25 ± 0.08 vs 2.18 ± 0.13; p-value = 0.027). Finally, we found that right thalamus volume was smaller in NLp when compared with XXp (83.21 ± 2.56 vs 85.26 ± 1.65; p-value = 0.045).

Discussion: Our findings let hypothesized that the microchimeric cells could accumulate in the cortical areas, modulating the neuropathological processes associated to MS.

Conclusion: In a multifactorial background, the microchimeric fetal cells could modulate the inflammatory and neurodegenerative mechanisms underlying the MS, influencing the disease features.

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PEDIATRIC-ONSET MULTIPLE SCLEROSIS: PREVALENCE, INCIDENCE AND DISEASE FEATURES OF PEDIATRIC-ONSET PATIENTS IN WESTERN SICILY

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Background and aims: Approximately 2–10% of individuals with Multiple Sclerosis (MS) experience their first episode as a child. The aims of this study were to calculate the prevalence and incidence of pediatric-onset multiple sclerosis (POMS) in the provinces of Palermo and Trapani and to compare the clinical, paraclinical, and radiological features of POMS with the adult-onset form (AOMS).

Methods: We used data collected in a previous multi-centre study on epidemiology of MS in Western Sicily to estimate the prevalence of POMS in the provinces of Palermo and Trapani and its incidence between 2010 and 2018. In the second part of the study, we used medical records to collect clinical, radiological, and paraclinical data from 173 POMS patients and 173, age- and sex-matched, AOMS patients (both group, age: 41.5 ± 13.7, male/female ratio: 54/119).

Results: We estimated that the prevalence of POMS in the provinces of Palermo and Trapani was 11.9 cases/100,000 inhabitants (7.8% of the MS prevalent cases) and its incidence was 0.2 cases/100,000 inhabitants/year (4.3% of the MS incident cases). In the case-control analysis, the POMS group had a higher prevalence of family history for MS (8.09% vs 2.89%, p-value <0.001). At onset, the two groups reported similar presentations, but the POMS patients showed a higher disability in cerebellum and brainstem (cerebellum FS: 0.64 ± 1.24 vs 0.25 ± 0.67, p-value = 0.009; brainstem FS: 0.72 ± 1.15 vs 0.37 ± 0.74, p-value = 0.020). The time-gap between onset and diagnosis was longer in POMS subjects (months: 77.3 ± 102.9 vs 27.9 ± 43.0, p-value: <0.001) and, in the same group, the diagnosis was based on clinical criteria in a higher percentage of patients (80.92% vs 65.90%, p-value <0.001). At follow-up, the time-gap between onset and progression was longer in POMS patients (22.6 ± 11.3 vs 12.1 ± 9.6, p-value: 0.004). These patients had also a longer disease duration at reaching EDSS 4.0 (18.9 ± 9.2 vs 8.2 ± 6.6, p-value <0.001) and EDSS 6.0 (26.4 ± 11.7 vs 12.0 ± 9.4, p-value <0.001).

Discussion: Overall, our findings indicate that the provinces of Palermo and Trapani are areas of middle-high risk for POMS and that POMS patients have several distinctive disease features.

Conclusion: In conclusion, our results suggest that a more profound knowledge of POMS is necessary to better suit the disease management to the early-onset patients.

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MANAGEMENT OF OCRELIZUMAB IN MS PATIENTS DURING THE COVID-19 PANDEMIC: AN OBSERVATIONAL REGISTRY-BASED STUDY

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Objective: Concerns have emerged during Covid-19 pandemic about management of Disease Modifying Therapies (DMTs) in patients with Multiple Sclerosis (pwMS). In particular, Ocrelizumab (OCR)-treated pwMS faced possible delays of scheduled infusions due to disruption of MS Centers activities as well as safety worries during lockdown periods. Aims of the present study are to assess changes of OCR infusion schedule in Italian pwMS during the first wave of COVID-19 pandemic (observation period: February-June 2020) and to investigate predictive factors determining delaying of OCR infusions.

Materials and methods: Data were extracted from the Italian MS Register database. pwMS with an OCR infusion scheduled during the observation period and at least two previous OCR infusions were selected. Demographics (age, gender), disease characteristics (MS phenotype, disease duration, Expanded Disability Status Scale score, number of previous OCR infusions) and location of MS Centers among three Italian macro-regions (North, Center, South) were tested as potential predictors for treatment delay using univariable and multivariable linear model analyses.

Results: Five-hundred ninety-nine pwMS (343 F/256 M; 411 Relapsing MS/188 Progressive MS) from 65 MS centers were included in the analysis. Mean interval between two OCR infusions was 28.1 weeks (SD 2.72) before the observation period compared to 30.8 weeks (SD 5.45) during the observation period, with a mean delay of 2.7 weeks ($p < 0.001$). No clinico-demographic factors emerged as predictors of infusion postponement, except for location of MS centers in the North of Italy (4.7 weeks vs 1.5 in the Center and 1.6 in the South). Such a difference was confirmed in multivariate analysis ($p < 0.001$) adjusting for pre-lockdown mean OCR infusion schedule.

Discussion and Conclusions: This large registry-based study shows that OCR infusions were significantly delayed during the first wave of COVID-19 pandemic in Italy. The location of the MS Centers in Northern Italy was the only predictor of OCR infusion postponement. This geographical area corresponds to the region in Italy that was hit first and more strongly by Covid-19 pandemic. The observed delay in OCR infusions disruptions of MS centers activities due to a drastic reduction of healthcare workers availability (because of infection/quarantine and/or reallocation in Covid Units) and concerns about using an immunosuppressive DMT like OCR during a new virus pandemic with many uncertainties.

EVALUATING CENTRAL VEIN SIGN IN PEDIATRIC ONSET MULTIPLE SCLEROSIS (POMS) DIAGNOSIS

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Aims: To assess the diagnostic performances of Central Vein Sign (CVS) and 40% rule in a cohort of 10 pediatric onset multiple sclerosis patients (POMS).

Materials: 10 POMS and 12 adult onset multiple sclerosis (AOMS) patients underwent 3T-MRI; 3D sagittal T2-FLAIR, 3D sagittal T1 MPRAGE and 3D sagittal segmented echo-planar imaging (EPI) were performed. CVS assessment was performed according to current guidelines.

Methods: Differences in terms of lesion volumes and numbers were assessed with ANOVA analysis while difference in terms of patients fulfilling the CVS 40% threshold rule was evaluated with Chi-square test.

Results: 10 POMS patients [(female: 60%; mean (SD) age and disease duration: 13.5 (1.7) and 1.6 (1.7), median (range) EDSS 1 (1-2)] and 12 AOMS [(female: 58%; mean (SD) age at disease onset and disease duration at MRI: 38.5 (15.2) and 1.7 (1.3), median (range) EDSS 1 (0-6.5)] patients were included in the analysis. No differences were found in FLAIR lesion number ($p = 0.84$) and FLAIR lesion volume ($p = 0.19$) between the two groups. The percentage of CVS+ lesions was 53.3% in POMS and 71.7% in AOMS. 3 out of 10 POMS patients did not meet the 40% threshold rule for MS diagnosis while all AOMS patients would have been correctly diagnosed ($p=0.041$). Mean number of periventricular lesions excluded from CVS assessment (confluent feature, >1 vein passing throughout the lesions) was higher in POMS than AOMS population [11.6 (13.5) vs 3.1 (3.2); $p=0.047$)].

Discussion: In pediatric patients differential diagnosis of demyelinating lesions is challenging because of the high incidence of ADEM and the presence of ADEM-like onset in POMS. In POMS population, disability is attained at earlier age and early diagnosis and treatment may decelerate disease progression. CVS is already considered a biomarker for CNS demyelinating lesions in MS. In AOMS a cut off of 40% CVS+ lesions (40% rule) has been proposed to radiologically distinguish MS from non-MS diseases. According to current CVS definition, confluent lesions are to be excluded in lesion assessment. In our POMS population more periventricular confluent lesions were excluded with respect to AOMS and 40% rule was not satisfied in 3 patients out of 10.

Conclusions: The 40% threshold rule showed a worse performance for MS diagnosis in POMS population. Periventricular location of confluent white matter lesions in POMS patients may represent a crucial issue for CVS accuracy in this population and alter the diagnostic accuracy of 40% rule.

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IMPACT OF HIGHLY ACTIVE IMMUNOTHERAPY ON ACUTE AND CHRONIC NEUROINFLAMMATION IN AGGRESSIVE MULTIPLE SCLEROSIS

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Background: The impact of highly active immunotherapies, including autologous-hematopoietic-stem-cell-transplantation (AHSCT), on the resolution of acute and chronic CNS inflammation in aggressive multiple sclerosis (aMS) is unknown.

Aims: To compare the time-of-onset and the intensity of different immunotherapies in reducing CNS inflammation within MS lesions and in normal-appearing white matter (NAWM) in people with aMS.

Methods: Nineteen aMS patients underwent 3T-MRI during MS breakthrough, at 6 and 12 months after new treatment initiation. Acute inflammation was assessed through the analysis of (i) new gadolinium enhancing lesions, (ii) lesion volume (LV) changes during follow-up (FU) and (iii) through the analysis of multi-compartment spherical-mean-technique (SMT) diffusion metrics, reflecting inflammatory oedema and tissue integrity, in MS lesions and NAWM. Chronic inflammation was evaluated through the longitudinal assessment of paramagnetic-rim-lesions (PRL) on phase images (n=15).

Results: The study cohort included 8 subjects treated with AHSCT, 5 with ocrelizumab, 3 with natalizumab and cladribine (mean age 37, SD=9). Median number of baseline gadolinium-enhancing lesions was 4 (IQR=2-6). At 6 months, 0/8 AHSCT-patients had new/gadolinium-enhancing lesions vs 4/11 in the other treatment group. LV decreased by 1.8mL (SD=4.6) in AHSCT-treated patients and by 0.73mL (4.7) in the other treatment group. The NAWM of AHSCT-treated patients exhibited a greater reduction in extra-axonal mean-diffusivity and transversal-diffusivity, reflecting reduced extracellular water and increased myelin integrity respectively (-0.03vs+0.03 and -0.03vs-0.002 respectively, $p<0.01$). SMT-diffusion parameters within MS lesions stabilized over FU, without significant differences between the two treatment groups. At baseline, 12/15 patients exhibited at least one PRL. The median number of PRL per patient was 2 (IQR=1-3), representing 5% (IQR=1.5-10%) of total MS lesions. Over FU, 0/4 in the AHSCT-group exhibited new PRL appearance vs 3/11 patients in the other treatment group. In 3 patients (2 AHSCT treated patients, 1 treated with cyclophosphamide followed by ocrelizumab), a reduction in rim intensity was observed.

Conclusions: AHSCT allows faster and more pronounced resolution of CNS inflammation than other highly active immunotherapies. PRL are frequent in patients with aggressive MS and their appearance might be limited by the use of intense CNS-penetrant immunosuppression.

ANTERIOR AND POSTERIOR VISUAL PATHWAY INVOLVEMENT IN MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY DISORDERS (MOGAD) PATIENTS: AN OCT AND MRI STUDY

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Background: Despite the frequent involvement of the visual system in MOGAD, studies evaluating the anterior and posterior visual pathway in this disease are scarce. We aimed to investigate the presence of retinal damage independent of optic neuritis (ON) and to explore the existence of anterograde degeneration after ON in MOGAD.

Methods: Cross-sectional, retrospective study of 27 adult MOGAD patients and 23 healthy controls (HC). Clinical, OCT, and MRI data were collected. Peripapillary retinal nerve fibre layer (pRNFL) and ganglion cell inner plexiform layer (GCIPL) were obtained using Heidelberg Spectralis. FreeSurfer7 was used to obtain the lateral geniculate nucleus (LGN), occipital volume fractions (to total estimated intracranial volume), and occipital cortical thickness. For the anterior visual pathway, the analysis was conducted using eyes, classified based on the history of ON (EON+ and EON-) and compared to HC-eyes. The analysis of OCT and brain volumetric measures was conducted comparing MOGAD-ON, MOGAD-NON and HC. The ANCOVA with Bonferroni-adjusted post hoc test was used to test differences between groups and linear regression analysis to evaluate OCT/MRI associations; age, and time from disease onset to OCT were considered as covariates.

Results: 20 (74.1%) patients had a prior ON. Median pRNFL and GCIPL thickness (um) was significantly reduced in EON+ vs EON- and HC (pRNFL:73 (29-98, 92 (56-105), 97.5 (81-117), p<0.001; GCIPL:55.88(37.49-71.80), 68.61(49.16-79.22) 73.12(66.49-79.58), p<0.001). pRNFL and GCIPL thickness had a negative correlation with the number of ON episodes (β=-0.622, p<0.001; β=-0.422, p=0.041). The LGN volume fraction was lower in MOGAD-ON compared to HC (0.33(0.28-0.43) vs 0.38(0.29-0.47), p=0.005). The occipital cortical thickness was lower in MOGAD-ON compared to MOGAD-NON and HC (p=0.002). In MOGAD-ON patients, pRNFL correlated with LGN volume (β=0.583, p=0.02), occipital volume fraction (β=0.506; p=0.012) and occipital thickness (β=0.464, p=0.004). LGN volume fraction showed a significant association with occipital volume fraction (β=0.506; p=0.013).

Conclusion: Compared to HC, MOGAD patients have a decreased retinal thickness mostly driven by ON eyes and the number of ON episodes. Our findings also suggest retinal damage can be present in asymptomatic eyes. MOGAD-ON patients present retinal, subcortical, and cortical atrophy in the visual pathway compared to MOG-NON and HC, suggesting an anterograde degeneration.

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THE CLINICAL OVERLAP BETWEEN MULTIPLE SCLEROSIS AND SUBACUTE COMBINED DEGENERATION DUE TO VITAMIN B12 DEFICIENCY: A CASE REPORT

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Aims: Vitamin B12 deficiency is a systemic disease that often affects the nervous system. One of the most prevalent manifestations is Subacute Combined Degeneration (SCD) of the spinal cord. Multiple Sclerosis (MS) is an inflammatory demyelinating disease affecting the central nervous system (CNS), which preferentially affects young women.

Materials: A 47-year-old female presented low back pain associated with painful spasms and a sensation of "electric shocks" that started from the spine and then spread along the lower limbs bilaterally. There was also loss of sensation in the lower limbs bilaterally up to the inframammary region, reduction of strength in the 4 limbs and urinary urge.

Methods: Spine MRI showed multiple hyperintense lesions in FLAIR images extending throughout most of the cervical cord and a hyperintense lesion in FLAIR images in the dorsal cord. Furthermore, hyperintense demyelinating lesions in FLAIR sequences were present in the hemispheric white matter in the frontal and parietal lobes, suggesting the diagnosis of MS. Somatosensory evoked potentials (SEPs) were abnormal in both upper and lower limbs. CSF analysis showed an inflammatory pattern with an increase of total proteins and IgG and the presence of oligoclonal bands. Blood chemistry analysis showed vitamin B12 deficiency (85 pg/ml, with a normal range of 191-663 pg/ml) and the positivity of APCA.

Results: After the diagnosis of vitamin B12 deficiency, intramuscular application of cobalamin was started at a dose of 5000 IU every two days. After the treatment, we have seen an improvement in both motor and sensory symptoms. The patient was also diagnosed with multiple sclerosis and started DMT.

Discussion: The clinical case reported above shows an overlap between the symptoms of Multiple Sclerosis and Subacute Combined Degeneration, that can therefore be masked and undiagnosed.

Conclusion: We presented this case because clinical manifestation of myelitis can be similar in MS and SCD due to vitamin B12 deficiency and the concomitant presentation of the two pathologies is not very frequent. Our case highlighted the importance of not neglecting the various diagnostic hypotheses, even if the diagnosis of Multiple Sclerosis is clear.

COVID-19 COURSE AND VACCINATION IN A LARGE POPULATION OF MULTIPLE SCLEROSIS PATIENTS: RESULTS OF AN ITALIAN MULTICENTER PATIENT-CENTERED SURVEY (COVIMPSAT)

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Background and aims: COVID-19 pandemic caused a significant disruption of clinical activities at Multiple Sclerosis (MS) Centers. As part of a national multicenter survey (COVId Ms Patients SATisfaction survey – COVIMPSAT) aimed at collecting patients' opinion regarding the quality of care and information received from MS Centers (MSC) during the first pandemic waves, we report data about COVID-19 infections and vaccination cycle and how they were managed by the MSC.

Materials and methods: In April-May 2021, 16 Italian MSC developed and sent a digital (35-item) survey by email to their patients. Statistical analyses were performed with SPSS, version 25.

Results: 1670 people with MS (pwMS; 67.3% women) completed the survey. 169 (10.1%) reported a diagnosis of COVID-19 infection: 63% were symptomatic, while 37% were not. As regards treatment for COVID-19, only 3% of the patients were hospitalized. The impact of COVID-19 infection on MS-related neurological symptoms was as follow: 69.3% of pwMS stated that the severity of their MS-related symptoms remained stable, 21.5% reported a worsening of pre-existing symptoms, 7.4% affirmed that new neurological symptoms emerged, while only 1.8% reported an improvement of MS-related symptomatology. At the time of the survey, 60.6% of pwMS were inoculated at least one dose of COVID-19 vaccine. Vaccination appointments were scheduled by: MSC staff alone (44.9%), MSC staff together with the general practitioner (17.5%), the general practitioner alone (16.1%), other Institutions (12.1%), and by the patients themselves (9.3%). At the moment of the survey 39.4% of pwMS were not vaccinated yet. The three major reasons for not being vaccinated yet were: being already on a vaccination list (40.8%), willing to be vaccinated but without an appointment (17.6%), still undecided or not willing to be vaccinated (19.3%).

Discussion: The results of this multicentrer survey revealed a low hospitalization rate of pwMS, in line with previous studies [1]. In the majority of the sample, COVID-19 symptomatology did not have a significant impact on MS-related neurological symptoms. MSC promoted and facilitated vaccination procedures and scheduling, alone or in combination with the general practitioner, in more than half of pwMS.

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COVID-19 INFECTION IN MS PATIENTS AND RISK OF FOLLOWING CLINICAL/MRI DISEASE ACTIVITY: A PROPENSITY SCORE MATCHING STUDY

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Objectives: Several studies in literature suggest that viral infections may trigger multiple sclerosis (MS) relapses. Among these, respiratory tract infections seem to be the most frequent. To date, there are very few data about the association between COVID-19 infection and the risk of relapses in MS. Objective of our study was to evaluate the risk of clinical/MRI disease activity after COVID-19 infection in patients with MS.

Materials and methods: We prospectively collected all incident cases of COVID-19 in a population of approximately 1500 MS patients followed by the MS Center of the AOU Città della Salute e della Scienza di Torino University Hospital, from March 2020 onwards. Clinical features and outcome of the COVID-19 infection, and MS clinical/MRI outcomes in the 6 months following COVID-19 infection were recorded. Propensity score matching was used to compare MS clinical/MRI outcomes over 6 months between patients with or without COVID-19 infection, matched for age, sex, disease duration and MS disease-modifying treatment.

Results: 143 patients with COVID-19 infection were identified: 103 females, 40 males, with median age of 46 (range 18-82 years). 132/143 had a relapsing-remitting form of MS, while 11 had a progressive form (primary/secondary). 127/143 subjects were under disease modifying treatments at the time of the infection. 68/143 patients had already received at least one vaccine dose at the time they contracted the infection. Outcome of COVID-19 was usually favorable with mild disease not requiring hospitalization; severe disease was observed in 14 patients, two of whom died. Symptoms suggestive of long COVID (defined as persistence of symptoms after 4 weeks from the resolution of the infection) were observed in 43 patients (30%). In multivariate forward logistic regression, the only variable predictive of long COVID was anti-CD20 therapy (OR 2.42, $p = 0.027$). No significant differences were found in MS clinical/MRI outcomes (NEDA-3 at 3 and 6 months) after COVID-19 infection, compared to matched MS patients without COVID-19 infection (NEDA-3 at 3 months 78.3% vs 84.8%, p = n.s.; NEDA-3 at 6 months 66.2% vs 76.1%, p = n.s.).

Conclusions: COVID-19 infection does not appear to influence the risk of MS clinical/MRI disease activity in the months following the infection. Persistence of symptoms suggestive of long Covid is quite common in MS patients.

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OCRELIZUMAB AS TARGETED THERAPY IN A B-CELL MEDIATED RELAPSE AFTER ALEMTUZUMAB FAILURE IN RRMS: A CASE REPORT

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Aims: A patient-based approach is required in the treatment of multiple sclerosis (MS). This approach must be guided by clinical and laboratory

markers that can highlight a specific immunopathological mechanism underlying the inflammatory activity of the disease.

Methods: We present a case of a 44-years-old female patient diagnosed with relapsing remitting multiple sclerosis (RRMS) in 2008. Her baseline Expanded Disability Status Scale (EDSS) was 2 and she started disease-modifying therapy (DMT) with interferon beta-1a, followed by fingolimod and dimethylfumarate, all interrupted for ineffectiveness for clinical relapses. In April 2019, with an EDSS of 5,5, she undergoes first alemtuzumab cycle and second one in July 2020. In April 2021 she presented a severe clinical relapse with gait ataxia, dysarthria, mild dysphagia and urinary incontinence. MRI displayed large demyelinating outbreak that extended from the globose nucleus to the middle and upper cerebellar peduncle and to the lower homolaterally follicle; this outbreak had incomplete peripheral impregnation. No clinical benefit was seen after 11 days of intravenous methylprednisolone (IVMP) treatment (500mg/die). Intravenous immune globulin (IVIG) five days treatment was experimented in order to evaluate a benefit on steroid-resistant relapse, but stopped on third day for side effects with no clinical change and a stable EDSS at 6.5 on neurological examination. A typing of lymphocyte subpopulations was carried out and patient's immunological profile showed an increased values of CD19+ B-cells. This suggested that B-cells overpopulation may be the immunopathological mechanisms underlying the reactivation of inflammation. Based on this increased type B immune component, it was decided a drug switch to ocrelizumab as a targeted therapy. Two doses of ocrelizumab 300 mg were administered 15 days apart.

Results: On the fifteenth day, before the second dose, a typing of the lymphocyte subpopulations was repeated and it showed a clearing of the CD19+ lymphocyte population. A new control MRI was performed with evidence of contrast enhancements resolution and extension reduction of the enhancing lesions previously detected. On January 2022 she undergoes to second 600 mg Ocrelizumab cycle whit almost complete recovery of symptoms (EDSS: 4.5) and a stable radiolological picture.

Conclusions: B- and T-Cell subtyping should be performed in alemtuzumab treatment failure and an early ocrelizumab drug switch should be considered in those cases where a B-cell overexpression is evidenced.

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FUNCTIONAL CORRELATES OF INTELLIGENCE QUOTIENT AND COGNITIVE ABILITIES VARY ACCORDING TO MATURATION IN PEDIATRIC MS

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Objectives: Clinical and cognitive features of pediatric multiple sclerosis (MS) differ from adult-onset patients. In pediatric MS, cognitive impairment was found to be associated with posterior and subcortical resting state (RS) functional connectivity (FC) abnormalities. However, the effect of brain maturation on RS FC and its possible interaction with cognitive features has never been studied. Aim of this study was to test maturation effects on neuropsychological profiles and RS FC in key cognitive and motor networks of pediatric MS.

Methods: Seventy-six pediatric MS patients underwent a neuropsychological assessment of Wechsler-Intelligence-Scales for Intelligent Quotient (IQ), Semantic/Phonemic Verbal Fluency Test (SVFT/PVFT), Symbol Digit Modalities Test (SDMT), Coding Design (CD) and Block Design (BD) subtests, Trial Making Test (TMT-A/B). In 58 right-handed MS patients and 22 matched healthy controls (HC), RS FC within executive, language, motor, default-mode and basal ganglia networks was estimated. To test maturation effects, between-group RS FC comparisons and correlations with cognitive scores were assessed by splitting pediatric MS in those below the age of 16 years (B16) (n=46) and those above or equal 16 years (A16) (n=30).

Results: The most frequently failed tests were CD (21.1%), TMT-B (15.8%), TMT-A (10.5%) and SDMT (9.2%). B16 performed worse than A16 patients at the TMT-A (p=0.01). In B16 patients, a widespread reduction of RS FC vs HC was observed for the basal ganglia, sensorimotor, executive and language networks. A16 patients showed reduced RS FC in basal ganglia, sensorimotor and language networks as well, but they also showed increased fronto-parietal RS FC in these networks. In B16 patients, reduced basal ganglia, executive and sensorimotor RS FC correlated with worse BD, CD, TMT-B and PVFT scores (r=range 0.36-0.48, p=range 0.005-0.04). In A16 patients, reduced sensorimotor RS FC was associated with lower IQ and worse BD/CD scores (r=range 0.44-0.60, p=range 0.002-0.03). In A16 significant correlations were also found between increased default-mode, executive and sensorimotor RS FC and worse BD, CD, TMT-A, TMT-B and PVFT scores (r=range -0.40 to -0.49, p=range 0.01-0.04).

Discussion: While B16 patients showed severe RS FC reduction, especially in the basal ganglia network, which was associated with worse cognitive scores, A16 patients also presented maladaptive RS FC increase in default-mode, executive and sensorimotor networks.

Conclusions: Maturation significantly impacts on RS FC abnormalities and on their association with cognitive performances.

OCRELIZUMAB EFFECT ON HUMORAL AND CELLULAR IMMUNITY IN MULTIPLE SCLEROSIS AND ITS CLINICAL CORRELATES: A 3-YEAR OBSERVATIONAL STUDY

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Objectives: We aim to evaluate 3-year effects of ocrelizumab (humanized anti-CD20 monoclonal antibody for the treatment of multiple sclerosis-MS) on total lymphocyte count, lymphocyte subpopulations, neutrophils and immunoglobulins: (1) when compared with pre-infusion assessment; (2) over the course of treatment; and (3) possible clinical correlates of the observed immunological modifications.

Methods: This real-world observational cohort study has been conducted on prospectively collected data from 78 MS patients (mean age 47.8±10.5 years; females 48.7%) commencing on ocrelizumab from 2018, with mean follow-up of 36.5±6.8 months. Clinical data and blood samples were collected every three months. Total lymphocyte count and subpopulations were assessed on peripheral blood using flow cytometry. Serum immunoglobulins were evaluated with nephelometry.

Results: When compared with pre-infusion values, we observed reduction of total, CD19 and CD20 lymphocyte counts; however, after the first infusion, their levels remained substantially stable. Over time we observed a progressive reduction of CD8 lymphocytes, while no changes were observed for CD4, CD27, CD3CD27, CD19CD27. After the first infusion, we observed reduction in IgG, which further decreased during the follow-up. Higher probability of EDSS progression was associated with reduced modulation of CD8 lymphocytes.

Discussion and Conclusions: Ocrelizumab affects both humoral and cellular immune response. Disability progression over the follow-up was associated with lower CD8 cytotoxic T lymphocytes reduction. Changes in humoral response are immediate and sustained, while modulation of cellular immunity occurs progressively through regular re-treatment and is related to clinical stability.

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SAFETY AND EFFICACY OF A THIRD BOOSTER DOSE OF BNT162B2 MRNA COVID-19 VACCINE IN PATIENTS WITH MULTIPLE SCLEROSIS TREATED WITH OCRELIZUMAB OR FINGOLIMOD

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Objectives: Patients with Multiple Sclerosis (pwMS) treated with Ocrelizumab (OCR) and Fingolimod (FNG) have shown a blunted humoral response to the first two doses of the BNT162b2 mRNA Covid-19 vaccine. The assessment of the safety and the humoral response to a third booster dose of the same vaccine is therefore relevant within this population. The aim of our study was to investigate the safety and the humoral response to a third booster dose of the BNT162b2 mRNA vaccine in pwMS on OCR/FNG, comparing it with age- and sex-matched healthy controls (HCs).

Material and Methods: Serum samples were collected from HCs and pwMS treated with OCR or FNG at the following scheduled time points: before the first of two vaccine doses (T0); 8 (T1), 16 (T2), 24 (T3) weeks after the first dose; within 8 weeks before (T0b) and after (T1b) the booster dose. IgG antibodies to SARS-CoV-2 trimeric spike protein (Anti-TSP IgG) were quantified and expressed as binding antibody units (BAU)/mL.

Results: 40 HCs and 47 pwMS (28 on OCR and 19 on FNG) were included in the study. All (100%) HCs mounted a positive (>33.8 BAU/mL) humoral response at T1 and preserved it until (T2-T3-T0b) and after (T1b) the third booster dose. At T0b only 12 (42.9%) pwMS on OCR and 6 (31.6%) on FNG were positive while, at T1b 16 (57.14%) pwMS on OCR and 16 (84.2%) on FNG, passed the threshold of positivity. Anti-TSP IgG titers in HCs were significantly higher than those of pwMS on OCR and on FNG at all time points, while no differences were found at all time points between pwMS on OCR and those on FNG. HCs showed a significant higher (relative) increase of Anti-TSP IgG levels at T1b with respect to OCR ($p<.001$) and FNG ($p=.032$) groups. The increase of Anti-TSP IgG levels in the pwMS on FNG was significantly higher than those in the OCR group ($p<.001$). No sociodemographic, clinical, or laboratory variables were able to predict the increase of anti-TSP IgG levels between T0b and T1b. Neither clinical relapses nor severe adverse events were reported in pwMS after each of the three doses of vaccine during the follow-up period.

Discussion and Conclusions: The administration of a third booster dose of BNT162b2 mRNA Covid-19 vaccine to OCR- and FNG-treated pwMS is able to revive the humoral response, independently of any demographic, clinical or laboratory variable, and confirms a good safety and tolerability profile, not only in terms of adverse events but also in terms of MS relapses.

DYSAUTONOMIC SYMPTOMS IN MULTIPLE SCLEROSIS: CHARACTERISTICS AND DETERMINANTS

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Objectives: Dysautonomic symptoms (DS) are common in Multiple Sclerosis (MS), but relatively little explored. The aim of this study has been to assess frequency and characteristics of DS in MS population, also evaluating the possible relationship with clinical features and MS severity.

Materials and methods: The study included a group of MS patients recruited at the MS Centre of the University of Cagliari. Demographic (gender, age) and clinical features [disease duration, disability level assessed using the Expanded Disability Status Scale (EDSS)] (1), disease modifying therapy (DMT)] were collected for each patient. In addition, each patient completed the Italian validated version of the Composite Autonomic Symptom Score-31 (COMPASS-31) (2) to assess the presence and the severity of DS. Descriptive analyses, Pearson correlations and linear regression analyses were performed by using SPSS for Mac version 20.

Results: The study included 82 patients with mean age of 38.2 ± 11.6, of these 19 (23.2%) were male. Mean disease duration and EDSS score were respectively 11.6 ± 9.4 years and 2.5 ± 1.8 points. The Compass-31 scores reported in the domains of orthostatic, vasomotor, secretory, gastrointestinal, bladder and pupillary functions were compared between the two sexes, showing higher Compass-31 scores in female patients (24.4 ± 18.1 versus 14.9 ± 11.7 in male; $p=0.005$), as well as higher orthostatic domain score (10.9 ± 11.1 versus 3.7 ± 9.6 in male; $P=0.01$). A correlation of EDSS score with secretory ($p=0.041$) and urinary ($p=0.038$) functions scores were reported by Pearson analysis; no significant correlation was identified in the other Compass-31 domains with respect to disease duration and patient age. Finally, regression analyses showed that higher Compass-31 score, indicative of more dysautonomic symptoms, was associated to female gender ($p=0.008$) with a trend of significance for EDSS

score (p=0.05), and higher EDSS score influencing both secretory (p=0.014) and bladder function (p=0.048).

Conclusions: Our data seem to suggest that MS-related DS are more frequent in female patients, especially with regards to orthostatic intolerance. Among the clinical variables examined the EDSS is the only one to determine a higher frequency of DS regardless of age and disease duration. Further investigations into larger cohorts are needed to confirm these results.

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EFFECT OF OCRELIZUMAB TREATMENT ON RETINAL ATROPHY: A SINGLECENTER PROSPECTIVE OBSERVATIONAL STUDY

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Aims: Given the paucity of data regarding the effect of Ocrelizumab (OCR) on retinal atrophy, we aim to provide first experience data regarding the effect of OCR on retinal thinning in patients with relapsing-remitting (RR-) and progressive (P-) multiple sclerosis (MS) and investigate whether rates of peripapillary retinal nerve fiber layer (pRNFL) and ganglion cell+inner plexiform layer (GCIPL) atrophy differ according to response to treatment over a follow-up (FU) period of 2 years.

Methods: Patients starting OCR at the MS Center of the University of Genoa underwent spectral-domain optical coherence tomography (SD-OCT) scans at baseline and at 2-years FU. Demographic characteristics and effectiveness outcomes throughout FU were collected. NEDA3 status was defined as absence of relapses, disability worsening, MRI activity. Eyes with previous optic neuritis were excluded. Atrophy rates of pRNFL and GCIPL at different timepoints and their differences between groups were assessed with repeated measures ANCOVA accounting for age, sex, disease duration, MS phenotype and previous treatments.

Results: A total of 65 MS patients were included in this study. A total of 53 patients reached the 2-years FU and entered the final analyses [34 RR-MS and 19 P-MS; females: 57%; mean age and disease duration: 40.7+11.1 and 8.7+10.6 years; median (range) EDSS: 3.5 (0-6.5)]. No significant differences were observed between baseline and FU pRNFL (95.41±10.18vs93.86±10.75 μm respectively: p=0.91) and GCIPL (80.37±10.12vs79.32±10.07 μm respectively: p=0.61) thickness. Retinal thinning was similar between RR-MS (pRNFL: -1.66±2.31 μm; GCIPL: -0.69±3.05 μm) and P-MS patients (pRNFL:-1.31±2.69 μm; GCIPL:-1.69±1.85μm) (p=0.79 and p=0.16, respectively). While no GCIPL atrophy was observed in patients achieving NEDA3 status during FU (baseline vs FU thickness:-0.36±3.17 μm), a reduction in GCIPL thinning was observed in patients who lost NEDA3 (baseline vs FU thickness: -1.71±2.71 μm: p=0.029). At logistic regression, mean GCIPL reduction correctly classified 77.4% of patients as NEDA3 at 2 years (R 0.45; p=0.024).

Conclusions: The overall stability of pRNFL and GCIPL thickness over 2-years FU suggests a neuroprotective effect of OCR treatment in RR-MS and P-MS patients. A more pronounced retinal thinning was observed in patients loosing NEDA3 throughout FU. Our findings support the role of GCIPL in monitoring treatment response, though should be confirmed by larger studies.

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RUN IN STUDY ON THE SAFETY AND TOLERABILITY OF A FASTING-MIMICKING DIET IN RELAPSING REMITTING MULTIPLE SCLEROSIS: PRELIMINARY DATA

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Objective: To investigate safety and tolerability of fast-mimicking diet (FMD) in patients with relapsing-remitting Multiple Sclerosis (RRMS). Secondary objectives were to assess patients' compliance to FMD, changes in nutritional status/body composition, and the effect of FMD on general health status.

Methods: Patients were asked to undergo three cycles of 7-days FMD (1100 kcal on day one and 800 kcal on days 2-7) every 60 days in addition to standard therapy with first-line therapies. During days of calorie restriction patients were called every day by the dietician to evaluate the tolerance towards the diet. Blood samples and anthropomorphic parameters including BMI, weight, and phase-angle (PHA) were collected before and after each cycle. Changes terms of general health status - including disability, fatigue, depression, and cognitive functions - and MRI activity were determined at baseline and after month 6. Differences before and after the cycles were assessed with paired samples t-test.

Results: We included N=14 patients [female: 71%; mean (SD) age and disease duration: 41(9.8) and 9.8(6.3); median(range) EDSS: 2(0-3)]. To date, a total of 7 patients completed all 3 cycles, 5 completed 2 cycles, 1 patient only completed the first cycle. One patient withdrawn the consent to participate before starting the diet, while 2 patients dropped after 2 cycles due to nonadherence. According to the Common Terminology Criteria for Adverse Events (CTCAE), patients reported grade 1 fatigue(N=8), headache(N=6), vomiting(N=2), sleepiness(N=1), nausea(N=1), hypertension(N=1), depression(N=1), chills N=1),

constipation(N=1), and back pain(N=1), and grade 2 impaired concentration(N=1) and presyncope(N=1). No significant changes in terms of BMI, body weight, PHA, blood count and kidney function after every cycle were observed. A mild increase in aspartate-aminotransferase (AST) after the first (19vs25 U/L; p=0.046) and second (18vs29U/L; p=0.007) cycles as well as in creatinine-phosphokinase (CPK) after the second cycle (73vs101 U/L; p=0.009) emerged. All blood test values remained within the normal limits. No changes in disability status or MRI activity were observed in the 7 patients that completed the experiment.

Conclusions: No safety concerns regarding FMD in RRMS patients emerged. We observed only moderate symptoms grade 1 and 2 together with an overall stability in terms of body composition, nutritional status and blood tests. Diet adherence may represent a barrier to the feasibility of large studies. A mild increase in AST and CPK occurred, though such observation should be confirmed by larger analysis. We are still recruiting patients with the aim to have safety and tolerability data in a larger population of patients.

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THE EFFECT OF CLADRIBINE AND FINGOLIMOD TREATMENTS ON RETINAL ATROPHY: PRELIMINARY FINDINGS

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Aims: To investigate and compare the impact of cladribine (I course) and fingolimod treatments on retinal atrophy in a cohort of relapsing remitting multiple sclerosis (RRMS) patients.

Methods: In this ongoing study, patients starting cladribine or fingolimod underwent spectral-domain optical coherence tomography (SD-OCT) scans at baseline and at 12-months FU. Eyes with previous optic neuritis were excluded. Atrophy rates of peripapillary retinal nerve fiber layer (pRNFL) and ganglion cell+inner plexiform layer (GCIPL) at different timepoints and their differences between groups were assessed with repeated measures ANCOVA accounting for age, sex, disease duration.

Results: A total of 27 patients were included in the analysis, [12 cladribine and 15 fingolimod; females: 53%; mean (SD) age, disease duration, and ARR in the previous year: 42.9 (13.4) years, 13.26 (10.11) years, and 0.26 (0.68); median (range) EDSS: 1.5 (0-5)]. No differences in terms of age, gender, disease duration, ARR, EDSS, and baseline pRNFL or GCIPL thickness were found between the two groups. At 1-year FU, no significant differences were observed between baseline and FU pRNFL (99.54±12.61 vs 98.26±12.62 μm respectively: p=0.18) and GCIPL (81.45±0.01 vs 81.88±7.75 μm respectively: p=0.96) thickness. Retinal thinning over FU was similar between patients treated with cladribine (pRNFL: -0.90±2.36 μm; GCIPL: -0.16±2.26 μm) or fingolimod (pRNFL: -1.57±0.97 μm; GCIPL: -0.61±1.61 μm) (p=0.34 and p=0.47, respectively).

Conclusions: Although our preliminary findings show an overall stability of pRNFL and GCIPL thickness over 1-year in patients treated with cladribine (I course) and fingolimod, our results need to be confirmed by larger analyses, which should also take into account the impact of the second course of cladribine treatment.

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THE ROLE OF RIM LESIONS IN PREDICTING LONGITUDINAL BRAIN AND RETINAL ATROPHY

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Objectives: In multiple sclerosis (MS), paramagnetic rim lesions (PRLs) are thought to reflect chronic active inflammation which may lead to a progressive neuronal damage. Loss of brain volume has been reported to be higher in patients with PRLs. However, the role of PRLs in predicting retinal atrophy has not been explored. With this study we aim to assess whether PRLs are associated with patients' brain and retinal atrophy over follow-up (FU).

Methods: In this ongoing study, we included MS patients who underwent 3T MRI and spectral domain optical coherence tomography (SD-OCT) at baseline and during the subsequent FU [median (range) FU: 16 (12-24) months]. At baseline, white matter lesions were stratified as PRLs and no-PRLsby visual inspection on GRE-phase images and QSM maps. Baseline and FU values of brain volumes and ganglion cell-inner plexiform layer (GCIPL) thickness were also collected. After adjusting for sex, age, disease duration and MS phenotype, the association between number of PRLs at baseline and changes in terms of percentage-brain-volume-change (PBVC) or rates of GCIPL atrophy (difference between baseline and FU GCIPL thickness) was explored with linear regression models, while ANCOVA was used to investigate

differences in term of PBVC and retinal. atrophy between patients in patients with < 4 PRLs and those with ≥4 PRLs.

Results: A total of 25 MS patients were included [female: 64%; RRMS phenotype: 84%; mean (SD) age and disease duration: 38 (11.8) and 6.8 (6.3); median (range) EDSS: 2 (0-6.5)]. At baseline MRI, median (range) number of PRLs was 1 (0-7); 17/25 patients had at least one PRLs, 6/25 had>4 PRLs. Mean (SD) PBVC and GCIPL atrophy over FU were -0,48 (1.05)% and 0.72 (1.2) μm, respectively. The baseline number of PRLs was able to significantly predict PBVC (B=-0.202, 95% CI: -0.396 - -0.008; p=0.042) and GCIPL thickness reduction (B=0.225, 95% CI: 0.001-0.448; p=0.049). We observed higher rates of PBVC (- 0.89+0.92 vs -0.35±1.08) and more pronounced GCIPL atrophy (1.56±1.66 vs 0.4±1.01) in patients with>4 PRLs as compared to those with < 4 PRLs (p=0.05 and p=0.028, respectively).

Conclusions: We observed an association between higher number of PRLs and more pronounced brain volume or retinal thickness loss over FU. Our findings confirm and strengthen the role of PRLs as a marker of disease severity in MS.

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EFFECTS OF CURRENT DISEASE MODIFYING THERAPIES FOR MULTIPLE SCLEROSIS ON ACQUIRED IMMUNITY AGAINST COMMON INFECTIOUS DISEASES: A PILOT LONGITUDINAL STUDY

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Introduction. Disease-modifying treatments (DMTs) for Multiple Sclerosis (MS) act at different levels of the immune system. Several studies have showed that some DMTs may impact the response to vaccines, particularly against SARS-CoV2, and the maintenance of pre-existing immunity. The aim of this study is to evaluate the impact of DMTs on acquired immunity against common infections in MS patients.

Materials: This longitudinal study consecutively enrolled all relapsing MS patients referring to the MS Centre of the University of Catania in the period between January 2021 and May 2022. Patients previously treated with DMTs or corticosteroids within 1 month from the blood collection were excluded from the study.

Methods: Serum level of antibodies against varicella-zoster virus (VZV), tetanus, measles, mumps, rubella, herpes simplex 1 (HSV1), herpes simplex 2 (HSV2), citomegalovirus (CMV), Epstain Barr virus (EBV) and hepatitis B virus (HBV), were detected in all MS patients before starting therapy (T0) and after 6 months (T1). Data about lymphocyte counts, lymphocyte subset counts and serum immunoglobulins (Ig), and history of infections or vaccination against common infectious agents were also collected.

Results: A total of 188 patients with mean age 38.3±12.2 years, 111 (59%) females, were finally enrolled. Twenty-six (13.8%) were treated with interferons or glatiramer acetate (IFN/GA), 25 (13.3%) with dimethyl-fumarate (DMF), 21 (11.2%) with teriflunomide, 20 (11.3%) with ocrelizumab or rituximab (OCR/RTX), 36 (19.1%) with natalizumab (NTZ), 25 (13.3%) with cladribine (CLD), 25 (13.3%) with sphingosine 1-phosphate receptor (S1P) modulators, and 10 (5.3%) received no treatments. At T1, the levels of antibodies against VZV, measles, rubella, HSV1 were reduced in RTX/OCR and in CLD groups. Patients treated with RTX/OCR also showed a significant reduction in the antibodies against HBV. Patients treated with S1P modulators showed significantly increased levels of antibodies against VZV, measles, and mumps. In the RTX/OCR group, the antibody rates were associated with serum Ig dosage. No correlations were found between antibodies rates and lymphocytes counts in all the groups.

Discussion: Our results showed that DMTs may impact the immune response to infections and vaccinations.

Conclusion: These findings from a small cohort of MS patients exposed to a wide spectrum of MS immunotherapies may have important implications for the risk assessment of infections for MS DMTs.

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REAL-WORLD EFFECTIVENESS OF CLADRIBINE FOR PATIENTS WITH MULTIPLE SCLEROSIS: A SICILIAN MULTICENTRIC EXPERIENCE (REWIND STUDY)

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Objective: Cladribine is considered a highly effective therapy in terms of reduction of relapse risk and disability accumulation in patients with relapsing-remitting multiple sclerosis (RRMS). This real-world study aimed to evaluate cladribine effectiveness in a cohort of patients belonging to different MS centers in Sicily, Italy.

Materials and methods: This longitudinal study screened all MS patients referring to seven Sicilian MS centers and treated with cladribine in the period between 11th March 2019 and 31st October 2021. Data about Expanded Disability Status Scale (EDSS), relapses, previous treatments, adverse events (AEs) and magnetic resonance imaging (MRI) before starting therapy, after 12 (T12) and 24 months (T24) were collected. Patients who have switched from other DMTs were further divided according to the efficacy profile, moderately active treatment (MAT) and highly active treatment (HAT).

Results: A total of 217 patients, 152 (70%) women, with mean age of 38.4 ± 11.3 years and mean disease duration of 102.7 ± 80.7 months, were enrolled. Of these, 50 (23.0%) were naïve to treatment and 167 (77%) switched from another disease modifying therapy (DMT). Out of 141 (65% of 217) patients who completed the first year of treatment, about 90% were EDSS progression free, 80% remained relapse-free, and 48% were MRI activity-free. A higher percentage of relapse-free patients was found in the MAT group in comparison with the HAT group (89.8 vs 60.7, p= 0.002). Out of 121 (55.8%) patients who completed the second year of treatment, about 80% were EDSS progression free, 88% remained relapse-free, and 48% of patients were MRI activity-free. Unadjusted annualized relapse rate at T24 for the entire cohort was 0.18, with lower results in patients switching from MAT (0.11) compared to HAT (0.34).

Discussion: We confirmed that cladribine is an effective treatment for MS, in particular in naïve patients and in those who have switched from MATs.

Conclusion: Results from our study may drive the clinician to use cladribine earlier in the MS treatment management, also in the light of its favourable therapeutic burden and the potential to keep the patient treatment-free for several years.

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ANTI-SARS-COV-2 NEUTRALIZING ANTIBODIES IN MS VACCINATED PATIENTS: A PROSPECTIVE FOLLOW-UP

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Objectives: To evaluate the neutralizing capacity of anti-SARS-Cov-2 antibodies (nAbs) after the complete vaccination cycle with anti-SARS-Cov-2 mRNA vaccines, and the duration of the neutralizing, in people with Multiple Sclerosis (pwMS) naïve or under therapy compared to Healthy Subjects (HS).

Methods: Sera were collected from 95 pwMS and 30 HS, before, during and after each vaccination cycle (first, booster and fourth dose) with anti-SARS-Cov-2 mRNA vaccines. nAbs titers were measured with an ELISA test that detects IgG against the Receptor Binding Domain (RBD) of the SARS-CoV-2 Spike protein; their neutralizing ability was evaluated through an in vitro antiviral test using SARS-CoV-2 pseudovirions engineered with the Spike protein.

Results: pwMS showed a lower nAbs production with respect to HS. This was mainly due to a lower anti-RBD IgG production, accompanied by an impaired ability to neutralize virus, in pwMS under high efficacy therapies, especially anti-CD20 Abs and fingolimod. However, the booster dose induced seroconversion of the majority of pwMS under fingolimod and ocrelizumab and of the totality of patients treated with cladribine, indicating that a booster dose could be fundamental in those pwMS that did not develop nAb after the first vaccination cycle.

Discussion: pwMS are able to elicit an efficient immune response able to block SARS-CoV-2 infections in the majority of cases. Furthermore, we confirmed that cladribine treatment does not compromise the development of a specific humoral response, whereas for ocrelizumab and fingolimod, a significant nAb response, even if lower, can be achieved with further vaccinations such as the booster or the fourth dose.

Conclusions: Results obtained from this study will be useful for the management of pwMS in relation to their therapy and for any future vaccination campaign.

EFFICACY OF OFATUMUMAB IN TREATMENT-NAIVE, FIRST-SWITCH AND LATE-SWITCH PATIENTS: INSIGHTS FROM THE ALITHIOS OPEN-LABELEXTENSION STUDY

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Objective: To compare clinical and MRI outcomes in patients initiating OMB early versus switching to OMB after one or multiple previous DMTs in the ASCLEPIOS I/II and ALITHIOS studies.

Background: Ofatumumab (OMB), a fully human anti-CD20 monoclonal antibody, reduced annualized relapse rate (ARR), MRI lesion activity, and delayed disability worsening versus teriflunomide (TER) in relapsing multiple sclerosis (RMS) patients who were treatment-naïve (TN) or previously treated (PT) with disease-modifying therapies (DMTs) in the Phase 3 ASCLEPIOS I/II trials. All patients entering the ALITHIOS extension study were switched to open-label OMB allowing further insights into OMB efficacy in TN/PT patients and after first and late DMT switch.

Design/Methods: Outcomes from ASCLEPIOS I/II (ARR, time-to-6-month confirmed disability worsening [6mCDW], number of Gd+T1 lesions, and annualized T2 lesion rate) for TN and PT patients are presented here. Further analyses to be presented at the congress will compare these outcomes in ASCLEPIOS (up to 30 months treatment) with outcomes over 18 months in ALITHIOS (i.e., post-switch to open-label OMB; data cut-off: 25-Sep-2021) in the following four groups: 1) Early TN: TN patients randomized to OMB in ASCLEPIOS I/II and continued OMB in ALITHIOS); 2) First switch: TN patients randomized to TER in ASCLEPIOS I/II and switched to OMB in ALITHIOS; 3) Late switch: patients PT with ≥1 DMTs, randomized to TER in ASCLEPIOS I/II and switched to OMB in ALITHIOS; 4)PT-Longer term: patients who were

PT, randomized to OMB in ASCLEPIOS I/II and continued OMB in ALITHIOS.

Results: In ASCLEPIOS I/II, 1882 patients were randomized and OMB versus TER reduced the ARR by 51% and 53% in the TN (n=749) and PT (n=1133) subgroups, respectively. For 6mCDW, the risk reductions were 36% and 28%; new/enlarging T2 lesions were reduced by 83% and 85%, respectively. Gd+ T1 lesions were reduced by 95% across both subgroups. These findings were in line with the overall ASCLEPIOS I/II population. The analysis from ALITHIOS will be based on the 1367/1882 (72.6%) patients who entered open-label extension study.

Conclusions: OMB shows consistent efficacy in patients who were TN or switched from other DMTs. Further insights from ALITHIOS on efficacy outcomes following the initiation of OMB early versus first and late switch will be presented at the congress.

RISK OF SHORT-TERM RELAPSE IN PATIENTS WITH MULTIPLE SCLEROSIS SWITCHING FROM NATALIZUMAB TO CLADRIBINE

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Background: Natalizumab (NTZ) is an highly effective treatment in relapsing-remitting Multiple Sclerosis (RRMS) patients, however NTZ withdrawal is associated with disease reactivation mostly occurring within 6 months. Several exit strategies have been proposed to minimize this risk, nevertheless the best management is still an area of active research, with no conclusive indications1. Cladribine (CLAD) tablets is approved for highly active RRMS patients, but limited data are available on its use after NTZ2.

Aims: To determine early risk of relapse after switching from NTZ to CLAD3

Methods: A retrospective observational study was conducted in RRMS patients starting CLAD after NTZ discontinuation. The main variables analyzed were percent of patients experiencing a reactivation of disease activity or radiological activity in the first 6 months.

Results: 9 RRMS patients (7 women, mean age 42±11,5 years, median EDSS before CLAD 1.0 (IQR 1-3), mean disease duration 10±4 years, mean annualized relapse rate in the previous 12 months 0,18±0,4, median number of NTZ infusions 52±39, mean time from NTZ to CLAD 29±10 days) were included. In the first 6 months in the follow-up after CLAD started, nobody experienced clinical relapse or MRI activity/progression after NTZ withdrawal.

Conclusions: Switching to CLAD represents a promising exit strategy from NTZ in patients with high risk of progressive multifocal leukoencephalopathy or poor treatment response. However further data and a larger sample size are needed to confirm these findings.

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DIFFERENCES IN AGE-RELATED RETINAL AND CORTICAL ATROPHY RATES IN MULTIPLE SCLEROSIS

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Objective/Background: To assess and compare rates of neurodegeneration in retina and brain throughout the MS disease course in a well-phenotyped longitudinal cohort. It is critical to understand if neuroaxonal loss in MS is continuously linear or declines with time [1,2,3].

Materials/Methods: We analyzed 598 MS patients (mean age 45.3±11 yrs; disease duration 11.6±9.7 yrs), who underwent longitudinal OCT imaging annually for a period of 4.5±2.4 yrs. Longitudinal MRI scans (study period of 10±3.4 yrs) were available from 434 patients (mean age 41.8±9.6 yrs; disease duration 8±8.3 yrs). The primary outcome parameters were macular ganglion cell–inner plexiform layer (GCIPL) volume and cortical gray matter (CGM) volume. To evaluate the rate of loss, linear mixed-effects modeling with subject-specific intercepts and slopes were fitted using restricted maximum likelihood estimation. The association between the slope of decline in the anatomical structure and the age of entry in the cohort (categorized by the MRI cohort's age quartiles) was assessed by linear regression models.

Results: The rate of CGM volume loss declined minimally with increasing age of study entry (ASE):1.3%/yr ASE<35yrs; 1.1%/yr ASE=35-41yrs;0.97%/yr ASE=41-49; and 0.9%/yr ASE>49 years. The rate of GCIPL thinning was highest in patients in the youngest ASE quartile, fell by nearly 50% in the following ASE quartile, and then stabilized across ASE:0.7%/yr for ASE<35yrs; 0.29% for ASE=35-41yrs; 0.34% for ASE=41-49yrs; 0.33% for ASE>49yrs.

Discussion/Conclusions: An age-dependent reduction in rates of retinal and cortical volume loss during RRMS suggests deceleration in neurodegeneration in the earlier period of disease and further suggests that the period of greatest inflammatory activity is also the period with the greatest neuroaxonal loss. The observed difference in neurodegeneration between the CGM and retina could be due to differences in the architecture of the tissues, varying susceptibility to degenerative injury, or differences in the sensitivity and specificity of OCT and MRI in detecting tissue atrophy.

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MYELIN WATER FRACTION OF THE CORPUS CALLOSUM IS A ROBUST MEASURE OF REMYELINATION IN A DOUBLE BLIND-PLACEBO CONTROLLED CLINICAL TRIAL

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Objective/Background: To define the potential for MRI myelin water fraction (MWF) to capture remyelination in MS, to determine the optimal location for measuring myelin recovery, and to help guide trial design for future reparative and remyelinating trials. There are currently no validated imaging methods for structurally demonstrating myelin restoration. As a consequence of the pathological prominence of plaques in MS and the pathobiological understanding of the disease gleaned from the development of immunomodulatory agents, research in myelin repair has focused on lesions. Historically, the regions of the brain where remyelination is measurable have not been determined because of the lack of means to engender myelin repair. Our group performed the first successful double-blind, placebo-controlled remyelinating trial (ReBUILD) in MS, using visual electrophysiology as the primary outcome [1]. Whole-brain MWF showed no evidence of improvement while on the study drug.

Materials/Methods: Fifty subjects (average age ± SD of 40.1 years ± 10.0, average EDSS ± SD 2.1 ± 1.0, and average disease duration ±SD of 5.1 years ± 5.0) underwent 3T MRI at baseline, months 3 and 5. Half of the cohort was randomly assigned to group 1 and received treatment from baseline through 3 months, whereas the other half (group 2) received treatment from 3 months to 5 months post-baseline. This secondary analysis focused on brain regions rich in myelin (corpus callosum, optic radiations, and corticospinal tracts). We computed the myelin water fraction changes occurring in the normal-appearing and lesional white matter.

Results: MRI-derived myelin water fraction improved in the normal-appearing white matter of the corpus callosum, in correspondence with the administration of remyelinating treatment with clemastine. Unequivocal treatment-related changes were not detected within lesions or within the normal-appearing white matter of the optic radiations and corticospinal tracts.

Discussion/Conclusions: This study provides the first positive identification of an MRI correlate of therapy-induced remyelination in a clinical trial (ReBUILD) with a technique that can be employed in a clinically feasible time. Moreover, our work strongly suggests that significant myelin repair occurs outside of lesions. This demonstrates that significant myelin repair is likely to occur outside of lesions and has the potential to shift the focus of our scientific interest beyond the lesion environment and enable the more rapid development of therapeutics capable of myelin regeneration.

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NEUROPSYCHOLOGICAL SCREENING IN SUBJECTS WITH PEDIATRIC ONSET MULTIPLE SCLEROSIS (MS)

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Aims: The aim of this observational study was to investigate the prevalence of pediatric onset Multiple Sclerosis (MS) in the local outpatients service and the concomitant presence of cognitive impairment.

Material and Methods: A total of 362 MS outpatients followed-up in the service were re-screened for pediatric onset MS. The following standardized neuropsychological tests were administered to those selected: Breaf Repeatable Neurospychological Battery, Stroop Test [1] and verbal fluency [2]; testing to obtain information about selective attention skills and speed of information processing, verbal and visual-spatial learning, working memory and information updating, inhibition of non-relevant responses, verbal fluency and set shifting skills.

Results: A pediatric onset MS was diagnosed in 15 cases (4.1%). Of the 15 subjects selected, 7 agreed to undergo full clinical interview and extensive neuropsychological battery. The selected subjects had a mean age of 27.5 years and mean education of 13.8 years, median age of disease onset was at 14 years. All suffered of Relapsing Remitting MS. At the neuropsychological screening interview 6 subjects showed abnormalities in at least one subset of the Breaf repeatable neuropsychological battery and/or the stroop test according to Amato criteria.

Discussion: The prevalence of pediatric onset MS in our cohort was similar to other case series although hardly comparable. Cognitive impairment in MS is widely documented in literature [3]. Appearing in all MS phenotypes and being common in all age groups, where, depending on the type of study and the criteria applied, there is a prevalence of 33% in the under 18 population and between 34% and 65% for adults. Seen the large abnormal findings observed in our cohort a deeper monitoring of cognitive functions in pediatric onset MS is thereby encouraged.

Conclusion: Harmonizing timing and modalities adopted for neuropsychological screening could represent a valid support to collect information about the course of the disease in the early onset patient population. This may help to identify patients at increased risk of cognitive decline and worthy of targeted clinical investigations.

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ESTIMATING LONG-TERM EFFECT OF SIPONIMOD ON DISABILITY PROGRESSION VERSUS VIRTUAL PLACEBO IN SPMS USING RPSFT MODEL: EXPAND DATA UP TO 7 YEARS

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Objectives: In the ongoing EXPAND-extension, SPMS patients treated with continuous siponimod (siponimod in core + extension) had significantly reduced the risk of both 6-month confirmed disability progression (6mCDP) by 22% versus placebo-siponimod (PS: placebo in core/siponimod in extension) switch group over up to 5 years (intent-to-treat: ITT analysis). Long-term (LT) comparison of siponimod with placebo was not possible since placebo patients transitioned to open-label siponimod at the end of EXPAND-core (median 21 months). Here we present the LT efficacy of continuous siponimod (LT-CS) versus corrected virtual placebo (LT-VP) by using Rank Preserving Structural Failure Time (RPSFT), a method that adjusts for treatment switching in trials with survival outcomes, and uncorrected IIT analysis (LT-PS) in the overall SPMS population and in the subgroups of active (a) SPMS and non-active (na) SPMS patients in the EXPAND study with up to 7 years of follow up.

Materials: The analysis included patients who received ≥1 dose of siponimod or placebo in the EXPAND- core and offered a switch to open-label siponimod in the ongoing EXPAND-extension (ITT population: siponimod N=1099, placebo N=546; data cut-off: October 2020, with a duration of up to 7 years).

Methods: Time to 6mCDP was assessed for LT-CS versus LT-VP and LT-PS groups.

Results: In the overall population, the hazard ratio (HR) [95% confidence interval (CI)] for time to 6mCDP for LT-CS was 0.67 [0.52; 0.87] versus LT-VP and 0.78 [0.67; 0.92] versus LT-PS, resulting in the median time to 6mCDP delay by 62% (40.8 months [mo] vs. 66.1 mo) and 29% (51.1 mo vs. 66.1 mo), respectively. In patients with aSPMS, the HR [95% CI] for time to 6mCDP for LT-CS was 0.58 [0.42; 0.81] versus LT-VP with 79% delay (38.8 mo vs. 69.3 mo) and 0.69 [0.55; 0.87] versus LTPS with 44% delay (48.0 mo vs. 69.3 mo) in the median time to reach 6mCDP. In patients with naSPMS, the HR [95% CI] for time to 6mCDP for LT-CS was 0.80 [0.51; 1.26] versus LT-VP and 0.89 [0.71; 1.12] versus LT-PS, corresponding to 44% delay (45.5 mo vs. 65.4 mo) and 19% delay (55.1 mo vs. 65.4 mo) in the median time to reach 6mCDP, respectively.

Conclusions: This analysis based on a longer follow up of EXPAND study, confirms the utility of the RPSFT virtual placebo arm to estimate long term treatment benefits of siponimod and supports its sustained efficacy up to 7 years in reducing the risk of progression and prolonging the time to 6mCDP in SPMS patients.

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MULTIPLE SCLEROSIS ONSET AFTER COVID-19: A CASE REPORT AND A REVIEW OF THE LITERATURE

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Objectives: SARS-CoV-2 infection has been associated with several neurological syndromes in the spectrum of demyelinating disorders; however, reports of Multiple Sclerosis (MS) onset concurrent with Coronavirus Disease 2019 (COVID-19) remain very rare.

Materials and methods: We describe the case of a new-onset MS in close temporal relationship with an otherwise mild COVID-19 course; moreover, we present a review of the previously reported cases.

Results: A 38-year-old man experienced an acute onset of diplopia and dizziness two weeks after a mild SARS-CoV-2 infection. His neurological exam showed a wall-eyed bilateral internuclear ophthalmoplegia with upbeat nystagmus evoked in upgaze only. Brain MRI showed a lesion in the medial dorsal pons, consistent with his symptoms, and further white matter lesions in the CNS without contrast enhancement, and CSF analysis was positive for oligoclonal bands; therefore, a diagnosis of Multiple Sclerosis was formulated. To date, eleven cases of MS onset after COVID-19 have been reported. Four patients developed symptoms two-to-three weeks after COVID-19 diagnosis, two of them after one month, two after two months, one after four months, and one after six months. A single case reports the concurrent onset of neurological symptoms along with a nasopharyngeal swab positivity for SARS-CoV-2. CSF oligoclonal bands were detected in seven cases out of nine lumbar punctures performed. In four cases, MRI features were described as an atypical pattern in size and location of the demyelinating lesions, showing larger than MS typical plaques and also distributed in deep structure. All these patients were safely treated with corticosteroids, with clinical improvement.

Discussion: The close temporal relationship between SARS-CoV-2 infection and the onset of neurological symptoms suggests that a parainfectious immune-mediated demyelinating disease may have occurred, in line with the previous evidence of an association between viral infections and MS onset or relapse. A SARS-CoV-2 neuroinvasive potential has been reported through the disruption of the Blood-Brain Barrier, acting as a possible gateway for brain-homing of pathogenic B and T lymphocytes; moreover, some cases of COVID-19 showed high levels of IFN-γ and IL6 and a skewing towards Th17 cells, the principal T lymphocyte subsets involved in MS pathogenesis.

Conclusions: Even if there are few reports, our case highlights the possibility that SARS-CoV-2 infection could play a role in the onset of the disease as a triggering factor, possibly causing an immunological shift towards autoimmunity.

PREDICTION OF THE INFORMATION PROCESSING SPEED PERFORMANCE IN MULTIPLE SCLEROSIS USING A MACHINE LEARNING APPROACH IN A LARGE MULTI-CENTER MRI DATASET

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Objectives: Magnetic resonance imaging (MRI) has markedly improved the understanding of the mechanisms associated with cognitive deficits in Multiple Sclerosis (MS). However, which MRI markers are the most closely related to cognitive performance of MS patients is still unclear. Our objective was to test the hypothesis that Machine Learning (ML) techniques may select the brain structural MRI volumes that, along with demographic and clinical data, better predict, at a single subject level, cognitive status in patients with MS, assessed by Symbol Digit Modalities Test (SDMT).

Materials and methods: We used the multicenter 3T-MRI dataset of the Italian Neuroimaging Network Initiative to extract multimodal data of 540 MS patients. We applied appropriate and "state of the art" methodology for the harmonization of MRI data acquired in different centers. We developed an advanced machine learning pipeline to identify brain structural MRI volumes that, along with demographic and clinical data, predict information processing speed (IPS) performance, assessed with the SDMT, of MS patients. We trained, validated, and tested powerful supervised estimators, i.e., Support Vector Machine, Random Forest, and eXtreme Gradient Boosting (XGBoost), following a rigorous validation scheme to obtain robust and reliable generalization performance of cognitive performance prediction. We carried out both a classification and a regression task based on SDMT scores feeding each model with different combinations of demographic data, clinical information, and structural MRI volumes.

Results: For the classification task the best performance (area under the receiver operating characteristic curve equal to 0.75) has been achieved by the XGBoost classifier trained with EDSS scores, thalamus, and lesion volumes. For the regression task the best performance (mean absolute error = 0.96 (0.01) [mean (SD)]) has been achieved by the XGBoost regressor trained with age, EDSS scores, thalamus, hippocampus, and lesion volumes.

Discussion: Our results showed good performance and XGBoost proved to be the best estimator and confirmed that damage of relevant gray matter structures, such as the thalamus and hippocampus, is among the most relevant predictors of cognitive performance in MS.

Conclusions: Our ML approach using a comprehensive set of brain structural measures extracted from a large multicenter 3T-MRI dataset showed a good performance in predicting cognitive impairment in MS. This novel approach confirmed how the involvement of some cognitive hubs of the brain, such as the thalamus and the hippocampus, are more relevant than focal WM damage (i.e., T2LV) in the prediction of cognitive performance in MS.

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DETERMINANTS OF RELAPSE ASSOCIATED WORSENING IN AN ITALIAN REGISTRY COHORT: THE ROLE OF AGE AND PYRAMIDAL PHENOTYPE

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Objective: To investigate the predictors of incomplete recovery after the first relapse in Italian MS registry cohort of relapsing-remitting MS (RRMS) patients who started first-line disease-modifying therapy (DMT) and the association with time to obtain Expanded disability status scale (EDSS) 4.0, in a five-year epoch.

Materials and Methods: This is a multicentre retrospective analysis of prospectively collected data from the Italian MS Registry on RRMS patients, who started first-line DMTs from January 1, 2013, to December 31, 2019. For each relapse, the functional system score (FSS) was used. Each FS is scored on a scale from 0 (no disability) to 5 or 6 (more severe disability). To determine recovery, the difference between each FS during the relapse and before the onset of relapse was calculated. Three categories were identified: without sequelae, indicating complete recovery without any residual disability (0 points); mild sequelae (1 point in one FS); severe sequelae (2 points in one FS or 1 point in two FSs or any other higher combination). Time to EDSS score $\geq$ 4.0 was calculated as the time between the first relapse and the time when an EDSS score $\geq$ 4.0 was first reported.

Results: 2,676 patients fulfilled the required criteria. A total of 767 patients had at least 1 relapse within 5-years therapy. Complete data to determine sequelae were available for 447 patients; 189 had no sequelae (42.3%), 100 had mild sequelae (22.4%), and 158 had severe sequelae (35.4%). Older age correlated with worse sequelae (proportional OR = 1.02, 95%CI 1.01–1.04; p = 0.004), as the occurrence of a second relapse before the DMT starting (proportional OR = 1.72, 95%CI 1.01–2.92; p = 0.044). The pyramidal phenotype, adjusted for age and other phenotypes, was associated to a 1.95-fold higher risk of severe or moderate sequelae (proportional OR = 1.95 95% CI 1.35–2.80; p < 0.001). The number of patients with a baseline EDSS score < 4.0 was 2,399; 112 (5%) obtained

an EDSS score ≥ 4.0 at the last evaluation at 5 years. The 5-year worsening-free survival (EDSS score ≥ 4.0) was 88.2% (SE = 1.2%). In this model, being older, having a higher baseline EDSS score and first pyramidal relapse were associated with an increased risk of having a 5-year EDSS score ≥ 4.0. All variables were confirmed also in the multivariable model.

Discussion: Age and pyramidal phenotype of relapses were the strongest predictors of incomplete recovery after the first relapse and were also related to relapse-associated worsening when we consider the disability milestone EDSS 4.0.

Conclusions: All these factors should be considered with emphasis on a therapy tailored to the individual patient.

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IS IT TIME FOR OCRELIZUMAB EXTENDED INTERVAL DOSING IN RELAPSING REMITTING MS? EVIDENCE FROM AN ITALIAN MULTICENTRE EXPERIENCE DURING COVID-19 PANDEMIC

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Objectives: We aimed to collect real-world Italian data on patients with relapsing-remitting MS (RRMS) treated with Ocrelizumab (OCR) during the COVID19 pandemic. We aimed to compare standard interval dosing (SID) and Extended Interval Dosing (EID) in terms of disease activity.

Materials and Method: We enrolled all RRMS patients who received maintenance doses of OCR from January 2020 to June 2021. Data were extracted in December 2021. We considered all infusions occurring during the index window, defined as A, B, and C. Infusion A was the last before COVID 19 pandemic. A-C interval was considered for the analyses. SID or EID was defined according to the time interval between infusions (6 months+4 weeks for EID). Disease activity was defined as clinical (new relapses) and radiological (new lesions on T1-gadolinium or T2-weighted sequences in magnetic resonance imaging, MRI). It was analyzed during the A-C interval and six months after infusion C.

Results: A total cohort of 278 patients (174 on SID and 104 on EID respectively) was enrolled and included in the analyses. Patients who received OCR on EID had a longer disease duration and a higher rate of vaccination against severe acute respiratory syndrome coronavirus 2 ($p < 0.05$). EID increased the risk of MRI activity during the A-C interval (OR 5.373, CI 95% 1.203-24.001, p=.028). The rate of CD19+ B cells depletion was inversely related both to clinical and MRI activity along with the A-C interval.

Discussion: EID seemed to be associated with a higher risk of MRI activity occurrence. CD19+ B cells depletion was a protective factor against disease activity.

Conclusions: EID needs to be carefully weighed in OCR-treated patients.

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SIPONIMOD STABILISES PHYSICAL DISABILITY SCORES IN PEOPLE LIVING WITH SPMS AFTER 2 YEARS OF TREATMENT: ANALYSIS FROM THE NOVARTIS GLOBAL MANAGED ACCESS PROGRAM

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Objectives: In the Phase III EXPAND trial, siponimod demonstrated significant reductions in the risk of confirmed disability progression (CDP) and confirmed worsening of cognitive processing speed in comparison to placebo (broad secondary progressive MS [SPMS] population). However, most regions (including European Union) approved siponimod for the treatment of active SPMS. Real-world effectiveness data for siponimod in the clinical setting are still scarce.

Objectives: To describe demographic and clinical characteristics and characterise EDSS score changes in people living with SPMS (plwSMPS) receiving siponimod under the manage access program (MAP): Global Siponimod MAP cohort (BAF2001M cohort).

Materials: The BAF2001M cohort is an umbrella program Novartis implemented to facilitate patient access to siponimod when marketing authorisation is pending (under physician request) in the absence of satisfactory alternative therapies. The program started in March 2019 and is on-going. Target population included adult patients with SPMS diagnosis and EDSS score <7 from Mar 2019-Jan 2021. From Jan 2021 onward access to the MAP required SPMS with active disease.

Methods: Treatment selection and patient monitoring was based on physician assessment. No regular visits or data entry or collection were mandatory. Baseline characteristics include country, age, gender, relapse, MRI activity in the last 2 years, EDSS, and cognition evaluation.

Results: A total of 632 cases were analysed (153 excluded from the analysis due to local country restrictions). Mean age was 52.3 (SD: 8.7) years, 60% were females, and median EDSS was 5.5 (interquartile range: 4.5-6.5). Around 51% had a relapse in the last 2 years, 54% had prior cognitive evaluation, and 52% had an MRI scan in the last 2 years (48%

showed activity). Mean change in EDSS from baseline was around -0.02/-0.03 at the months 6, 12, 18 and 24 (not statistically significantly different from baseline). Approximately 94% (140/149) patients improved or were stable at month 24. Further analysis to be presented at congress.

Conclusions: In a heterogenous cohort of 620 plwSPMS (including non-active SPMS) receiving siponimod in a real-world clinical setting, the vast majority improved or stabilised their EDSS score over 2 years. Interestingly, this patient population was older than the EXPAND study population and, with approximately half demonstrating relapse/MRI activity, supports siponimod's effectiveness in a broad SPMS population.

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OPTICAL COHERENCE TOMOGRAPHY IN DEMYELINATING DISEASES: ANY DIFFERENCES IN RETINAL NEURODEGENERATION AMONG MULTIPLE SCLEROSIS AND MYELIN OLIGODENDROCYTE GLYCOPROTEIN-ANTIBODY ASSOCIATED DISEASE? A LONGITUDINAL MONOCENTRIC EXPERIENCE

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Background: Optical coherence tomography (OCT) allows the assessment of retinal layers thickness, thus permitting to identify and evaluate over time the neurodegenerative process in demyelinating diseases, like Multiple Sclerosis (MS) and Myelin Oligodendrocyte Glycoprotein-antibody associated disease (MOG-AD). We investigated OCT features in a cohort of MOG-AD and relapsing remitting multiple sclerosis (RRMS) patients.

Materials and methods: We obtained OCT scans from MOG-AD and RRMS patients referred to IRCCS Mondino Foundation. We compared Retinal Nerve Fiber Layer (RNFL) and Ganglion Cell Layer (GCL) thicknesses among MOG-AD and RRMS groups and assessed GCL and RNFL thinning rates during the follow up (FU) period.

Results: Our cohort included 34 patients: 13 with MOG-AD and 21 with RRMS. Mean age was 35 years (SD 9.6). At disease onset, 20 patients experienced monolateral optic neuritis (ON; 10 RRMS and 10 MOG-AD), 4 patients experienced myelitis with motor symptoms; 10 patients developed sensory symptoms. OCT scans were obtained during remission phase at mean 2.9 years (SD 3.4) from disease onset. Considering 20 eyes with ON, mean GCL thickness was lower in RRMS (65 Î¼m, SD 9) than in MOG-AD (70 Î¼m, SD 9). In unaffected eyes mean GCL thickness was similar between groups (79 Î¼m in RRMS, SD 10, and 81 Î¼m in MOG-AD, SD 9). Considering 14 patients without history of ON, mean GCL and RNFL were similar between RRMS and MOGAD: mean RNFL thickness was 82 Î¼m in both groups (SD 4); mean GCL thickness was 98 Î¼m (SD 7) in RRMS and 100 Î¼m (SD 6) in MOGAD. In 8 patients with ON (4 RRMS and 4 MOG-AD) we obtained a follow-up OCT at 1(SD 1,8) mean year since the first one; no ON relapses occurred in FU period. Mean percentage of GCL reduction in affected eyes at FU was similar among groups (0,025% in RRMS, 0,017% in MOG-AD).

Discussion: According to our data, GCL thickness is lower in RRMS patients with ON than in MOG-AD ones, suggesting that ON in RRMS could be more severe than in MOG-AD. Moreover, in our study GCL thinning rates over time seem to be overlapping among groups: this data could suggest that the neurodegeneration entity could be similar in the two groups after an ON episode.

Conclusions: OCT represents an emerging technique for the assessment and quantification of neurodegeneration in demyelinating diseases. OCT could be useful to differentiate among MS and MOG-AD and to assess the neurodegenerative process in these disorders.

A REAL LIFE OBSERVATIONAL PROSPECTIVE STUDY ON EFFICACY AND SAFETY OF SIPONIMOD IN A MONOCENTRIC POPULATION OF SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS

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Background: Siponimod is a selective sphingosine 1-phosphate receptor 1 and 5 modulator recently approved for the treatment of secondary progressive multiple sclerosis (SPMS). Its efficacy was evaluated in the randomized clinical trial EXPAND, but few data from real-life studies are available to date. The aim of this study is to analyze efficacy and safety of siponimod in a real life monocentric population.

Materials and methods: Clinical and neuroradiological efficacy and safety of siponimod were prospectively analysed in a monocentric population of SPMS patients (pts) consecutively treated at the MS Center Neurology 2 of the University Hospital of Careggi (Florence). Clinical and neuroradiological parameters were collected every six months. We also have collected serum biomarkers at baseline then every six months.

Results: Sixteen pts were included: 50% were female, mean age of 50.3 (42.7-64.1) years, mean disease duration of 15.3 (3.7-30.4) years, mean time since conversion to SPMS of 2.9 (1.3-6.6) years, median EDSS at baseline of 5 (3-6.5), 4 patients needed walking assistance. Mean follow up was 7.6 (16-2.) months, being at least 1 year in 3 pts. Two pts were naïve, 3 pts were switchers from cyclophosphamide, 4 pts from fingolimod, 4 pts from dimethyl fumarate and 3 pts from interferon. Regarding efficacy, no patients had clinical relapse or neuroradiological activity, EDSS remained stable at 6 months and 1 year compared to baseline. It was observed a slightly reduction of T25FW and 9HPT scores at 1 year and the majority of pts reported subjective reduction of fatigue and increase of self-reporting walking performance. Overall, 31.2% of patients experienced adverse events. Two pts reported palpitation at the beginning of treatment with spontaneous resolution in 2 weeks. One patient developed hepatotoxicity with persistent mild elevated levels of transaminases but not levels that caused treatment discontinuation. No pts discontinued treatment due to persistent lymphopenia, but 87.5% of pts developed grade 3 lymphopenia after 1 month of treatment. Only one patient discontinued treatment due to the occurrence generalized seizure. Two pts had SARS-CoV-2 infection with cough and fever, one of this received antiviral therapy (remdesevir).

Conclusions: Effectiveness and safety of siponimod from this real-life cohort are aligned with data from the EXPAND trial, but longer follow up is needed to confirm its clinical and neuroradiological efficacy and especially its safety in real life population.

LOW-CONTRAST VISUAL ACUITY TEST (LCVA): A PREDICTOR OF DISABILITY IN EARLY MULTIPLE SCLEROSIS

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Multiple sclerosis (MS) is a chronic inflammatory disease of central nervous system (CNS) characterized by demyelination and neurodegeneration, which is detectable also in the early stages of disease and leads to the progression. Disease phenotype is extremely variable, changing from individual to individual, and to date little is known about markers that can reliably predict disease course. Low-contrast visual acuity test (LCVA) has been identified early on as a promising outcome measure in terms of visual impairment in multiple sclerosis [1]. In several studies it has also been associated with early impairment of the visual system and an increased number of demyelinating lesions [2,3].

Objective: The purpose of our work is to identify whether the LCVA, in a group of patients in the early stage of disease, effectively predicted possible clinical outcome measures in terms of disability and disease progression. Materials: We studied a group of 79 patients diagnosed with relapsing-remitting multiple sclerosis (RR-MS), characterized by low disease duration and low expanded disability status scale (EDSS) at diagnosis, who did not experience past episodes of retrobulbar optic neuritis or visual disturbances in clinical history and did not present latent optic pathway damage detected at visual evoked potentials (VEP) at diagnosis.

Methods: We performed clinical assessments at the time of diagnosis, carrying on all patients LCVA measurements at 2.5% (seen letters) and 1.25% (seen letters), prospectively evaluating by EDSS the clinical course and accumulation of disability over the following years (in 62 patients) and over the following two years (in 56 patients).

Results: We found a negative linear correlation between LCVA 2,5% and EDSS at the first (Spearman's Rho, coefficient of correlation -0.340, p=0.005) and second year (Spearman's Rho, coefficient of correlation -0.414, p=0.002) after diagnosis, in absence of significative correlations between LCVA 1,25% and the same parameters (EDSS at first year p=0.159, EDSS at second year p=0.249), independently from the disease modifying therapy (DMT) administered after diagnosis.

Discussion and conclusions: In line with previously published findings concerning samples heterogeneous in clinical phenotype and disease stages, our work emphasizes the role of LCVA 2,5% as an easy-to-use method to identify, to a potential extent and from the early stages of disease, a risk of disability in patients with MS.

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A REDUCED SPECIFIC HUMORAL AND T-CELL RESPONSE TO THE THIRD DOSE OF MRNA COVID-19 VACCINE IN MULTIPLE SCLEROSIS PATIENTS UNDER IMMUNOSUPPRESSIVE THERAPIES

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Background: Vaccination campaign to contrast the spread of SARS-CoV-2 has raised the issue of vaccine immunogenicity in frail populations, especially multiple sclerosis (MS) patients on disease modifying therapies (DMTs).

Materials and methods: Before (T0) and after 2 months from booster dose of mRNABNT162b2 vaccine (T1), MS patients under DMTs and healthy donors (HDs) were enrolled. For both T0 and T1, anti-Spike (S) antibody titer as well as IFNg, IL2 and TNFa T cells production upon S peptide libraries stimulation were assessed. According to DMTs mechanism of action, MS patients were stratified into immunosuppressive (such as fingolimod, cladribine, ocrelizumab, and alemtuzumab) and immunomodulating (natalizumab) groups [1]. "Activated" cells were defined as T cells producing any of IFNg or IL2 or TNFa while polyfunctional T cells were defined as those simultaneously producing all 3 cytokines. All possible combinations of intracellular expression of IFNg, IL2, and TNFa in cytokine-producing T cells were evaluated.

Results: Sixteen MS patients (11 females/5 males, median age [IQR] 41.5 [34.3-48.8] years) and nine HDs (7 females/2 males) were enrolled. An increase of anti-S antibody titers at T1 compared to T0 in both MS and HDs was seen (1930 [85.75-5895] and 198.5 [80.73-1140] BAU/ml, respectively, p=0.0017; 3590 [1575-10850] and 320 [124.1- 662.0], respectively, p=0.0039). Reduced percentage of CD4 and CD8 "activated" and CD4 polyfunctional T cells were observed in MS compared to HDs at T0 (CD4: 1.025 [0.795-1.275] and 1.640 [1.325-2.245], respectively, p=0.0111; CD8 1.0 [0.603-1.328] and 1.65 [1.315-2.360], respectively, p=0.0135; CD4: 0.045 [0.029-0.089] and 0.10 [0.10-0.125], respectively, p=0.0211). Stratifying MS population, only immunomodulating showed an increase in anti-S antibody titers production at T1 (5410 [2655-9893] and 871 [175.3-1360], respectively, p=0.0313), while a reduced production was seen in immunosuppressive compared to immunomodulating and HDs (369.5 [49.8-1975] and 5410 [2655-9893], respectively, p=0.0172; 369.5 [49.8-1975] and 3590 [1575-10850], respectively, p=0.0431]. At T0 in immunosuppressive patients a reduced percentage of "activated" CD4 and CD8 T cells was observed when compared to HDs (0.875 [0.658-1.025] and 1.64[1.325-2.245], respectively, p=0.0020; 0.91[0.53-1,293] and 1.65[1.315-2.36], respectively, p=0.019). While, at T1 a reduced percentage of CD8 polyfunctional T cells was seen in immunosuppressive patients when compared to HDs (0.036[0.019-0.065] and 0.1[0.048-0.1291], respectively, p=0.0232).

Conclusion: Both humoral and T cell specific response to vaccination in MS patients seems to be significantly influenced by different DMTs mechanism. Moreover, a higher percentage of TNFa and a reduced IFNg production was observed, mainly in immunosoppressive group.

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ANALYSIS OF THE IMMUNE REPERTOIRE IN MULTIPLE SCLEROSIS PATIENTS EXPERIENCING RELAPSES

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Aims: Relapses are the distinctive feature of multiple sclerosis (MS) and represent the clinical manifestation of a damage in the central nervous system induced by a burst of autoimmune inflammatory insult. The study of global characteristics of the immune repertoire during relapses is an innovative approach to characterize this phenomenon. The aim of the study is to investigate characteristics of the immune repertoire in MS patients experiencing relapses.

Methods: T-cell receptors (TCR) CDR3 sequences were obtained from DNA extracted from whole blood collected from 144 untreated relapsing-remitting MS subjects according to the ImmunoSEQ hsTCRB kit (Adaptive Biotechnologies®). Among them, patients were classified as: "relapsing patients" if they experienced a clinical relapse at the time of blood sampling (considering a window of ±30 days from sampling) (n=12) or "relapse-free patients" when no clinical relapses occurred within ±1 year (n=16). The inverse of the Simpson's Index was calculated as representative of the immune repertoire diversity, while repertoire architecture was evaluated through the construction of CDR3 sequences networks using the Levenshtein distance to define connections. Analyses were performed with immunarch and R packages. Target prediction of the relevant clonotypes was performed with TCRMatch.

Results: No differences were observed in terms of diversity, while we observed a reduced degree of connection in relapsing patients compared to relapse-free patients (P = 0.036 including age, sex and productive clones as covariates, median = 0.167 and 0.184 respectively in "relapse" and "relapse-free" groups). Focusing on highly shared clonotypes in relapsing individuals (shared among >50% of the relapsing individuals and absent in all the relapse-free group), we identified 5 clonotypes showing a potential ability to bind viral proteins, mainly Epstein-Barr virus and Cytomegalovirus, as well as to human antigens such as MBP (Myelin Basic Protein).

Discussion and conclusions: The similarity landscape of CDR3 amino acid sequences constitutes the clonal architecture of the immune repertoire and reflects its antigen recognition breadth. Our results suggest that the immune repertoire undergoes changes during a clinical relapse toward a repertoire that is more prone to recognize more antigens. Preliminary analyses on target prediction suggest shared clonotypes among relapsing patients targeting viral and myelin antigens.

MULTIPLE SCLEROSIS AND PAST EXPOSURE TO ALLERGY: INVESTIGATING THE ROLE OF AGE, TYPE OF ALLERGEN AND GEOGRAPHY IN THE ENVIMS DATA

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Introduction: Based on the "hygiene hypothesis", early life exposure to microorganisms ("old friends") is hypothesized to drive the immune system towards autoimmune diseases such as multiple sclerosis (MS) or allergic disorders. These conditions depend on different immune pathways. According to the known Th1/Th2 paradigm, an inverse association between autoimmune and allergic diseases is suggested, but the literature is conflicting.

Objective: To provide clues on the epidemiological trends between history of allergies in childhood or adolescence and MS onset in two different populations differing for distribution of environmental factors and MS incidence.

Methods: We used data collected from the Italian and the Norwegian populations through the EnvIMS study, a large multinational case-control population-based study and based on a self-administered postal questionnaire (EnvIMS-Q). Cases were identified from national or regional population-based MS registries, according to McDonald or Poser criteria, age of 18 years or older, disease onset 10 years or less before the study start. Population-based sources were used to identify 4:1 controls, frequency matched to cases on sex, age and geographical area. The results were adjusted for many confounders.

Results: We included 611 Italian cases and 1161 controls, and 886 Norwegian cases and 1616 controls. No association was detected between allergies (onset at any age) and MS in both populations considered. When considering instead the age of allergy onset and the specific allergens, MS was directly associated with allergy to pollen with onset at 11-20 years in women and to animal hair with onset 11-20 years in men, among Norwegians. A trend towards a more prevalent exposure to food and dust allergy among women with allergy onset at 0-10 years was observed in the Italian study participants.

Conclusions: Our findings support the direct association between history of allergy during early life and MS risk, depending on sex, type of allergen and age at allergy onset. The association also varies depending on the population, suggesting a geographical interaction with environmental and/or genetic factors affecting the risk for both diseases. We hypothesize that the regional differences in the exposures to "old friends" may partially explain our findings.

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NATALIZUMAB ADMINISTRATION IN RELAPSING REMITTING MULTIPLE SCLEROSIS: THE EASIER STUDY

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Introduction: EASIER is a multicenter, observational, cross-sectional study investigating the consumption of healthcare resources, including healthcare professional (HCP) active working time, and costs associated with the current natalizumab intravascular (IV) administration, and the potential impact related to the adoption of subcutaneous (SC) route.

Methods: EASIER study is made of 3 parts: 1) time and motion study conducted to measure healthcare resources and working time needed in clinical practice for natalizumab IV administration using a digital-data-collection-tool operated directly by HCPs; 2) HCP structured questionnaire-based estimation of the potential impact of natalizumab SC vs IV-administration; and 3) patient survey on the burden of natalizumab administration.

Results: Nine Italian multiple sclerosis (MS) centers measured 404 IV natalizumab administration procedures, administered 297 patient questionnaires; 26 questionnaires were completed by HCPs. Patients had a mean of 52 (range 1-176) previous IV-administrations and spent a mean (median, IQR) of 152 (130, 94-184) minutes in the center per each IV-procedure, with IV infusion covering 50% of the total. If patient travel time is included, an average of 5 hours is dedicated to each IV-administration. Active working time by HCP amounted to 29 minutes per IV-administration procedure, 70% of which by nursing staff. With adoption of the SC route, HCPs estimated a 50% reduction in patient procedure time, and 55% lower HCP active working time. When national costs were considered, this translated into a 63% cost reduction for the MS center per natalizumab administration procedure.

Conclusions: SC natalizumab administration will reduce consumption of patient and HCP times per procedure, and associated costs.

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INTRATHECAL IGM SYNTHESIS AS PROGNOSTIC BIOMARKER IN MULTIPLE SCLEROSIS

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Objectives: To evaluate intrathecal immunoglobulin M synthesis (ITMS) as a risk factor for a second demyelinating event (DE) in patients with Clinically Isolated Syndrome (CIS)/early MS, as compared to the previously established risk and protective factors. To explore, by quantitative brain MRI analysis, radiological characteristics of patients with (ITMS+) and without ITMS (ITMS-).

Materials: Comprehensive CSF data, including oligoclonal immunoglobulin G (IgG) bands (OCB) and calculated intrathecal IgM and IgG production, were collected in a prospective study of 142 patients at their first DE. We excluded patients with alternative diagnoses and a primary progressive course.

Methods: ITMS was assessed according to Reiber's non-linear function. We compared time to the second attack by using Kaplan–Meier curves and performed adjustment by Cox regression analysis. Quantitative baseline brain MRI analysis is ongoing.

Results: We included CIS/early MS with regular clinical and MRI assessments and at least one year of follow-up. ITMS occurred in 26 (22%) patients who did not differ in terms of age at onset, sex, baseline EDSS, as compared to ITMS- patients. By the end of follow-up, the majority (90%) of patients received a DMT. A second relapse occurred in 20 (77%) and 31 (55%) of ITMS+ and ITMS- patients, respectively ($p = 0.061$). ITMS+ patients had a shorter time to the second DE, with a median time of 1,9 years (95% CI = 0.8–3.1) for ITMS+ patients versus 5.8 years (95% CI = 2.1-20.0) for ITMS– patients ($n = 82$, $p < 0.001$). In multivariate Cox regression analysis (adjusted for age, sex, symptom at onset, baseline EDSS, IgG oligoclonal bands, presence/absence of brain gadolinium-enhancing lesion and DMT exposure), infratentorial symptom (aHR = 3.7, 95% CI 1.2-11.1, $p = 0.02$), spinal cord symptom (aHR = 10.8, 95% CI 2.3-51.0, $p = 0.003$), a higher EDSS score (aHR = 1.7, 95% CI 1.1-2.7, $p = 0.028$) and the ITMS (aHR = 5.6, p = 95% CI 1.5-21.2, 0.013) were associated with a higher risk of a second DE while the exposure to DMT decreased this risk (aHR = 0.3, 95% CI 0.2-0.6, $p = 0.003$). By categorizing treatment exposure and ITMS status, the highest risk of second DE was observed in ITMS+, untreated patients (aHR = 9.7, 95% CI 3.4-28.2, $p = 0.001$).

Discussion/Conclusion: Our study showed that, in patients with a first DE, the presence of intrathecal IgM, but not IgG, is associated with a higher risk of further attack.

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ONE-AND-A-HALF SYNDROME CAUSED BY POSTERIOR MEDIAN PONTINE LESION: A PECULIAR CLINICAL FINDING IN A PATIENT AFFECTED BY MULTIPLE SCLEROSIS

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Aims: Several abnormalities of eye movements are observed in Multiple Sclerosis (MS) [1,2,3]. One-and-a-half (1 + ½) syndrome is a rare complex gaze disturbance associated with pontine demyelination in MS [2,3].

Materials: A 28-year-old man, with no comorbidities nor familial history of neurologic disease, presented to our attention after a one-month onset of gait instability, followed by double vision after three weeks; the symptom was worse when looking to the left. Six months before he had complained of a left eye ptosis with double vision, which had spontaneously resolved. Furthermore, he had suffered from self-remitting episodes of lower limbs paraesthesias lasting a few days, over the course of the previous five years.

Results: Examination revealed gait ataxia with wide oscillations and mild telekinetic tremor. At the left horizontal gaze exotropia was observed with right eye adduction failure and left eye horizontal nystagmus. Severe right horizontal gaze limitation was present. Global strength was normal with brisk tendon reflexes and bilateral Babinski sign. Severe lower limbs hypopallesthesia was found. Blood examination was normal. CSF showed proteins slightly above the normal limits with raised IgG and IgM titres, Tibbling-Link index 1.8. Intrathecal oligoclonal bands synthesis was found. Visual evoked potentials were delayed in the right eye. MRI showed widespread and confluent T2/Fluid attenuated inversion-recovery (FLAIR) hyperintense lesions involving periventricular white matter, centrum semiovale, corona radiata, deep grey matter, brainstem, including pontine posterior median aspect, and spinal cord. Post-gadolinium enhancement was observed in two spinal lesions. A 5-gram intravenous methylprednisolone treatment was performed with near-complete resolution of the gait ataxia and mild benefit on the left-sided gaze. A diagnosis of MS was made.

Discussion and conclusions: Internuclear ophthalmoplegia (INO) is a gaze disorder caused by damage to the medial longitudinal fasciculus (MLF). In INO the homolateral eye to the MLF lesion shows reduced or absent adduction during the contralateral horizontal gaze [1]. 1 + ½ syndrome is a rare gaze disorder caused by damage to pontine paramedian reticular formation, abducens nucleus, or both and the ipsilateral MLF, with demyelination being the most common etiology in young individuals [3]. It manifests as horizontal gaze palsy on one side and INO in the contralateral gaze. 1 + ½ syndrome is often caused by median-paramedian lesions affecting the pontine tegmentum [2,3]; one lesion with such characteristics was observed at our patient's MRI.

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INTRATHECAL B CELLS ACTIVATION CORRELATES WITH MEMORY IMPAIRMENT IN MULTIPLE SCLEROSIS INDEPENDENTLY FROM BRAIN LESION LOAD

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Background and aims: Cognitive impairment (CI) is a common clinical feature of multiple sclerosis (MS). Its determinants are only partially known [1]. Cerebrospinal fluid (CSF) biomarkers may help in understanding the determinants of CI in MS [2]. Kappa IgG free light chain (FLC) index (k-index) is a sensitive biomarker of intrathecal B cells activation [3]. Herein, we investigated the association between k-index and CI in MS.

Methods: We selected people with MS (pwMS) who, at the time of the diagnostic work-up, underwent brain MRI, CSF analysis and a neuropsychological assessment with the Rao's Brief Repeatable Battery of Neuropsychological Tests (BRBN). k-index was assessed by nephelometry in a Siemens™ BN II automated analyser using N latex FLC kappa assay for CSF and serum (Siemens Healtheeners, Erlangen, Germany). Brain MRIs were performed with a 1.5 T magnet (General Electric Medical Systems, Milwaukee, WI, USA). SIENA-X 2.0 and automated identification and filling of brain lesions implemented on the SYNLAB platform have been used to calculate brain T2 lesions volume and number, T1 lesions volume and number, together with brain, cortical grey matter, thalamus, and hippocampal volumes.

Results: Thirty-nine pwMS (F:M 2.9, mean age 39.3±13.1 years, relapsing-remitting phenotype) were included in the study. k-index did not differentiate pwMS with and without global CI, spatial memory, information processing speed and verbal fluency impairment. On the contrary, k-index was higher in pwMS with verbal memory impairment (median 99.6, range 58.5-195.2 vs. median 37.2, range 2.3-396.9, $p<0.05$). On univariate analysis, k-index was negatively associated with SRT-LTS (β:-0.08 [95%CI:-0.1,- 0.04], $p<0.001$) and PASAT-3 (β:-0.03 [95% CI:- 0.07,0.02], $p=0.035$). In a multivariate model with SRT-LTS as dependent variable and k-index, brain T2 lesions volume, brain volume, cortical grey matter, thalamus and hippocampal volumes as independent variables, the association between k-index and SRT-LTS was confirmed (B:-7.9 [95%CI:-9.9,-5.9], $p<0.001$). In a similar model with PASAT-3 as dependent variable, the association with k-index was not confirmed (B:-1.4 [95%CI:-4.6,1.9], $p>0.05$).

Conclusion: In pwMS, k-index is negatively associated with verbal memory performance suggesting a possible direct detrimental effect of B cells activation on this cognitive domain, independent from network disconnection mechanisms linked to brain T2 lesion load.

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NATALIZUMAB RAPIDLY AND STRONGLY SUPPRESSES INFLAMMATORY DISEASE ACTIVITY IN PEDIATRIC-ONSET MULTIPLE SCLEROSIS

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Introduction: Pediatric-onset multiple sclerosis (POMS) is characterized by an aggressive course and early development of physical and cognitive disability.

Objectives: To evaluate the efficacy of natalizumab (NTZ) in POMS on clinical, radiological, and cognitive outcomes.

Methods: All POMS starting NTZ between June 2015 and October 2021 were enrolled in this single-centre, prospective study. Patients were evaluated every 6 months both clinically and radiologically and followed up for 31.0±17.6 months (6-71 months). No radiological (i.e., no evidence of new/enlarging white matter lesions nor gadolinium-enhancing lesion) or clinical (i.e., no evidence of clinical relapse or EDSS worsening) evidence of disease activity (rNEDA and cNEDA respectively) were evaluated at 12 and 24 months. In addition, survival analysis for overall NEDA condition (i.e., radiological and clinical) was also analyzed. As control, an EDSS-, disease duration, and gender-matched cohort of adult-onset MS starting natalizumab during the same period was enrolled.

Results: Thirty-seven POMS were enrolled in our study. None of POMS and 2 adult-onset patients experienced a clinical relapse (p=0.5) during the first 2 years of treatment. 29 POMS (78.4%) and 33 (76.7%, p=0.80) adult-onset MS fulfilled the rNEDA condition at 2 months, while between 12 and 24 months, 1 out of 26 POMS (3.8%) and 13 (30.2%) experienced a radiological disease reactivation (p=0.001). After 24 months of NTZ therapy, 80.8% of POMS and 60.5% of adult-onset MS fulfilled the NEDA condition (p=0.054). After month 24, no POMS experienced any radiological disease reactivation. Median EDSS value was 1.0 at month 12 and 24, and it did not change significantly during the follow-up (p=0.86). Indeed, only 2 patients had 0.5 increase confirmed after 6 months. NEDA condition was not associated to any clinical or demographic baseline variable. However, survival analysis revealed a trend for the risk of NEDA based on naïve- or switching- baseline status (Log rank p-value: 0.19).

Conclusions: NTZ is a highly effective treatment for POMS. While in adult-onset MS disease reactivation may occur during the first year of NTZ therapy, in POMS the effect of NTZ is rapid and stable. Our data further support the use of NTZ as first treatment choice in POMS.

SHIFTING FROM NATALIZUMAB TO ALEMTUZUMAB IN PEDIATRIC-ONSET MULTIPLE SCLEROSIS

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Introduction: Pediatric-onset multiple sclerosis (POMS) is characterized by an aggressive course and early development of physical and cognitive disability. The introduction of highly effective treatments at disease onset such as natalizumab) is strongly recommended. However, the JCV seroprevalence rate progressively increases in POMS, indicating the withdrawal of natalizumab and the shift to a different highly active treatment.

Objective: To evaluate in POMS withdrawing natalizumab for safety reasons the efficacy of alemtuzumab on clinical and radiological parameters.

Methods: All POMS shifting from Natalizumab to Alemtuzumab between August 2016 and October 2021 were enrolled in this single-centre, prospective study. Patient were evaluated every 6 months both clinically and radiologically and followed up for 30.4±18.7 months (6-64 months). No radiological (i.e., no evidence of new/enlarging white matter lesions nor gadolinium-enhancing lesion) or clinical (i.e., no evidence of clinical relapse or EDSS worsening) evidence of disease activity (rNEDA and cNEDA respectively) were evaluated at 12 and 24 months. In addition, survival analysis for overall NEDA condition (i.e., radiological and clinical) was also analyzed.

Results: Eleven POMS were enrolled in this study. After the first course 2 patients experienced a clinical relapse (18.2%), while in 4 (36.4%) MRI disclosed inflammatory disease activity. After the second course, one patient, who had at month 12 an active white matter lesion, experienced a clinical relapse, while none had a radiological relapse. Overall, at month 24 63.6% were NEDA. Since during the follow up 4 (36.4%) patients had further evidence of radiological disease activity, 5 (45.4%) POMS were NEDA at the end of their follow-up (mean: 30 months). However, last EDSS was stable (median of 1.0 at baseline and follow-up, p=0.33).

Conclusions: In POMS shifting from natalizumab to alemtuzumab is an effective option. The moderate NEDA condition needs to be further evaluated compared with pediatric cohorts not treated with alemtuzumab and with alemtuzumab-treated adult-onset MS.

ALEMTUZUMAB AND MATERNITY MANAGEMENT: TWO CASES OF PREGNANCY BETWEEN FIRST AND SECOND COURSE

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Introduction: Multiple sclerosis (MS) predominantly affects women in childbearing age requiring precise family planning in treatment approach. Only few disease-modifying treatments, especially among highly active drugs, are approved during pregnancy and lactation. Alemtuzumab is a monoclonal anti-CD52 antibody potentially teratogenic, since IgGs are known to cross the placenta [1]. For this reason, contraceptive measures should be used until the fourth month after each administration. We

describe here two cases of pregnancy within 5 months after the first alemtuzumab infusion.

Case 1: A 30-year-old woman, with relapsing remitting (RR)-MS and significant radiological activity, was a candidate for treatment with natalizumab, considering her desire for maternity. However, since JCV positivity was detected, we decided to start alemtuzumab in January 2021, with benefit. She became pregnant in June 2021 and delivery was induced at 41+5 weeks. The female newborn was healthy with a normal growth. The patient remained clinically and radiologically stable after delivery. She decided to postpone her second course of alemtuzumab to July 2022 to proceed breastfeeding.

Case 2: A 39-year-old woman, diagnosed with RR-MS in 2013, was treated with natalizumab for highly active disease. Moreover she was looking for pregnancy. However, in 2019, MRI showed new multiple active lesions, so we decided to switch to alemtuzumab, which was started in April 2019. After 5 months she became pregnant. Delivery was induced at 33+6 weeks, in April 2021, and the male newborn was healthy with a regular growth. A month after delivery, a clinical and radiological relapse occurred, requiring the second administration of alemtuzumab in June. For persistent radiological activity, a third course was necessary a year later.

Discussion and Conclusion: Our two patients presented highly aggressive MS controlled with alemtuzumab. There was accurate family planning, matching the patients' desire for maternity with MS therapy. Both pregnancies and deliveries went regularly, and the newborns were healthy. However, while the first patient remained clinically and radiologically stable after delivery, the second one presented with important radiological activity, in contrast with the evidence that alemtuzumab-treated patients appear to have a lower relapse-rate in the postpartum [2]. Further research is needed for pregnancy planning. In fact, even if alemtuzumab is classified as pregnancy category C drug, some recent evidence [3] shows that there is not a significant difference, even in the abortion rates, between women conceiving before or after the 4-month window. Therefore, alemtuzumab might be considered a safe alternative in compliant women looking for pregnancy.

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LEPTOMENINGEAL ENHANCEMENT IN PROGRESSIVE MULTIPLE SCLEROSIS IS ASSOCIATED WITH HIGHER RISK OF FUTURE DISABILITY PROGRESSION AND PERSISTS ON LONG TERM FOLLOW-UP DESPITE HIGH EFFICACY THERAPIES

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Introduction: Leptomeningeal enhancement (LME) has been described as a potential biomarker of meningeal inflammation in Multiple Sclerosis (MS).

Aim: To assess LME in a cohort of patients with progressive MS (pMS) and its correlation with disease variables over prospective follow-up.

Methods: This study was performed on a cohort of 130 pMS patients (primary or secondary progressive), including also early pMS with active disease. Patients were imaged yearly using a standard 1.5T MRI (according to MAGNIMS recommendations). Post contrast CUBE 3D FLAIR sequences were used for LME detection. Image analysis was performed for brain and upper spinal cord volume and for normalized T2 lesion volume (nT2LV). Presence of LME was correlated with clinical and MRI variables at baseline and during follow-up. Furthermore, neuropathological features and distribution of meningeal inflammation were assessed in a post-mortem cohort of 12 MS and 20 control brains, in order to draw inferences on the pathological substrates of LME.

Results: In this cohort, mean age was 54.2 years, mean EDSS at baseline was 5.8. MRI disease activity at baseline was present in 13.9% of patients. High efficacy treatment (HET) was used in 48.3% of patients. Mean duration of follow-up was 18.4 months (range 12-36). LME at baseline MRI was present in 26.7% of patients, most of which (67.7%) showed multiple LME. No significant differences were observed for LME between patients treated and not treated with HET (27.5% vs 25%). LME was associated with higher baseline EDSS (OR 1.86, p=0.01), higher age (OR 1.06; p=0.01), active disease at baseline MRI (OR 3.70, p=0.03), higher ventricle volume (p=0.004), lower normalized brain volume (p=0.008), while it was not associated with nT2LV or mean upper cervical cord area. LME was unchanged in most patients over follow-up, independently from HET use. Presence of multiple LME at baseline MRI was independently associated with EDSS increase in the past 2 years (OR 5.99, p=0.004) and with higher risk of future EDSS increase during follow-up (Cox regression: OR 4.07, p=0.019). Neuropathological data suggested that LME in MS might be the expression of both leptomeningeal inflammation and post- inflammatory leptomeningeal fibrosis.

Conclusions: LME is frequently detected in pMS patients using standard 1.5 T MRI, is associated with a more aggressive disease, and is independently predictive of past and future progression of disability.

PROGRESSIVE MOTOR NEURON SYNDROMES WITH SINGLE CNS LESIONS AND CSF OLIGOCLONAL BANDS: NEVER FORGET SOLITARY SCLEROSIS!

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Objectives: To describe 3 patients with progressive motor impairment due to single CNS inflammatory-demyelinating lesions matching the definition of solitary sclerosis (SS), a rare variant of multiple sclerosis (MS), and to discuss its differentiation from motor neuron diseases (MNDs).

Materials: Patient 1, 66-year-old female; patient 2, 39-year-old male; patient 3, 42-year old female.

Methods: Clinical evaluation; neuroimaging (MRI of brain and spinal cord, brain 18F-FDG PET); neurophysiological investigations (transcranial magnetic stimulation, TMS; needle electromyography, EMG); CSF examination.

Results: All 3 patients had progressive motor deficits of the limbs (patient 1, left spastic hemiparesis; patient 2, right spastic hemiparesis; patient 3, proximally-predominant left upper limb weakness with slight atrophy of left upper girdle muscles and fasciculations of left biceps and triceps brachii). In all patients, MRI of brain and spinal cord disclosed a single small T2-hyperintense lesion: in the right anterior paramedian upper medulla (patient 1), in the median-left paramedian anterior lower medulla (patient 2), and in the left paramedian anterior cervical spinal cord at C4 level (patient 3). In patients 1 and 2, TMS showed reduced amplitude and abnormal morphology of motor evoked potentials (MEPs) and increased central motor conduction time (CMCT) in the affected limbs, while needle EMG demonstrated reduced temporal recruitment of motor units in the same limbs. In patient 3, TMS showed reduced amplitude of MEPs recorded from the right limbs and increased CMCT for upper limbs, while needle EMG revealed chronic neurogenic changes in C5-C7 muscles of the left upper limb. Brain 18F-FDG PET in patients 1 and 2 was normal. CSF analysis demonstrated normal basic parameters and unmatched oligoclonal bands as per intrathecal IgG synthesis in all three patients. DISCUSSION. The three cases are consistent with the diagnosis of SS, an entity still needing thorough clinical and pathophysiological characterization. Due to the usual upper motor neuron (UMN) features of progressive motor impairment, the clinical picture of SS can overlap with primary lateral sclerosis (PLS). However, whereas our first 2 cases mimicked Mill's syndrome, i.e. the hemiparetic variant of PLS, the third one is rather reminiscent of ALS, manifesting with clinical and neurophysiologic signs of LMN pathology.

Conclusions: Our case series contributes to further phenotypically characterize SS, illustrates the challenges of its differentiation from PLS, and suggests widening the spectrum of MNDs whose differential diagnosis should comprise SS, namely including ALS. Moreover, it underlines the importance of CSF analysis in demonstrating a CNS immune-mediated process.

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A GENETIC ASSOCIATION STUDY ON IRON METABOLISM GENES HIGHLIGHTS HYPOXIA-INDUCIBLE FACTOR-1 ALFA AS A POTENTIAL DRIVER OF CHRONIC ACTIVE INFLAMMATION IN PROGRESSIVE MS

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Introduction and aims: Iron enrichment has been detected by recent advanced magnetic resonance imaging at the edges of the chronic active lesions, a hallmark of progressive multiple sclerosis (pMS). Iron accumulation in such lesions mirrors the molecular profile of the disease-associated microglia but, so far, its biological meaning is not clear. We investigated whether variants in genes implicated in iron metabolism may affect the susceptibility to develop progressive MS.

Materials and Methods: We tested the association between 66,769 Single Nucleotide Polymorphisms (SNPs) positionally or functionally mapping to 319 genes involved in iron metabolism and disease course in 946 MS patients, comparing 250 benign relapsing-remitting disease duration "(=>20 years, EDSS<= 3.5) patients" versus primary (n=409) and secondary (n=287) progressive MS patients.

Results: The top-associated signal was led by the rs11621525 variant, with the A allele being protective towards the progressive course (p=5.62E-07; OR=0.53) and passing the multiple testing correction. The SNP maps to the Hypoxia-Inducible-Factor-1-alfa (HIF1A) gene, a key player in iron metabolism, cell response to hypoxia and regulation of Th17/Treg lymphocytes balance. HIF1A was also recently recognized as an important gene for the microglia of chronic active lesions in a single-nuclei RNA sequencing study [1]. Previous evidence has shown that the rs11621525_A allele is able to down-regulate the expression of HIF1A in whole blood in healthy subjects, and to affect the methylation profile of HIF1A promoter. We also confirmed this effect in the Peripheral Blood Mononuclear Cells (PBMCs) of an internal cohort of 78 naïve MS patients (p=0.034). In addition, we found a trend for association between HIF1A expression in PBMCs and serum neurofilament levels, a marker of ongoing inflammation and neurodegeneration, in RR-MS patients (n=26, p=0.08).

Discussion and Conclusions: We found that a genetic variant in HIF1A impacts the susceptibility to develop progressive MS. As an important factor in mechanisms shared between cell response to hypoxia, iron metabolism and Th17-related inflammation, HIF1A is an interesting candidate for further functional exploration in chronic inflammation in pMS.

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ASSESSING PREDICTORS OF NEDA-3 STATUS ACHIEVEMENT IN RELAPSING REMITTING MULTIPLE SCLEROSIS: A SINGLE CENTER EXPERIENCE

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Objectives: No evidence of disease activity-3 (NEDA-3) is a composite outcome defined by the absence of relapse, disability worsening and magnetic resonance imaging (MRI) activity. This study aimed to identify the prevalence of NEDA-3 status achievement and to describe factors associated with the failure in its attainment in a prospective cohort of RRMS patients.

Material and methods: We included all the consecutive RRMS patients followed at the Bari MS Center from 2010 with a first visit within one year from disease onset and with ≥1 visit per year. DMTs exposure was classified on the basis of the efficacy and mechanism of action of the first DMT prescribed in moderate efficacy (ME) and high efficacy (HE) DMTs. Percentages of patients exposed to ME and HE DMTs reaching NEDA-3 status at 2 and at 5 years of follow-up were compared using the chi-square test. A multivariable logistic regression model was built to estimate the association of demographic and clinical factors with the risk of not achieving NEDA-3 status.

Results: A cohort of 450 patients (female patients n=303, 67%) with a median (IQR) follow-up of 6.5 ± 0.3 years was analysed. Patients who started their treatment history with HE DMTs (n=82, 18.2%) reached a NEDA-3 status at 2 and 5 years more frequently than those who received a ME DMTs (47% vs 28%, p=0.001; 45% vs 24%, p=0.001, respectively). The multivariable logistic regression model revealed that female sex and a longer time between disease onset and first DMT start were significant risk factors of not achievement of NEDA-3 status at 2 (OR, 95%CI: 3.5, 1.65-7.44; 1.8, 0.67-2.97, respectively) and 5 years of follow up (2.51, 1.65-6.44; 1.2, 1.09-2.06, respectively).

Discussion: In the constantly evolving scenario of treatment of MS, the investigation of NEDA-3 status still provides an interesting insight into the therapeutic effectiveness of DMTs. The identification of the optimal timing of treatment starts for achieving the best control on long-term disability accumulation is a critical discussion point in clinical practice, whereas the shorter time from disease onset to DMT start was found to be associated with a reduction of disability accrual. [1] Treatment response has traditionally been assessed based on relapse rate, MRI lesions and disability progression, highlighting the superiority of HE DMTs in fulfilling these outcomes. [2]

Conclusions: Demographic and clinical baseline characteristics are predictors of NEDA-3 status over the long term. HE DMTs demonstrate superiority in preventing disease activity.

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LONG-TERM EFFICACY OF OFATUMUMAB IN PATIENTS WITH RELAPSING MULTIPLE SCLEROSIS

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Objective: To assess the long-term efficacy of ofatumumab treatment for up to 4 years in patients with relapsing multiple sclerosis (RMS).

Background: Ofatumumab, a fully human anti-CD20 monoclonal antibody, demonstrated superior efficacy versus teriflunomide in the Phase 3 ASCLEPIOS I/II trials in RMS patients. Evaluation of the long-term efficacy of ofatumumab treatment is important.

Design/Methods: This analysis (data cut-off: 25-Sep-2021) will include cumulative data from patients randomized to ofatumumab/teriflunomide in the ASCLEPIOS I/II trials (core study) and the ongoing, open-label, ALITHIOS extension study. Patients will be analyzed in two groups: those randomized to ofatumumab in the core (continuous group) and those randomized to teriflunomide in the core with potential switch to ofatumumab in the extension (switch group). Annualized relapse rate (ARR), disability worsening (time-to-3-month/6-month confirmed disability worsening), disability improvement (time-to-6-month confirmed disability improvement), and brain MRI outcomes (number of Gd+T1lesions and annualized T2 lesion rate) will be assessed.

Results: Overall, 1882 patients who were randomized in the ASCLEPIOS I/II trials (ofatumumab/teriflunomide: 946/936) will be included. Baseline demographics and disease characteristics have previously been reported for the ASCLEPIOS I/II trials (mean age, ~38 years; female, ~68%, mean EDSS, ~2.9; mean ±SD of number of Gd+T1 lesions: ~1.5±3.9; mean volume of T2 lesions, ~13.2 cm3). Previously reported data showed superiority of ofatumumab versus teriflunomide in reducing ARR, suppressing MRI lesion activity, and delaying disability worsening. In total, 690/946 patients treated with ofatumumab and 677/936 patients treated with teriflunomide entered ALITHIOS. The between-group analysis over a period of up to 4 years shows a cumulative benefit with the earlier initiation of ofatumumab.

Conclusions: Long-term, continuous ofatumumab treatment up to 4 years showed sustained efficacy on relapses, MRI lesions, and risk of disability worsening. The low rate of relapses and MRI lesions observed in the core phase were at least sustained, if not further reduced, during the extension phase, showing continued efficacy on these outcomes with up to 4 years of treatment. Patients switching from teriflunomide to ofatumumab in the extension phase demonstrated pronounced reductions in relapses and MRI lesions. Sustained differences in relapses, MRI lesion activity, and the risk of disability worsening observed in the continuous versus the switch group highlight the value of earlier initiation of high-efficacy therapy, ofatumumab compared to a lower efficacy therapy.

EFFECT OF SIPONIMOD ON THE MSWS-12 AND MSIS-29 IN PATIENTS WITH SPMS FROM THE EXPAND STUDY

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Objectives: In the Phase 3 EXPAND study in SPMS, siponimod showed a favourable effect on the 12-item Multiple Sclerosis Walking Scale (MSWS-12). Treatment effects on 29-item Multiple Sclerosis Impact Scale (MSIS-29) and MSWS-12 were further investigated by applying clinically meaningful cut-offs based on literature, in addition to the change from baseline.

Materials: Of 1651 patients randomized 1327 completed the EXPAND core study (median duration 21 months).

Methods: Change from baseline for MSIS-29 was assessed using a mixed-effect repeated measures model. Time to 6-month confirmed progression (6m-CP) was assessed using a Cox regression model with meaningful cut-offs defined as ≥7.5 (MSIS-29) and 4/6/8/10 (MSWS-12) points in the overall population and active/non-active SPMS and age ≤/>45 years subgroups.

Results: In the overall population, increases from baseline in MSIS-29 physical and psychological scores were significantly reduced with siponimod versus placebo. Risk of 6m-CP in the MSIS-29 physical score also decreased in the overall population (hazard ratio [HR] 0.81, p=0.034), active SPMS (0.76, p=0.055) and age ≤45 years (0.63. p=0.005) subgroups. Trends favouring siponimod were observed for 6m-CP in MSIS-29 psychological score. On MSWS-12 pronounced reductions in 6m-CP risk were observed with more stringent cut-offs of 6/8/10 points in the overall population (HR 0.75-0.80, p<0.05), active SPMS (0.72-0.74, p<0.05) and age ≤45 years (0.67-0.71, p<0.05) subgroups.

Conclusions: Siponimod reduced the increase in MSIS-29 and MSWS-12 scores and the risk of clinically meaningful confirmed progression in SPMS patients. The effect was more apparent in younger (age ≤45 years) or active SPMS patients. EXPAND: ClinicalTrials.gov Identifier: NCT01665144; https://clinicaltrials.gov/ct2/show/NCT01665144

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A FUNCTIONAL COMPOSITE ENDPOINT TO CHARACTERIZE DISEASE PROGRESSION IN PATIENTS WITH ACTIVE OR NON-ACTIVE SPMS

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Objectives: Composite endpoints (CEPs) capture disease progression more comprehensively as they account for functions not or not optimally captured by Expanded Disability Status Scale (EDSS) alone. A previous analysis, combining SDMT and EDSS, demonstrated high sensitivity in determining treatment effects. Here, 9-Hole Peg Test (9HPT) and Timed 25-Foot Walk Test (T25FWT) are included with SDMT and EDSS in the construction of CEPs. By exploring novel CEPs more relevant to secondary progressive multiple sclerosis (SPMS), we may be able to better characterize progressive disease including differences in active and non-active SPMS.

Methods: In this post hoc analysis, two definitions for time to 6-month confirmed disease progression (6mCDP) were applied for all SPMS patients participating in the EXPAND Core study and in subgroups with active and non-active disease: CEP1 based on EDSS (1-point/0.5-point worsening from baseline of ≤5/>5, respectively), or ≥4-points worsening on SDMT, or 20% increase in 9HPT and CEP2 that in addition to CEP1 included the component of 20% increase in T25FWT (only for patients with baseline EDSS ≤5.5, since T25FWT was unstable in patients with higher baseline EDSS in the EXPAND study).

Results: Risk reductions of 6m-CDP in the overall, active and non-active SPMS patients assessed by EDSS alone were 26% (0.74 [0.60;0.92] p=0.006), 37% (0.64 [0.47;0.87] p=0.004), 13% (0.87 [0.64;1.19] p=0.376) respectively. Risk reductions of 6m-CDP in the overall, active and non-active SPMS patients assessed by CEP1 were 27% (0.73 [0.62;0.86] p<0.001), 30% (0.70 [0.55;0.88] p=0.003), 21% (0.80 [0.63;1.01] p=0.061) respectively. Risk reductions of 6m-CDP in the overall, active and non-active SPMS patients assessed by CEP2 were 25% (0.75 [0.64;0.88] p<0.001), 29% (0.71 [0.57;0.89] p=0.003), 19% (0.81 [0.64;1.02] p=0.070) respectively.

Conclusions: Adding SDMT and 9HPT to the EDSS assessment (CEP1) allows detection of treatment effects on a broader spectrum of symptoms in SPMS compared with EDSS alone, including in patients with non-active disease. Addition of T25FWT in CEP2 did not increase precision of HR ratio estimates.

EXPAND: ClinicalTrials.gov Identifier: NCT01665144

https://clinicaltrials.gov/ct2/show/NCT01665144

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– L Kappos, A Bar-Or, BAC Cree, RJ Fox, G Giovannoni, et al. EXPAND Clinical Investigators - Siponimod Versus Placebo in Secondary Progressive Multiple Sclerosis (EXPAND): A Double-Blind, Randomised, Phase 3 Study; Lancet (2018) Mar 31;391(10127):1263-73

INJECTION-RELATED REACTIONS WITH SUBCUTANEOUS ADMINISTRATION OF OFATUMUMAB IN RELAPSING MULTIPLE SCLEROSIS: DATA FROM CLINICAL STUDIES AND POST MARKETING EXPERIENCE

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Objective: To characterize the risk of injection-related reactions (IRRs: systemic and local-site) observed in relapsing multiple sclerosis (RMS) patients treated with ofatumumab in clinical trials and post-marketing surveillance.

Background: In the core ASCLEPIOS I/II trials, IRRs were predominantly reported with the first ofatumumab injection. Most were mild-to-moderate in severity and non-serious in nature. No life-threatening/hypersensitivity reactions leading to discontinuation were observed. Updated information on IRRs is now available from the open-label extension study ALITHIOS and post-marketing surveillance.

Design/Methods: Data from patients treated with ofatumumab in the core ASCLEPIOS I/II trials and ALITHIOS study (overall, N=1969; patients who received continuous ofatumumab, N=1292; patients newly switched from teriflunomide to ofatumumab, N=677) and post-marketing surveillance (cut-off: 29-Jan-2021) were included in the analysis. Incidence of both systemic and local-site IRRs, their severity and seriousness were reported. The most commonly associated symptoms are summarized.

Results: Systemic/local-site IRRs were observed in 24.6%/11.5% in overall; 25.6%/13.2% in continuous and 22.6%/8.3% in newly-switched groups. Upon first injection, incidence of systemic/local-site IRRs in overall, continuous, and newly-switched groups were 17.4%/2.9%, 17%/3.4%, and 18.2%/2.1%, respectively. Majority (99.5%) were mild-to-moderate (Grade 1/2) in severity. No life-threatening IRRs were observed during the study. In the overall population, systemic and local-site IRRs led to treatment discontinuation in 5 and 1 patient, respectively. The most common systemic IRR symptoms (≥5%) with all injections were fever, headache, chills, fatigue, and local-site IRR symptoms (≥3%) were erythema/redness and pain. From the post-marketing, 6 serious cases were assessed as potential systemic IRRs (HCP/non-HCP: 2/4): 1 patient was hospitalized with weakness. In addition, 5 patients reported serious hypersensitivity reactions (HCP/non-HCP: 1/4) including 1 anaphylaxis.

Conclusions: Systemic and local-site IRRs reported upon first injection with ofatumumab in the ALITHIOS trial and post-marketing surveillance were mostly mild-to-moderate in severity. These results are consistent with the Phase 3 ASCLEPIOS I/II trials.

EVALUATION OF DETERMINANTS OF THERAPY SWITCH IN RELAPSING MULTIPLE SCLEROSIS: A STUDY FROM THE ITALIAN MS REGISTER

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Objectives: Many recent studies have focused on patients with relapsing multiple sclerosis (RMS), a term that includes active relapsing remitting (RR) and secondary progressive (SP) MS [1]. This study aims to assess the characteristics of RMS patients in the Italian Multiple Sclerosis Register (IMSR), evaluating disease modifying therapy (DMT) switches due to disease activity.

Material and methods: RRMS and SPMS patients with ≥5-year follow-up and ≥3 EDSS scores were extracted from the IMSR. We first determined the proportion of active patients during DMT exposure, defined with at least one relapse in the last 2 years of follow-up. The effect of demographic and clinical factors and DMT exposure on the risk of treatment switch was assessed using multivariable logistic regression models. The role of DMTs exposure was assessed in 2 different models:

last recorded DMT or last DMTs grouped according to efficacy and mechanism of action (MoA) (moderate efficacy (ME), high efficacy (HE) DMTs, anti-CD20 drugs).

Results: Applying the inclusion criteria, we retrieved a cohort of 21,174 RRMS and 1153 SPMS patients. We identified 4161 RR (19.7%) and 578 SP (50.1%) active patients, of whom 2694 (56.8 %) switched DMT. RMS patients were significantly younger, less disabled and more frequently affected by a RR disease course in comparison with not active patients. The multivariable logistic regression model revealed that Alemtuzumab (OR 0.08 95% CI 0.02-0.37), Natalizumab (OR 0.48 95% CI 0.30-0.76), Ocrelizumab (OR 0.1 95% CI 0.02-0.45) and Rituximab (OR 0.23 95% CI 0.06-0.82) were protective factors against treatment switch due to relapses in comparison with Interferon beta exposure. Our model also revealed that the use of HE DMTs was a protective factor against the treatment switch due to a relapse (OR 0.43 95% CI 0.31-0.59), especially considering anti-CD20 drugs (OR 0.14 95% CI 0.05-0.37) in comparison with the use of ME DMTs.

Discussion: Optimization of therapy in patients with suboptimal disease control provides better chances of improving long-term outcomes, preventing, or delaying accrual of neurological disability [2]. Our results highlight clinical relevance of high-efficacy drugs as protective factor against the treatment switch due to a relapse, demonstrating the leading role of an individual assessment of disease characteristics in the choice of treatment for both treatment naïve and switchers patients [3].

Conclusions: Clinical disease activity is an important trigger of treatment switch in RMS patients. HE DMTs, especially anti-CD20 agents, significantly reduce the risk of disease activity in RMS.

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PROGRESSION INDEPENDENT OF RELAPSE AND RELAPSE ASSOCIATED WORSENING ACCORDING TO AGE IN MULTIPLE SCLEROSIS

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Background: Confirmed disability accrual (CDA) in Multiple Sclerosis (MS) results from worsening associated to relapse (RAW) and progression independent of relapse activity (PIRA). Age is a key determinant of CDA. [1]

Objectives: To estimate age at and time to first CDA, RAW and PIRA events and the age-related EDSS longitudinal trajectories.

Methods: MS patients with ≥5-year follow-up and ≥1 visit every 6 months were selected from the Italian MS Registry. Time (years) from the first visit and the birthdate to the first CDA, RAW and PIRA events were evaluated in the whole cohort by using multivariable Cox models. A longitudinal model for repeated measures (LMMRM) was applied to evaluate the disability trajectories in 3 subgroups of patients stratified according to age at onset: ≤18 years–pediatric onset (POMS), 19-49 years–adult onset, >49 years–late onset (LOMS).

Results: 3777 MS patients were included (median [IQR] age: 31.40[24.7-39.4]). A first CDA event occurred in 1037 patients (27.5%). PIRA accounted for the 81.2% (n=842) of CDA events. Median ages at and median time to the first CDA, PIRA and RAW events were (33.9[27.3-42.6], 2.0[1.3-3.0]), (34.5[27.6-43.2], 2.1[1.3-3.1]) and (32.5[24.9-40.4], 1.6[1.0-2.7]), respectively. The cumulative incidence of CDA, PIRA and RAW increased with age, being 0%, 0% and 0% at 10 years; 1.7%, 1.3% and 0.5% at 20 years; 10.8%, 9.0% and 3.5% at 30 years; 25.3%, 21.6% and 7.8% at 40 years; 44.1%, 39.1% and 14.4% at 50 years; 64.9%, 60.8% and 24.1% at 60 years; 81.3%, 78.7% and 27.7% at 70 years. LOMS patients (n=227) presented a 39% increased risk of reaching a first CDA event (p=0.05) and a 51% increased risk of reaching a PIRA event (p=0.03) in comparison to POMS (n=268); the risk of reaching a RAW event did not differ between the 3 groups. The LMMRM showed that the slope of disability trajectories significantly diverged between POMS and LOMS from the beginning of the follow-up (Year 1: delta-EDSS 0.3 (0.1-0.5), p<0.001) and reached the value of 0.6 (0.4-0.8, p<0.0001) at year 5.

Conclusions: Our results confirm that PIRA is the major determinant of CDA across all age groups. The incidence of both PIRA and RAW events increases with age, which becomes much more evident after the age of 20 years. POMS patients show a slower disability accrual in comparison to older patients. This could likely be due to more efficacious compensation mechanisms and better treatment response which decline with age.

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THE NATALIZUMAB WEARING-OFF EFFECT

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Objectives: Natalizumab (N) is a monoclonal antibody highly effective in the treatment of relapsing remitting multiple sclerosis (RRMS) patients. Its use in JCV positive patients is restricted by progressive multifocal leukoencephalopathy (PML), the main adverse event, the risk of which increases in relation to the number administrations. Recently, extended dose administration protocols have been used to reduce the risk of PML. However, this strategy is often associated to the perception of a "wearing-off effect" (WOE) in some patients. Based on this, the present study evaluated the frequency of WOE and the characteristics of patient who presented it, also analyzing aspects of quality of life.

Material and Methods: RRMS patients that had received a minimum of 8 natalizumab infusions were asked to complete 5 questionnaires: the Multiple Sclerosis Impact Scale (MSIS-29), Short Form-12 Health Survey (SF-12), Fatigue Severity Scale (FSS), Apathy Evaluation Scale (AES) and a general questionnaire regarding the wearing-off effect.

Results: The study includes 75 patients, 62 (82.7%) of which are female. Average age is 39.1 ± 9.1 years old; the disease duration is 2.4 ± 1.6 anni; average EDSS is 2.4 ± 1.6. Average number of infusions is 64.2 ± 39.7 and the time interval between the final two infusions is 38.7 ± 8.6 days. 12 (16%) are JCV positive patient; 37 (49.3%) individuals reported a wearing-off effect. Pearson test ($p>0.001$) shows a significant correlation between scores obtained on SF-12, MSIS-29 and FSS scales and a higher level of disability (EDSS score); instead, no association has been observed between AES scale, number of infusions and the time interval between the last two doses. The linear regression analysis was used to determine factors influencing the number of end-of-dose symptoms which were found to be associated with EDSS score ($p=0.029$), whereas the number of infusions and the extend-dose protocol were not. Finally, it seems the longer the interval between the two infusions ($p=0.0039$) is, the worse balance disturbances become.

Discussion and Conclusions: Our data show that the WOE is found in almost half of the patients treated with natalizumab; that is consistent with other studies [1-3]. Considering the benefits of the extended-dose protocol, especially for JCV positive individuals, it's important to know which patients are most exposed to WOE's risk and why.

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THE IMPACT OF EARLY INTRODUCTION OF HIGHLY EFFECTIVE TREATMENT IN PEDIATRIC ONSET MULTIPLE SCLEROSIS

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Objective: Pediatric-Onset Multiple Sclerosis (POMS) is characterized by disease onset before 18 and a lower risk of disability in the first ten years after diagnosis than adult-onset MS (AOMS) [1]. However, POMS reach disability milestones, e.g., walking with a cane, younger than AOMS. As there is high inflammatory disease activity in children, the early introduction of a highly effective disease modifying treatment (HET) seems to be a promising strategy. The aim of the present case series is to provide data on the management of POMS by describing the treatment sequencing to second-line therapies in 5 POMS and report the impact HET had on disease activity.

Materials and Methods: This retrospective case-series includes all the consecutive POMS patients treated at the Multiple Sclerosis Centre, Piacenza, Italy, between January 2015 and March, 2022. Two of five POMS patients were administered HET as initial therapy after diagnosis. Treatment sequencing, relapses and MRI have been collected during the follow-up. MS diagnosis was formulated according to Mac Donald criteria 2010 revision until 2018 and Mac Donald 2017 revision since 2018. DMDs effectiveness was assessed by No Evidence of Disease Activity-3 status (NEDA-3). HET was defined according to He and colleagues as DMDs that reach more than 50% reduction on relapse rate [2].

Results: Average age at onset was 12.8 year (range 9-14 years), average age at diagnosis was 13 years (range 9-15 years), male gender frequency was 60%, mean follow up was 5 years (range 3-7), mean EDSS at last visit was 0.4 (range 0-1.5), average pre-treatment annualized relapse rate was 1.65 (range 0.8-2.8). There was no sign of disease activity in the 2 cases treated by HET, i.e., no relapses, no disability accrual and no MRI activity (NEDA-3 status), during the three-year follow-up.

Discussion: It was observed that a prompt diagnosis and HET administration led to good outcomes. Although there is a paucity of evidence-based data, a large propensity score matched observational study on POMS reported better outcomes when HET was adopted [3].

Conclusion: Further studies are needed to better define the role of HET as initial treatment in POMS.

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A CROSS-SECTIONAL AND LONGITUDINAL ANALYSIS TO ASSESS THE ASSOCIATION BETWEEN RESERVE, DISABILITY AND FATIGUE IN PATIENTS WITH MS

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Objective: One of the most debilitating and common symptoms in multiple sclerosis (MS) is represented by fatigue. Individual resilience could affect motor and cognitive fatigue, as already proven in MS patients for cognitive and motor disability. In order to test this hypothesis, we explored the association between clinico-demographic features, brain structural damage and fatigue.

Materials and methods: We prospectively enrolled fifty-four MS patients, who underwent clinical examination (including Expanded Disability Status Scale-EDSS, Symbol Digit Modalities Test-SDMT and Beck Depression Inventory II-BDI) and MRI acquisition at baseline and after a mean follow-up of 14 months. We evaluated physical and cognitive MS-related fatigue using the respective Modified Fatigue Impact (MFIS) subscales (MFIS-P and MFIS-C). Structural brain damage was quantified in terms of white matter (WM) lesions load (JIM 6.0) and brain volume (SIENA and SIENAX). Percent change over time (%c) for clinical scores and MRI variables were also computed. We estimated a cognitive reserve index (CRI) by evaluating educational level, premorbid IQ and the participation in cognitive leisure activities. Brain reserve was expressed as sex adjusted intracranial volume (ICV). We used bivariate correlations (preliminary screening) and hierarchical linear regressions to establish the cross-sectional association between putative risk factors (age, gender, phenotype, EDSS, SDMT-z, BDI, log transformed WM lesion load and normalized brain volume-NBV, brain reserve, cognitive reserve) and fatigue scores. We tested partial correlations between baseline features, their %c and fatigue scores %c, accounting for follow-up interval in order to analyze the impact of risk factors on fatigue changes over time.

Results: The cross-sectional analysis revealed associations between MFIS-P and age, EDSS, BDI, NBV (r ranging from 0.01 to 0.001) and, marginally, brain reserve (p=0.06). 32% of the variance in MFIS-P was accounted for in the full regression model (p=0.001), with BDI being the only variable to account for significant variance (p<0.001). MFIS-C was correlated with BDI (p<0.001). In the longitudinal analysis, we did not find any associations between baseline features, MFIS-P and MFIS-C %c. BDI %c was associated to MFIS-P and MFIS-C %c (r=0.55, p<0.001; r=0.57, p<0.001). Discussions: among the explored features, only BDI was strongly associated with both MFIS-P and MFIS-C, while brain reserve was only mildly associated. In the longitudinal analysis none of the baseline features was correlated with fatigue.

Conclusions: Depression was the only feature significantly correlated to physical and cognitive fatigue both at the cross-sectional and longitudinal analysis. Fatigue symptoms in MS patients were not affected by brain and cognitive reserve.

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RELATIONSHIP BETWEEN FATIGUE AND MOTOR DISABILITY CHANGES OVER TIME

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Objectives: Monitoring of Multiple Sclerosis (MS) patients increasingly relies on patient reported outcomes (PROs). High levels of fatigue are often associated to impairment in functional mobility and disability progression, but the relationship between changes in fatigue and objective disability scores over time remains largely unexplored.

Materials and methods: We prospectively collected clinical (Expanded Disability Status Scale-EDSS, Timed 25-Foot Walk Test-T25FWT, 9-Hole Peg Test-9HPT and Beck Depression Inventory II-BDI) and MRI data from fifty-four MS patients at baseline and after a mean follow-up of 14 months. Physical MS-related fatigue was evaluated with the specific subscale (MFIS-P) of the 21-items Modified Fatigue Impact scale (MFIS), according to recommendations from the MS Council for Clinical Practice Guidelines. White matter (WM) lesion load (JIM 6.0) and brain volume (SIENA and SIENAX) were assessed to estimate structural brain damage. We explored longitudinal changes in clinical variables using t-test. Percent change over time (%c) for clinical scores and MRI variables were also computed. Using bivariate correlations, we screened the association between MFIS-P %c and baseline clinico-demographic features (age, gender, phenotype, disease duration, follow-up interval), brain structural damage, percent changes in motor disability scores and depression. Finally, we tested the relationships between MFIS-P %c and objective disability measures %c using partial correlation analysis, accounting for possible confounders emerged from bivariate analyses.

Results: Clinical scores did not show significant changes over time. Mean percent changes in MFIS-P, EDSS, T25FWT, 9HPT, and BDI were 0.24, -0.05, 0.59, -3.77, and 1.39, respectively. Eighteen patients showed clinically meaningful worsening in one or more motor scales. Among explored variables, MFIS-P %c was correlated to T25FWT %c (r=0.52, p=0.001) and BDI %c (r=0.49, p<0.001). Accounting for BDI %c, MFIS-P %c was still correlated to T25FWT %c (r=0.46, p=0.006).

Discussions: Changes in MFIS-P in MS are associated with changes in motor performance. MFIS-P could represent an efficient tool to indirectly assess walking disability.

Conclusions: While the execution of walking tests in MS centers is limited by time and logistic constraints, preliminary or remote screening of subtle changes in walking performance could benefit from the administration of MFIS-P.

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PREGNANCY OUTCOMES AFTER EXPOSURE TO DIMETHYL FUMARATE IN AN ITALIAN MULTICENTRIC COHORT OF WOMEN WITH MULTIPLE SCLEROSIS

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Background and Objectives: Dimethyl fumarate (DMF) is a viable option for the treatment of relapsing-remitting multiple sclerosis (RRMS). However, as of now, there is limited evidence on the impact that the treatment has on pregnant women. The purpose of the present study is to deliver a retrospective, multicentric analysis on the safety around the exposure to DMF during pregnancy.

Materials and Methods: Women with RRMS treated with DMF before conception accidentally exposed to DMF during pregnancy were identified from the dataset of 27 Italian Multiple Sclerosis Centers. The study analysed the rate of live births, pregnancy loss, gestational age, length and weight of foetus, congenital and haematological birth defects.

Results: The study enrolled 131 women with RRMS with a total amount of 134 pregnancies. Upon conception the average age was 32,7 years (± 4,88). The foetus exposure to DMF has been in average of 39,41 days (± 28,44); 122 (91%) pregnancies resulted in live birth with a median gestational age of 40 weeks, 11 (8,2%) in abortion (<22 weeks) and 1 in stillbirth (> 22 weeks). The average measured length of the foetus was 49,34 cm (±2,6) and the average measured weight was 3,153 (± 425,37). Congenital anomalies were reported for 3/122 (2%) new-borns (2 cleft lip and palate and 1 interventricular defect) and hyperbilirubinemia for 1/122 (0,8%).

Discussions and conclusions: These results suggest that the early exposure of foetus to DMF is not associated with adverse pregnancy outcomes, including congenital and haematological anomalies. Reported outcomes are similar to previous studies and to the general population.

RISK OF INFLAMMATORY REACTIVATION FOLLOWING SARSCOV-2 VACCINE IN A LARGE COHORT OF MULTIPLE SCLEROSIS PATIENTS

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Objective: Whether vaccines play a role triggering or reactivating inflammation in Multiple Sclerosis (MS) has been long debated. There are few reports suggesting that Sars-Cov2 vaccines, as well as COVID-19 infection, may exacerbate relapses in MS. Studies on large cohorts are needed to establish the safety of Sars-Cov2 vaccines in the MS population. This study aims to assess the risk of clinical and radiological reactivation following Sars-Cov2 vaccines in patients with MS.

Materials and Methods: Patients with MS with known date of SarsCov2 vaccination were identified among those followed up at the Multiple Sclerosis Center of the Tor Vergata University Hospital. Data on clinical relapses and radiological activity (Gadolinium enhancing - Gd+- and new T2 lesions) in the 12 months before and after vaccination were extracted from clinical charts.

Results: We enrolled 751 patients (64,7% female, mean age 45.9 ± 11.63 years, 89.9% relapsing-remitting, 5.5% secondary progressive and 4.7% primary progressive, disease duration 11.2 ± 8.11 years, median EDSS 2.0 [1.0 - 4.0], 12.1% untreated, 41.1% treated with first line immunomodulators and 46.7% with second line high efficacy treatments). Among them, 96.7% received mRNABNT162b2 (Pfizer), 2% mRNA-1273 (Moderna) and 1.3% other COVID-19 vaccines. In the whole cohort we did not find a significant increase of the rate of patients with relapse in the 12 months after vaccines (2.3%) compared to the 12 months before (2,9%, McNemar test, p=0.5), as well as of the rate of patients with radiological activity (both 11.5%, McNemar test, p=0.13). Similar findings were obtained analyzing separately untreated patients, patients treated with first line and treated with second line drugs at the time of vaccination.

Discussion and Conclusions: Our preliminary results in a large monocentric cohort of MS patients suggest that vaccination with Sars-Cov2 vaccines does not induce disease reactivation. Further analyses are needed to confirm these findings.

THE CENTRAL VEIN SIGN TO DIFFERENTIATE MULTIPLE SCLEROSIS FROM MIGRAINE

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Objectives: The Central Vein Sign (CVS) has been demonstrated its potential in differentiating multiple sclerosis (MS) from its comorbidities. Migraine represents the most common MS mimic. The aims of this study were to investigate, in two cohorts including MS and migraine patients (i) the prevalence of CVS, (ii) the spatial distribution of CVS+lesions, (iii) the best CVS threshold able to differentiate them.

Methods: Sixty MS patients and 50 age and gender-matched migraine patients underwent a 3T MRI scan. A ROC-curve analysis was performed to identify the best threshold in terms of proportion of CVS+ lesions and the absolute number of CVS+ lesions able to differentiate MS from migraine.

Results: Lesion volume (LV) was different between CVS+ and CVS− lesions (median = 1273 mm^3 vs 181.5 mm^3 for MS cohort; median = 35.1 mm^3 vs 52.2 mm^3 for migraine cohort; $p<0.001$ for all). CVS+ LV and number were higher in MS with respect to migraine both considering whole brain and its subregions ($p<0.001$). The proportion of CVS+ lesions in juxtacortical and infratentorial areas was higher in MS than migraine ($p=0.016$ and $p=0.034$ respectively). The best CVS proportion-based threshold able to differentiate MS from migraine was 23% (sensitivity 90%, specificity 90.5%). The "pick 6" rule seemed to be preferable in terms of specificity with respect to the "pick 3" rule.

Discussion and Conclusions: A CVS proportion-based threshold of 23% is capable to distinguish MS from migraine with high sensitivity and specificity. The "pick 6" algorithm may be useful in the clinical setting.

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THE EFFECT OF OCRELIZUMAB VERSUS ORAL HIGHLY ACTIVE IMMUNOTHERAPIES ON WHITE MATTER MICROSTRUCTURE IN RELAPSING REMITTING MULTIPLE SCLEROSIS

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Objectives: Data regarding the effect of intravenous (ocrelizumab, OCR) and oral highly active immunotherapies (fingolimod, FINGO and cladribine, CLAD) on tissue repair as evaluated by microstructural diffusion analysis and brain atrophy in relapsing remitting (RR) multiple sclerosis (MS) are still sparse. The aims of this study were to compare the impact of different immunotherapies (OCR vs FINGO/CLAD) on white-matter microstructure and brain volumes in a cohort of RRMS patients.

Methods: In this ongoing study, RRMS patients underwent 3T-MRI at the time of treatment start and at 12-months follow-up (FU). Changes in percentage-brain-volume-change (PBVC) and multi-compartment spherical-mean-technique (SMT) diffusion metrics of the normal-appearing-white-matter (NAWM) were evaluated with repeated measures ANCOVA adjusted for sex, age, disease duration, baseline EDSS.

Results: A total of 83 patients were included in the analysis, [55 OCR and 28 FINGO/CLAD; females: 61%; mean age, disease duration, ARR previous year: 37.8+10.7, 8.6+8.5 years, 0.6+0.7; median (range) EDSS: 2 (0-6)]. At 1-year FU, 3/55 (5.4%) in OCR group had new/gadolinium-enhancing lesions vs 5/28 (17.8%) in FINGO/CLAD group. EXTRAMD (extracellular water) and EXTRATRANS (myelin damage) decrease, together with INTRA (fiber integrity) increase, was more pronounced in the NAWM of OCR treated patients with respect to FINGO/CLAD group ($p<0.001$ for all metrics). A trend was noted in PBVC between the two groups (-0.46%OCR vs -0.85% FINGO/CLAD; $p=0.065$).

Discussion and Conclusions: We observed a more pronounced effect in reducing CNS inflammation and axonal damage and in promoting myelin repair within the NAWM in OCR group as compared to FINGO/CLAD treated patients. A beneficial trend on brain atrophy was observed in OCR group but it has to be confirmed in further analysis.

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METABOLOMIC PROFILE CHANGES DURING PREGNANCY AND PUERPERIUM IN MULTIPLE SCLEROSIS: EXPLORING THE RELATIONSHIPS WITH DISEASE ACTIVITY

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Objectives: Pregnancy represents a protective condition for women with Multiple Sclerosis (MS) but is often accompanied by post-partum disease reactivation [1]. Several clinical and MRI predictors of disease reactivation in the post-partum were identified, while laboratory biomarkers have been less investigated [1,2]. Metabolomics represents a promising approach for the search for biomarkers, as it can capture the dynamic multi-parametric responses of a biological system [3]. Based on these considerations, the present study aimed to evaluate the metabolomic profile of MS women compared to healthy women (HC) during the three different biologic phases of fertile life, pregnancy and puerperium, also exploring the possible relationship with post-partum MS reactivation.

Methods: Serum samples of women with MS and HC during fertile life, pregnancy and puerperium were collected. Samples were analyzed by high-resolution nuclear magnetic resonance spectroscopy. Univariate and multivariate statistics were performed, also with the pathways' analysis.

Results: The blood samples of 155 MS women free from disease modifying treatments (68 during fertile life, 49 during pregnancy, 38 during post-partum; mean age 33.8 ± 4.7) and 68 HC (28 during fertile life, 26 during pregnancy, 14 during post-partum; mean age 31.8 ± 4.5) were analyzed. Significant metabolic differences resulted by the comparison of the three different biologic phases were found in both MS (R2X=0,5; R2Y=0,5; Q2=0,3; p<0,00001) and HC samples (R2X=0,5; R2Y=0,7; Q2=0,4; p<0,00001), with altered pathways principally related to biosynthesis activity, oxidative stress, energetic pathways and aminoacids metabolism (i.e. glutamate, aspartate and glycine metabolism). A comparison of HC and MS samples at each different phase were also performed, showing the most significant metabolomic differences in fertile life (R2X=0,4; R2Y=0,4; Q2=0,3; p<0,00001). An increase in tryptophan levels has been reported in postpartum MS women; however, no correlation with the disease activity observed in 34.2% of MS cases has been reported.

Discussion: The comparison between MS and HC subjects reveals that the main metabolomic differences are driven by the disease state, with more evident differences in the fertile phase. During pregnancy and puerperium, despite the presence of the disease state, the metabolomic signature related to the presence of the foetus prevails on the MS features.

Conclusion: Further studies aimed at evaluating the relationship between the metabolomic profile and the biological phases of the woman affected by MS are necessary to improve knowledge about the protective role of the pregnancy and evaluate novel potential biomarkers predictor of the disease activity.

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PAIN AND PAIN COPING IN MULTIPLE SCLEROSIS: RELATIONSHIPS WITH BRAIN ATROPHY

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Objectives: Among the invisible symptoms of multiple sclerosis (MS), chronic pain is among the most distressing. Classified as neuropathic, nociceptive or mixed pain, chronic pain is reported in approximately 20% of patients, and in some cases, it is so severe that it represents "a disease within the disease" [1]. Several putative mechanisms of MS pain have been hypothesized, although the relationship with the structural damage is still partially clarified. Recently, a multi-dimensional model of chronic pain has been proposed, identifying emotional and cognitive factors as determinants of its interference on daily activities [2]. Based on these considerations, the present study aimed to explore the frequency of chronic pain in MS, also exploring the relationships of pain severity and interference with brain MRI measurements.

Materials and Methods: Demographic and clinical characteristics of MS patients were collected and each subject completed the VAS scale, to define the intensity of the chronic pain, and the "pain self-efficacy questionnaire", to assess the pain interference and pain coping [3]. The presence of depressive symptoms was also evaluated using the BDI-II version. Thus, the patients underwent brain MRI, and the volumes of the whole brain (WB), white matter (WM), grey matter (GM) and deep grey matter structures were estimated using SIENAX. Linear regression analyses were performed to assess the study aims.

Results: 52 MS patients [21 (40.4%) male] with mean age of 45.1 ± 9.5 years and mean EDSS score of 2.7 ± 1.7 points were recruited. Of these, 19 (36.5%) presented with neuropathic pain, 20 (38.5%) with nociceptive pain, and 6 (11.5%) with mixed pain. A relationship of the intensity of the chronic pain (VAS score) with the female gender ($p = 0.022$), the type of pain presented (neuropathic, $p = 0.028$) and the level of disability ($p = 0.011$) was observed. Thus, the "Pain Self Efficacy" score resulted associated with lower MS duration ($p = 0.017$) and BDI-II score ($p = 0.006$), also observing an association with thalamic volume ($p = 0.021$).

Discussion and conclusion: Several evidences show that the perception of chronic pain is conditioned by emotional and cognitive factors [3]. Thalamus is an important structure in cognitive processes of which coping strategies are an expression. Further studies aimed to evaluate the relationship between MS damage, chronic pain and other determinants, such as emotional and cognitive factors, are needed to understand the mechanisms underlying chronic pain and the possible interventions.

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NATALIZUMAB IMPROVES MOTOR FATIGUE BY RESTORING ABNORMAL BRAIN NETWORKS CONNECTIVITY AND SENSORIMOTOR NETWORK ACTIVATION IN PEOPLE WITH MULTIPLE SCLEROSIS

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Introduction: Motor fatigue is one of the most common symptoms in people with Multiple Sclerosis (pwMS) and neuroinflammation may play a role in its pathogenesis. Natalizumab, a disease modifying treatment known to reduce neuroinflammation, has been suggested to improve fatigue symptoms. Preliminary evidence from our group suggested that motor fatigue in pwMS may be due to abnormal fatigue-related increase in brain networks connectivity and sensorimotor network activation.

Objectives and Aims: We tested the hypothesis that natalizumab may improve motor fatigue in pwMS by modulating cortical networks dynamics.

Methods: Here we present preliminary results from 24 patients with relapsing remitting MS tested 7±2 days before (T0), and 14±2 days after (T1) natalizumab infusion. Motor fatigue symptoms were assessed by clinical scales. Participants were asked to perform repeated blocks of first dorsal interosseous muscle (FDI) maximal voluntary contraction (MVC) until exhaustion. We measured the motor endurance index as the number of completed blocks*force exerted, normalized across participants. Peripheral, central, and supraspinal motor fatigue were assessed by twitch interpolation method using peripheral nerve stimulation and transcranial magnetic stimulation (TMS) over the primary motor cortex. We also measured fatigue-related changes in brain networks resting connectivity by means of resting-state EEG-based small world index (SWI), and sensorimotor network activation by means of source reconstructed TMS-evoked potentials (TEPs).

Results: PwMS showed significantly lower Fatigue Symptoms and Impacts Questionnaire (7 days) score ($p = 0.003$), significantly higher motor endurance index ($p = 0.049$), significantly less central fatigue ($p = 0.034$), and a trend for a reduction in supraspinal fatigue ($p=0.05$) at T1 compared to T0. Fatigue was associated with opposite effects on SWI in theta frequency band ($p=0.02$) and on TEPs (FDR corrected permutation-based analysis $p < 0.05$) at T0 compared to T1. Theta SWI and TEPs were increased post-fatigue at T0, whereas both were decreased post-fatigue at T1 as previously observed in healthy controls.

Discussion: Symptomatic improvement in fatigue with natalizumab was associated with reduction in motor fatigue as quantified by the neuromuscular assessment. Natalizumab reduced motor fatigue in pwMS by acting on its central rather than peripheral mechanisms. Natalizumab also normalized the fatigue-related modulation of brain networks resting connectivity and sensorimotor network activation.

Conclusions: Our results support the hypothesis that natalizumab improves motor fatigue in pwMS by restoring abnormal fatigue-related modulation of brain network activity. Also, the time course of the effects we observed suggests that natalizumab-induced effects on cortical activity may be mediated by neuroinflammation modulation.

SWITCHING FROM FINGOLIMOD TO SIPONIMOD IN SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS: A CASE SERIES REPORT

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Background and objectives: As a selective modulator of sphingosine 1-phosphate receptors 1 (S1P1) and 5 (S1P5), Siponimod has recently been marketed nationwide for patients with Secondary Progressive Multiple Sclerosis (MS) with evidence of disease activity.

Methods and Materials: We present a case series of 3 patients presenting a relapse in the following 3 months after switching from Fingolimod to Siponimod.

Results: In all three cases patients were switched from Fingolimod to Siponimod without a wash-out period. Case 1: a 47-year-old woman was started on Siponimod in October 2021 after 10 years of therapy with Fingolimod. About 3 months after Siponimod initiation she experienced a relapse characterized by left lower limb and inguinal hypoesthesia. Treated with a course of intravenous methylprednisolone 1000mg daily for 5 days, she achieved a complete remission of her symptoms. Case 2: a 36-year-old man was switched in February 2022 from Fingolimod to Siponimod after 11 years of therapy. Forty-five days after Siponimod initiation, he developed profound hyposthenia of the right lower limb. After corticosteroid treatment with intravenous methylprednisolone 1000mg daily for 5 days, he reported a complete remission of symptoms. Case 3: a 46-year-old woman started treatment with Siponimod in November 2021 after 5 years of therapy with Fingolimod. After 3 months she presented a relapse characterized by objective vertigo with only a partial remission following administration of intravenous methylprednisolone 1000mg daily for 5 days. The first two patients had been relapse-free since 2018, while the third patient had presented a similar relapse the previous year.

Discussion: Evidence suggests that overexpression of S1P receptors in reactive astrocytes occurs following Fingolimod discontinuation. Siponimod does not bind S1P3, and it was hypothesized that upregulation of S1P3 may be the mechanism behind relapses after switching from fingolimod to siponimod, by triggering a proinflammatory cytokine cascade via activation of nuclear factor-κB. In our cases, this hypothesis appears reasonable as relapses occurred between 4 and 16 weeks after Fingolimod cessation and this is consistent with the long-half time of fingolimod of 6-9days.

Conclusions: Studies on larger samples are needed to explore the efficacy and safety of Fingolimod to Siponimod switch in SPMS.

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LONGITUDINAL ASSESSMENT OF BALANCE IMPAIRMENT IN MULTIPLE SCLEROSIS IDENTIFY PATIENTS WITH SILENT DISEASE PROGRESSION

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Background: Since balance maintenance requires several coordinated CNS functions, it is particularly susceptible to subtle continuous damage

occurring in patients with multiple sclerosis (MS). Longitudinal balance assessment could help identifying patients with silent progression not evident at clinical examination.

Objectives: To assess balance performance over time in a cohort of MS patients with a Standing Balance Test (SBT).

Methods: 122 MS patients (109 relapsing-remitting,13 progressive) and 65 healthy controls (HC) underwent SBT and full clinical examination. Patients had a follow-up evaluation after a mean of 12.7months (SD=5.6). Theta scores (higher values indicating better performance) were derived and corrected for age/sex/height/weight by nuisance regression. Z-score were calculated (scores below 1.5 SD were considered abnormal). A worsening of >=-1 Z-score point was considered clinically meaningful. Disability progression was defined as an EDSS>1 increase if baseline EDSS<5.5 and EDSS>0.5 otherwise.

Results: At baseline, patients had lower theta scores than HC (0.39 vs 0.85, p<0.0001) and 27/122 were classified as having balance impairment. Balance-impaired patients had higher EDSS scores than balance-preserved ones (1.9 vs 3.2, p<0.0001). At follow-up, 45/122 patients had a worsening in Z-scores, with 15 (12%) having a clinically meaningful worsening. Although a trend was noted between pyramidal functional-system scores and theta Z-scores (spearman-rho=-0.17, p=0.066), only 6/45 patients with worsening balance had disability progression based on their EDSS scores. Among patients with balance-worsening, only 2/45 experienced a clinical relapse which in one case resulted in increased EDSS score.

Conclusions: Longitudinal assessment with SBT could be an useful tool to early detect silent progression in patients with MS and to prompt intervention with a rehabilitation specialist.

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HUMORAL EFFICACY OF THE THIRD SARS-COV-2 VACCINE DOSE IN MULTIPLE SCLEROSIS SUBJECTS UNDERGOING DIFFERENT DISEASE-MODIFYING THERAPIES

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Objectives: Our study aim to analyse the different profile of immune responses after novel SARS-CoV-2 vaccination in patients with multiple sclerosis (pwMS), receiving disease-modifying therapies (DMTs). Decisions for the third (3rd) vaccine (booster) dose have been further promoted by the emergence of new SARS-CoV-2 variants but the different short term humoral response in pwMs underwent to DMTs is still unclear.

Methods: We evaluated the humoral response to the BNT162b2 booster dose in a monocentric cohort of pwMS undergoing eight different DMTs, all without previous SARS-CoV-2 infection. We enrolled 65 pwMS and 9 healthy controls (HC) receiving the third dose of vaccine according to the recommendations of Italian Authority of Health.

Results: We observed that the humoral response to the booster dose in Interferon β-1a (IFN), Dimethyl fumarate (DMF)- and Teriflunomide (TERI)-treated pwMS was comparable to healthy controls (HC), while increased in Cladribine (CLAD)-treated pwMS. Additionally, the 3rd dose elicited a seroconversion in the 100% of pwMS under Fingolimod (FTY) and in the 65% of those under Ocrelizumab (OCRE).

Discussion: A third SARS-CoV-2 vaccine dose considerably enhances anti-Spike-specific antibody response in pwMS, specifically in those patients with a slower and or weaker immune response.

Conclusions: These results underlie the importance of the booster dose to enhance SARS-CoV-2 specific immunity, especially in immunocompromised subjects, such as pwMS under DMTs.

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DEPRESSION AFFECTS THE PERCEPTION OF PHYSICAL FATIGUE AND COGNITIVE PERFORMANCE IN MULTIPLE SCLEROSIS PATIENTS

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Objectives: Multiple Sclerosis (MS) is an inflammatory, demyelinating, and neurodegenerative disease of central nervous system. Fatigue is a common and disabling symptoms of MS, which impacts negatively on the quality of life since the first stage of the disease. Moreover, cognitive impairment is frequent in MS patients in particular in processing speed. It is also necessary to consider some confounding factors, such as depression, anxiety, fatigue, and sleep disturbances since they may influence the cognitive profile of patients. The aim of the study is to investigate the correlations between cognitive and psychological factors in a cohort of MS patients from a single center, considering the effect of the physical fatigue on cognitive performances.

Materials and Methods: Two hundred consecutive outpatients recruited from Bari University Hospital between March 2021 and March 2022 underwent a complete diagnostic workup, including processing speed and working memory (Symbol Digit Modalities Test [SDMT], fatigue level, by Fatigue Severity Scale (FSS), and depression (Beck's Depression Inventory BDI). One hundred and forty - three (F= 128; mean age=40,37 yy; DS=12,39) were diagnosed with MS.

Results: Correlations were made between the scores at the SDMT, BDI and FSS and revealed statistically significant correlations between SDMT and FSS (r=-0,185; p=0,009), SDMT and BDI (r=-0,229; p=0,001), FSS and BDI (r=0,564; p=<0,001). Correlations were further investigated with a mediation analysis type. There were no statistically significant direct correlations between FSS and SDMT (p=0,339), but indirect correlation mediated by BDI (p=0,032): thus, the total effect of mediation analysis showed that correlation between FSS and SDMT (p=0,008) were statistically significant.

Discussions and Conclusions: Our findings showed that cognitive performance at SDMT was not affected by patients' perceived level of

physical fatigue, but by levels of depression. In particular the presence of a high BDI score mediates the physical fatigue on cognitive performance impact.

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DISABILITY AND RELAPSE-RATE TRAJECTORIES IN NAÏVE PATIENTS ON ORAL DRUGS: RESULTS FROM THE ITALIAN MULTIPLE SCLEROSIS REGISTER

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Objectives: The availability of oral DMTs, improved treatment optimization in Multiple Sclerosis (MS). However, the impact of their different mechanism of action on disability accrual and relapses, must be further defined. Therefore, we aimed to evaluate the long-term effect of different oral disease-modifying therapies (DMTs) on trajectories of disability and relapses in a large naïve MS population.

Materials and Methods: We performed a multicentre, observational, retrospectively acquired cohort study, evaluating data in longitudinal way. We included treatment-naïve, Relapsing MS (RMS) adult (current age ≥ 18 years) patients from the Italian MS registry. All included patients started fingolimod (FIN), teriflunomide (TER) or dimethyl fumarate (DMF) within 6 months from the first visit and were exposed continuously to the same drug for 5 years, followed-up with ≥1 EDSS per year. Trajectories of disability and relapse-rate were evaluated by applying a longitudinal model for repeated measures with an autoregressive variance-covariance structure. The estimated values were adjusted for sex, age at disease onset, clinical onset (monofocal/multifocal), time to first DMT, Relapses in the year before treatment, Annualized Relapse Rate (ARR) during the follow-up, number of relapses and EDSS score before DMTs. Changes of EDSS and relapse-rate were evaluated within and between FIN, TER and DMF at each semester for 5 years.

Results: From 70,493 patients in the Italian MS Registry (data extracted on 31st March 2021), 112 FIN, 60 TER and 206 DMF patients met the inclusion criteria. Disability trajectories of the groups, paired for the listed covariates, showed a similar pattern over time. Both FIN and DMF patients showed a significant increase in EDSS from the 6th semester ($p=0.039$ and 0.044 respectively), while in TER, EDSS variations were significant from the 5th semester. The mean estimated delta-EDSS differences between TER and FIN increased (from -0.02 to 0.43), reaching statistical significance in the 5th year ($p=0.027$), as well as between TER and DMF (from -0.03 to 0.51). Trajectories of relapse-rate showed a significant reduction in each group immediately after the treatment start. Estimated changes of relapse-rate at each 12-month period were all significantly ($p<0.0001$) higher in both DMF and TER compared to FIN group.

Discussion and Conclusions: In our real-life cohort, the three oral DMTs showed a similar long-term effect on disability progression, while FIN proved to be more effective on relapse-rate.

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FUNCTIONAL NEAR INFRARED SPECTROSCOPY (FNIRS) AND COGNITION IN EARLY MULTIPLE SCLEROSIS: PRELIMINARY RESULTS FROM A PILOT STUDY

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Aims: Functional magnetic resonance imaging studies report different patterns of brain activation in patients with Multiple Sclerosis (pwMS) versus healthy controls (HCs) during cognitive tasks. Functional near-infrared spectroscopy (fNIRS) is a flexible alternative for measuring cortical hemodynamics. Therefore, we evaluated fNIRS patterns in a cohort of early-stage pwMS who underwent cognitive tasks.

Materials and Methods: We enrolled 11 early pwMS (disease duration from clinical onset: 0.8±0.6 years) and 10 HCs, matched for age and gender, who were tested by Brief Repeatable Battery of Neuropsychological Tests. Learning of new verbal information

(Selective Reminding Test and Delayed), visuospatial memory (Spatial Recall Test and Delayed), processing speed and working memory (Symbol Digit Modalities Test and Paced Auditory Serial Addicton Task) and Semantic Fluency (Word List Generation) were investigated. fNIRS data were acquired for each subject to investigate the variations of oxyhemoglobin in the prefrontal cortex (PFC) during an auditory oddball paradigm task. Task duration was 12 min. Using nirsLAB, we pre-processed and filtered the signal in the band-pass 0.002–0.2 Hz. Signals were then converted to optical intensities, then into oxyhemoglobin concentration changes. Demographic and neuropsychological differences were investigated using ANOVA and z-score tests included in the SPSS statistics. We considered sex and age effect introducing them in ANOVA as factor and covariate, respectively. Student's t-test was used to identify fNIRS channels wherein oxyhemoglobin concentration differed significantly between the two groups.

Results: PwMS (70% female, mean age 38.1±6.1 years) showed no cognitive impairment or fatigue. Selective Reminding Test showed worse scores in pwMS, both considering the long-term retrieval (corrected value=0.87±1.41 in HCs vs -0.42±1.09 in pwMS, p=0.03) and the consistent long-term storage (corrected value=0.97±1.21 in HC vs -0.47±0.6 in pwMS, p=0.023). We also found a greater PFC hemodynamic activation ($p<0.05$) in the pwMS compared to HCs during the first 4 minutes of the task duration.

Discussions and Conclusions: Consistent with previous fMRI studies, our results using fNIRS, show that impaired learning of new information in early-stage pwMS requires greater hemodynamic activation of PFC.These findings suggest that fNIRS can be a valid alternative tool for the detection of altered patterns of brain activation in pwMS.

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FLU-LIKE SYNDROME DUE TO INTERFERON-BETA INJECTIONS IS NOT ASSOCIATED WITH INCREASED ANXIETY, DEPRESSION, AND LOST WORKING DAYS IN MULTIPLE SCLEROSIS PATIENTS DURING THE SARS-COV-2 PANDEMIC

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Introduction: Interferon-ß (IFNß) is considered to be a well-tolerated drug in Multiple Sclerosis (MS) patients; in 2020, in Italy about 15.000 patients were treated with IFNß and about 70.000 in Europe. Two-thirds of patients assuming IFNß, however, can present with flu-like syndrome (FLS), which may include fever, chills, headache, muscle pain, and weakness. FLS symptoms are similar to those of COVID-19 infection and sometimes the two conditions may be confused or overlap.

Objective: Aim of this study was to evaluated anxiety, depression, and possible negative implications on work activities during the Sars-CoV-2 pandemic, in a group of Multiple Sclerosis (MS) patients at risk of FLS compared with FLS- free treatments.

Methods: The present study included patients treated with IFNß, glatiramer, and natalizumab for at least one year. Collected data included the diagnosis of COVID-19 infection, Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI), together with questions about FLS, change in work habits, use of antipyretics, anxiety, and depression.

Results: 100 patients (50 IFNß, 25 GA, and 25 natalizumab) were included in the study. Six patients in IFNß and 5 in the natalizumab group had a confirmed COVID-19 infection. 68% in the IFNß patients reported FLS and only one reported an increase in flu-like frequency during the pandemic; 14% reported lower compliance with treatment, and 40% reported uptake of antipyretics several times. Only one IFNß patient reported having lost more working days than the previous year. The average BAI (p=0.039) was higher in natalizumab group. Only one IFNß patient reported having lost more working days than the previous year. Approximately the same number of patients in the three groups reported to have presented more anxiety and depression than usual during the pandemics. Correcting these data by age, sex and EDSS to a multivariate analysis we did not find any statistically significant difference in terms of BAI and BDI-II between the three treatment groups.

Discussion and conclusions: To date, no cases of severe Sars-CoV-2 infections in patients treated with IFNβ have been reported. FLS were not perceived as COVID19-like symptoms but as expected by traditional pharmacological treatments indeed. Our data suggest that IFNβ adherence remains unchanged and that FLS does not increase anxiety, depression, and lost working days in MS patients during the Sars-CoV-2 pandemic, and that IFNß can be used safely.

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PRELIMINARY DATA OF AN ITALIAN MULTICENTER OBSERVATIONAL STUDY ON REAL-LIFE EXPERIENCE WITH CLADRIBINE IN NAÏVE PATIENTS

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Introduction: Cladribine is a semi-selective IRT with high efficacy. It is a deoxyadenosine (purine) analog that induces selective and transient reductions of CD19+ B cells and T cells, followed by reconstitution of adaptive immune function. Nadir of lymphopenia is nine weeks with up to 12 weeks to recover.

Aim: To evaluate the efficacy and safety of cladribine in a population of MS naïve patients.

Methods: A multicenter observational study in a cohort of naïve MS patients treated with cladribine. 11 Italian MS Centers participated, integrating clinical and neuroradiological parameters collected from patient's clinical records.

Results: 54 patients were included in this study. 70,4% were females, mean age of 30 years (±8.3), mean disease duration of 16.7 months (±21). Basal median EDSS 1.5 (range 1-6), mean number of relapses in the previous year 1,20 (±0.71). The majority of patients presented more than nine but less than 20 T2 brain lesions at basal MRI, mean Gd-enhancing lesions 2.59 (±3.45), mean T2 spinal lesions 2.73 (±2.15), mean Gd-enhancing lesions 0.50 (±0.73). 38/54 patients received the second year of therapy, and 24 patients had a 24-month follow-up. Improvement of the EDSS at 24 months 0.54 points (±0.89). 92,1% of patients were relapse-free at 12 months, and 87,5% at 24 months. New T2 lesions were present on 14/39 at 6, 4/32 at 12, and 2/17 at 24 months MRI. 5/32 patients presented new Gd-enhancing lesions at 12 months MRI, no one at 24 months. NEDA-3 was 63,6%. Two patients interrupted therapy after the first year, one for lack of efficacy and one for side effects (hepatitis), and five interrupted after the second year for lack of efficacy. No severe adverse events were reported.

Conclusions: These preliminary data in active MS patients confirm cladribine's efficacy and safety. Promising data on NEDA-3, relapse rate reduction and MRI activity were observed. We think that a naïve patient is an ideal candidate for a treatment with a semi-selective IRT with high efficacy. Our cohort disclosed low disability, young age, and short disease duration. Furthermore, a more extended observation and a larger number of patients are needed to confirm this data.

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INTRATHECAL INFLAMMATION AND CORTICAL DAMAGE ASSOCIATE WITH DISABILITY PROGRESSION INDEPENDENT OF RELAPSES IN EARLY MULTIPLE SCLEROSIS

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Objectives: Focal cortical damage is a negative prognostic factor for multiple sclerosis (MS)-related disability, being evident since early disease phases and associated with intrathecal meningeal inflammation. We aimed to evaluate the association between intrathecal inflammatory markers, cortical lesions (CLs) and progression independent of relapse activity (PIRA) in the first years after a diagnosis of relapsing-remitting MS (RRMS).

Materials and Methods: We followed-up 82 patients with RRMS (63F/19M, mean age 38.9±12.2 years, median EDSS 2[0-3.5]) for 5 years. All patients underwent lumbar puncture at the time of diagnosis, with assessment of 69 CSF inflammatory markers using immune-assay multiplex technique. All underwent regular clinical and neuropsychological assessment including Expanded Disability Status Scale (EDSS) assessment and symbol digit modalities test (SDMT) and a yearly 3T MRI brain and spinal cord scans that included evaluation of white matter (WM) lesion number and volume, cortical lesions (CLs) and volume (CLv), Gad+ lesions and spinal cord lesions. PIRA was defined as an 1-year confirmed Expanded Disability Status Scale (EDSS) score increased from baseline by 1 (0.5 if baseline EDSS≥5.5, 1.5 if baseline EDSS=0) confirmed 1 year later without temporal association with confirmed clinical relapses and the loss of 4 points or a 10% decrease in the performance of the SDMT with respect to the previous examination.

Results: At the end of follow-up 27 patients (33%) had disability accumulation: of these, 22 showed disability progression independent of relapses. 16 patients had decreased SDMT performance. Taken together, 31 patients had PIRA (35%), with slight increased age (mean 41.3 ±11y vs 37.5±12.8y, p=0.055), CLs (5.6±5.9 vs2.5±3.1, p=0.017) and CLv (510±577mm3 vs 227±307mm3, p=0.018) when compared with those without PIRA. After applying a random forest approach using minimal depth and times to root measures to 69 all markers, 10 cytokines/chemokines including MIF, CCL2, sTNFR1, sTNFR2, CXCL12, CXCL13, Osteopontin, LIGHT, CCL3, CCL13 were significantly associated with PIRA.

Discussion and Conclusions: Intrathecal inflammation and CLs associate with early disability progression independent from relapses in the first years after a diagnosis of MS. Results need to be validated in a larger cohort with a longer follow-up, that would include other instrumental measures of early MS progression.

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION DOES NOT AFFECT PARAMAGNETIC RIM LESION NUMBER IN AGGRESSIVE MULTIPLE SCLEROSIS: A PILOT STUDY

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Introduction: In people with multiple sclerosis (pwMS) iron paramagnetic rim (PRL) lesions detected by MRi seem a valid biomarker of chronic active lesions - compartmentalized inflammation, but longitudinal data on the effect of disease-modifying treatments (DMT) on PRL are lacking [1]. Besides efficacy, DMT bioavailability within the central nervous system (CNS) is a prerequisite for acting on such inflammation, and highly CNS bioavailable and effective drugs are used as conditioning protocol during

BEAM - autologous haematopoietic stem cell transplantation (aHSCT) [2].

Aim: To investigate the effect of aHSCT on PRL in pwMS, longitudinally assessing the variation of PRL number.

Methods: Patients with aggressive MS treated with aHSCT underwent serial brain MRis with a standardized protocol including susceptibility-weighted imaging (3T device), either before and after aHSCT or following aHSCT only. PwMS receiving alternative DMT were scanned with the same protocol at two timepoints at least 6 months apart (control group). The presence and number of PRL and T2 lesion loads were analysed. Values are reported as median (range).

Results: AHSCT group: 10 pwMS, including 3 relapsing-remitting (RR) MS scanned before and 6 to 14 months after transplant; and 7 (3 RR; 4 secondary-progressive – SP) MS who received the first MRi 23 (5 - 50) months following aHSCT and the subsequent scan after 14 (10 – 21) months. Control group: 11 pwMS (6 RR, 5 SP); median interscan period: 7 (6 - 12) months. Age and disease duration at inclusion were 43.5 (28 – 51) years and 15 (5 – 26) years in the AHSCT group, and 43 (18 - 59) years and 12 (1 – 29) years in the control group, respectively. Before aHSCT, PRL were detected in 2 of 3 patients and their number was unchanged over follow-up; disability was stable or improved in all the cases. PRL were observed in 7/7 pwMS with post-aHSCT only scans (median PRL number: 4; 1 - 11) and in 9/11 control patients (median PRL number: 2; 1 -4), without any changes in the subsequent MRi. Baseline T2 lesion load was stable over follow-up.

Discussion and conclusions: According to these preliminary results, aHSCT seems not to affect PRL number in aggressive MS patients over a one-year follow-up, despite disability stabilization. As the iron rim may persist at lesion edges even if a DMT would remove CNS-resident inflammation, long-term prospective observation in larger patient populations is needed to properly explore the impact of aHSCT on compartmentalized inflammation.

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REBOUND AFTER FINGOLIMOD WITHDRAWAL: A WIDE SPECTRUM RANGING FROM ISOLATED RADIOLOGICAL ACTIVITY TO ALTERATION OF CONSCIOUSNESS

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Multiple Sclerosis (MS) is a chronic demyelinating disease of the Central Nervous System. Fingolimod is an effective and generally safe disease-modifying treatment for relapsing-remitting MS, but treatment discontinuation can lead to disease reactivation in several cases.

Aims: To determine the proportion of MS patients facing disease reactivation after discontinuation of treatment with Fingolimod. To describe the clinical characteristics of reactivation and rebound after treatment withdrawal.

Materials and Methods: We prospectively collected clinical and radiological data about patients who discontinued Fingolimod between 2017 and 2021. Demographic characteristics, age at onset, EDSS score, MRI data, duration of Fingolimod treatment, concomitant medications, washout period and subsequent treatment have been collected.

Results: 56 patients have been included in the study. Among them, 17 (30.3%) experienced some degree of clinical reactivation. 6 cases (10.7%) have been classified as rebound, with a definition based on clinical and radiological activity higher than expected considering disease activity before beginning treatment with Fingolimod. Rebound cases experienced a mean increase of 3.2 in EDSS score. Notably, 5/6 (83.3%) patients experienced a complete recovery after clinical worsening during rebound period.

Discussion: Severe reactivation is a major concern after Fingolimod discontinuation in MS patients. In our study, we observed a clinical spectrum ranging from mild sensory disturbances to life threatening disease reactivation, including coma. Younger age and longer washout period were associated with significant clinical reactivation. Notably, nearly all the patients who experienced severe reactivation experienced a complete recovery, from a clinical point of view, at 1-year follow-up.

Conclusions: Severe reactivation after fingolimod discontinuation should be treated promptly, to achieve the best possible clinical outcome. When properly treated, MS patients experience, in most cases, a full recovery even after extremely severe clinical pictures.

EXPLORING THE REASONS BEHIND OCRELIZUMAB INFUSIONS DELAY DURING THE FIRST WAVE OF COVID-19 PANDEMIC IN ITALY: RESULTS OF A SURVEY AMONG MS CENTERS

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Introduction: MS centers (MSc) activities related to OCR management were strongly and diffusely hit during the first wave of COVID-19 pandemic. Concerns were mainly related to its immunosuppressive effects and the need for in-hospital administration.

Objective: To investigate changes in OCR schedule among Italian MS centers participating to the Italian MS Register during the first wave of COVID-19 pandemic and to identify factors determining such changes.

Materials and Methods: A quick online survey was sent to 65 Italian MSc in order to collect from them the following data: macro-region (North, Center, South) location, number of OCR-treated patients, modifications of OCR schedule and a list of factors potentially influencing the postponement of OCR infusions (i.e. age, co-morbidity, MS phenotype, number of previous OCR cycles, disease severity/activity, CD-20 lymphocytes count, distance to MS center, fear of infection, inclusion in a research trial, infections trend, shortage of medical/paramedical staff for reallocation/infection).

Results: Among 55 MSc who answered the survey, 50 (91%) declared to have suspended or extended OCR interval dosing for at least one patient. The MSc that didn't modify OCR schedule were all from the South of Italy (33% of all South MSc). Main factors influencing OCR schedule delay were advanced age/co-morbidity (70%) and pandemic trend in the area (72%), while recent MS-disease activity hindered OCR schedule modifications (65%).

Discussion: This study shows that most Italian MSc decided either to delay or suspend OCR treatment during the first wave of COVID-19 pandemic. Advanced age and co-morbidity and no evidence of recent MS-disease activity were the most relevant patient-dependent predictors of OCR postponement. Among patient-independent factors the most relevant factor was the local trend of infections. Contrary to what expected, the shortage of medical and/or paramedical staff in MSc did not come out as relevant. The disruption of OCR schedule during the first COVID-19 pandemic wave in Italy mostly reflected the geographical distribution and the impact on the National Health System of COVID-19 pandemic.

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FATIGUE AND COGNITIVE IMPAIRMENT IN A COHORT OF MULTIPLE SCLEROSIS PATIENTS

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Objectives: Fatigue and cognitive impairment affect Multiple Sclerosis (MS) patients, up to 80% and 43–70% respectively. Fatigue represents one of most disabling symptoms. Despite this, they are little investigated in routine visits, not valued in Expanded Disability Status Scale (EDSS) score and not included in NEDA (no evidence of disease activity) criteria. We proposed to evaluate fatigue in a sample of MS patients and to investigate possible correlations with cognitive functions.

Materials/Method: 27 patients (15 females, 12 males), 86% with relapsing–remitting MS and 14% with progressive forms, were recruited from Umberto I Hospital (Rome). Neurological examination with EDSS scoring and following tests were conducted: Mini Mental State Examination to exclude a coarse cognitive impairment, Fatigue Severity Scale (FSS) to evaluate fatigue; Beck Depression Inventory to evaluate depressive symptomatology, Behavioural Assessment of the Dysexecutive Syndrome (BADS) to assess executive functions and Brief Repeatable Battery of Neuropsychological Tests (BRB-N). BRB-N allows to assess verbal memory (Selective Reminding Test [SRT]), visuospatial memory (Spatial Recall Test [SPART]), information processing speed (Symbol Digit Modalities Test [SDMT], Paced Auditory Serial Addition Test [PASAT]) and verbal fluency (Word List Generation [WLG]). T-test for independent sample (fatigued [FSS≥36] vs not-fatigued [FSS<36] patients) and correlations between fatigue and cognitive tests in all three samples (global group, fatigued and not-fatigued patients) were performed.

Results: Fatigue is present in 33% of patients. Alteration of verbal fluency, visuospatial memory, information processing speed, executive functions, verbal memory is present in 70%, 44%, 30%, 26%, 15% of patients, respectively. Mean values of cognitive scores in the two sample (fatigued and not-fatigued patients) show significantly lower SPART, PASAT and BADS scores in fatigued patients. Correlation analyses highlight, in the global sample, a weak inverse correlation between fatigue and BADS1 and BADS5 scores (p=0.05; p=0.06).

Discussion: Fatigue pathophysiology is still little understood: not all studies have found correlations between lesion load and fatigue. A possible explanation is that fatigue could be more caused by lesion location and normal appearing white matter alterations. All these factors could determine disconnection of relevant brain areas. In particular disfunction of circuits between frontal cortex, basal ganglia and thalamus can correlate with fatigue. Even at the base of cognitive impairment there can be alterations of brain circuits.

Conclusion: Presence of correlations between fatigue and cognitive scores may suggest that alteration of some cerebral circuits causes both fatigue and cognitive impairment. This could be used in therapeutic field.

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PREVIOUS DISEASE MODIFYING TREATMENTS INFLUENCE THE LYMPHOCYTE SUBSET KINETICS OF PEOPLE WITH MULTIPLE SCLEROSIS SWITCHING TO OCRELIZUMAB

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Background: Recently, concern has been raised about previous disease-modifying treatments (DMTs) and the influence they might have on the clinical efficacy of ocrelizumab (OCR). During the first six-month period of treatment with OCR, patients switching from fingolimod (SF) were found to have a higher clinical activity than those switching from natalizumab (SN). We aimed to evaluate whether the previous DMT affects the lymphocyte subset kinetics of people with Multiple Sclerosis (MS) switching to OCR and whether the lymphocyte subset kinetics influence the clinical response to OCR.

Methods: This is a multicenter retrospective study based on prospectively collected data, including patients who have started or switched to OCR between January 2018 and April 2021. We grouped them by prior DMT into naïve-to-treatment (NTT), SF and SN. Differences in lymphocyte subset changes among the three groups were compared using analysis of covariance. A linear mixed model was applied to compare subset changes between patients with and without early inflammatory activity.

Results: After adjusting for age, sex, disease duration and clinical phenotypes, CD4+ and CD8+ cell count decrease was more pronounced in the SN group than in either NTT ($p=0.004$ and $p<0.001$) or SF ($p<0.001$ and $p<0.001$) groups. CD4+ cell count decrease was more pronounced in NTT than in SF patients ($p=0.030$). Patients with early inflammatory activity showed a less pronounced CD8+ decrease than stable patients ($p=0,0332$).

Discussion: After withdrawing natalizumab more lymphocytes (and particularly B cells) are available in the blood compartment to be targeted by OCR, contributing to the higher magnitude of B and T cell reduction. OCR exerts a stronger effect on T cell subsets (particularly on CD8 T cells) compared to other anti-CD20 drugs. Furthermore, T cell reduction after OCR administration could also be related to the presence in the peripheral blood compartment of a T cell subset expressing on the surface the CD20 antigen.

Conclusion: Previous DMTs influence the lymphocyte kinetics of people with MS switching to OCR. CD8+ cell decrease might account for early clinical response to OCR. Reassessment of these findings over a larger population may help optimize the switch.

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SEVERE AND BILATERAL SIPONIMOD-RELATED MACULAR EDEMA RAPIDLY AND SPONTANEOUSLY RESOLVES AFTER TREATMENT CESSATION IN SPMS

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Background: Siponimod, a selective sphingosine-1-phosphate receptor (S1PR) 1 and 5 modulator, was recently approved for treatment of active secondary progressive multiple sclerosis (SPMS). Macular edema (ME) is the build-up of fluid in the macula, namely between the inner and outer plexiform retinal layers, and can be observed during treatment with S1P modulators. This adverse event seems to have a higher incidence with Siponimod compared to Fingolimod, and sometimes can be massive and alarming [1,2]. We report a case of severe and bilateral Siponimod-associated ME, completely resolved after only 13 days from therapy discontinuation, pointing out the spontaneous, rapid and full reversibility of this phenomenon at the treatment withdrawal even when the clinical picture is critical.

Case report: A 50-year-old woman was followed by our Multiple Sclerosis (MS) Centre for a 12-year history of relapsing-remitting MS, treated with Natalizumab since the time of diagnosis. Her past medical history was unremarkable, namely no history of diabetes and uveitis was reported. Due to both EDSS progression from 6.0 to 6.5 in the last 2 years, in absence of clinical relapses, and presence of mild C2 spinal lesion enhancement evidenced by MRI monitoring, in line with European Medicines Agency (EMA) indications, the patient was switched to Siponimod 2 mg per day. Her baseline optical coherence tomography (OCT) and ophthalmologic examination were normal. No side effects were reported from the patient for the first 3 weeks of treatment, but at this point she presented an acute bilateral blurry vision, in absence of either ocular pain or dyschromatopsia. Urgent ophthalmological examination revealed a visual acuity of 20/50 in the right eye, and 20/70 in the left eye, no significant alteration of automated visual field, and mild bilateral mydriasis. Fundus oculi showed loss of foveal reflex and OCT scan revealed a cystoid ME in both eyes, more pronounced in the left eye. Ocular anterior segment examination was normal. Siponimod was immediately discontinued, and after 13 days the patients reported visual function recovery. She was tested for best corrected visual acuity (BCVA) which was 20/20 in both eyes, and OCT examination showed complete reabsorption of ME. The patient did not show rebounds of the ME after 2 months of monthly OCT follow-up.

Conclusion: Our case points out the spontaneous, rapid and full reversibility of Siponimod-associated ME at the treatment withdrawal even when the clinical picture is critical.

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COGNITIVE AND MRI PROFILE IN PRIMARY AND SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS

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Objectives: Studies comparing frequency and patterns of cognitive dysfunction between primary progressive (PP) and secondary progressive (SP) multiple sclerosis (MS) have yielded conflicting results. We examined the neuropsychological profile of PPMS and SPMS and investigated the relationship between cognitive functioning with structural and functional MRI abnormalities.

Materials: One-hundred eighty-three progressive MS patients (60 PPMS and 123 SPMS) and 75 healthy controls (HCs) underwent 3.0T MRI. MS patients were administered the Brief Repeatable Battery of Neuropsychological tests (BRB-N).

Methods: Four cognitive domain z-scores were determined from normative data, and then averaged to obtain a measure of global cognition (z-BRB-N). Using hierarchical linear regression analysis, the contribution of lesion volumes, normalized brain volumes, white matter fractional

anisotropy (FA) and mean diffusivity (MD) abnormalities, and resting state (RS) functional connectivity (FC) alterations to global cognition in PPMS and SPMS was investigated.

Results: Compared to PPMS, SPMS showed decreased FA and increased MD in the fornix, and lower RS FC within the basal ganglia network. The frequency of cognitive impairment was 32% in PPMS and 41% in SPMS (p=0.19). No significant differences were detected in mean z-verbal memory, z-visuospatial memory, z-attention/processing speed, z-verbal fluency and z-BRB-N between PPMS and SPMS. Linear regression analysis showed that lower z-BRB-N in PPMS was associated with decreased FA in the medial lemniscus ($\Delta R2=0.11$; p=0.01) and lower normalized gray matter volume ($\Delta R2=0.29$; p<0.001), while in SPMS lower z-BRB-N was associated with reduced FA of the fornix ($\Delta R2=0.35$; p<0.001) and lower normalized white matter volume ($\Delta R2=0.05$; p=0.03).

Discussion: PPMS and SPMS had similar neuropsychological profile. Cognitive dysfunction in PPMS and SPMS was related to distinct patterns of structural MRI abnormalities and involvement of different white matter tracts, while RS FC alterations did not contribute to explain their global cognitive functioning.

Conclusions: The different disease courses of PPMS and SPMS do not seem to affect the cognitive functioning in a detectably distinct manner, however the underlying pathological mechanisms produce more pronounced diffusion tensor and RS FC MRI abnormalities in SPMS than PPMS. This reflects the different structural substrates that contribute to explain cognitive dysfunction in these clinical phenotypes of MS.

FERTILITY, PREGNANCY AND CHILDBIRTH IN WOMEN WITH MULTIPLE SCLEROSIS: A POPULATION-BASED STUDY FROM 2018 TO 2020

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Objectives: We aim to evaluate fertility, pregnancy and childbirth outcomes in women with multiple sclerosis (MS), when compared with the general population, and in relation to clinical features and disease modifying treatments (DMTs).

Methods: This population-based study is a retrospective analysis of routinely-collected healthcare data (including DMT prescriptions), prospectively recorded from 2018 to 2020, on women with MS living in the Campania Region of Italy. Fertility, pregnancy and delivery outcomes were obtained from the Certificates of Delivery Assistance. Linkage to clinical registry was used to extract disease duration, expanded disability status scale (EDSS), and relapses.

Results: Out of 2748 women with MS in childbearing age, 151 women delivered 154 babies, with crude pregnancy incidence rate of 1.17 per 100 person-years. General fertility rate was 56.76 live births per 1000 woman with MS in childbearing age, compared with 107.09 in the Campania Region and 101.45 in Italy. When compared with women with MS without pregnancy, women with MS with pregnancy had younger age (Coeff=-5.41; 95%CI=-7.80, -3.02; p<0.01), shorter disease duration (Coeff=-6.20; 95%CI=-10.08, -2.32; p<0.01), lower EDSS (Coeff=-0.65; 95%CI=-1.11, -0.20; p<0.01), and higher relapse rate (Coeff=0.28; 95%CI=0.02, 0.55; p=0.03). DMT continuation during pregnancy was associated with lower birth weight (Coeff=-107.09; 95%CI=-207.91, -6.26; p=0.03). Exposure to DMTs with unknown/negative effects on pregnancy was associated with higher probability of birth defects (OR=8.88; 95%CI=1.35, 58.41; p=0.02). In particular, we recorded 5 cases of birth defects (Klinefelter syndrome, cleft palate with cleft lip, ostium secundum, short frenulum of lip, and low birth weight with death in the following 7 days), in women exposed to dimethyl fumarate, fingolimod or natalizumab within 3 months from conception. After delivery, DMT escalation strategy was needed in 18.8% women with MS, while 50.7% started on same/similar-efficacy DMTs, and 30.5% did not receive DMT. The probability of breastfeeding was higher in women who were treated with breastfeeding-safe DMTs (OR=5.57; 95%CI=1.09, 28.55; p=0.03).

Conclusions: Fertility rates in women with MS remain far below the general population. Family planning should be discussed in the early stages of MS (i.e., younger age, lower disability, shorter disease duration). Subsequent DMT decisions should aim at successful pregnancy, delivery, and breastfeeding outcomes, while maintaining disease control.

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PEGINTERFERON BETA-1A FOR THE TREATMENT OF MULTIPLE SCLEROSIS IN THE CAMPANIA REGION OF ITALY

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Background and goals: We aim to describe the real-world use of peginterferon beta-1a for the treatment of relapsing-remitting multiple sclerosis (RRMS), and to compare with other injectable disease modifying treatments (DMTs).

Methods: In this population-based study, we used 2015-2019 routinely-collected healthcare data of the Campania Region of Italy (e.g., DMT prescriptions, inpatients, outpatients, and, for a subset of patients, clinical registry), and included individuals with RRMS receiving new prescriptions of peginterferon beta-1a (n=281; age=38.8±12.3 years; females=70.5%; disease duration=8.4±8.3 years; EDSS=2.0 (1.0-6.5)), glatiramer acetate (n=751; age=46.0±11.4 years; females=67.1%; disease duration=9.8±8.2 years; EDSS=4.0 (1.5-8.5)), and interferon beta-1a sc (n=1226; age=39.7±11.7 years; females=66.5%; disease duration=8.2 ±6.5 years; EDSS=2.5 (1.5-6.5)). We computed adherence (medication possession ratio, MPR), escalation to more effective DMTs, hospitalization rates and costs. We used mixed-effect linear regression models (for adherence, hospitalization rates and costs), and Cox regression models (for escalation), to evaluate differences between peginterferon beta-1a (reference), glatiramer acetate, and interferon beta-1a.

Results: Adherence was lower in glatiramer acetate (MPR=0.91±0.1) (Coeff=-0.11; p<0.01), and interferon beta-1a (MPR=0.92±0.1) (Coeff=-0.08; p<0.01), compared with peginterferon beta-1a (MPR=1.01±0.1). The probability of escalating to more effective DMTs was higher for glatiramer acetate (14.9%) (HR=4.09; p<0.01), and interferon beta-1a (9.1%) (HR=3.35; p=0.01), compared with peginterferon beta-1a (4.9%). We found no differences in annualized hospitalization rates between glatiramer acetate (AHR=0.05±0.30) (Coeff=0.02; p=0.31), interferon beta-1a (AHR=0.02±0.21) (Coeff=0.01; p=0.97), and peginterferon beta-1a (AHR=0.02±0.24), but monthly costs for MS admissions were

higher for glatiramer acetate (49.45±195.27 EUR) (Coeff=-29.89; p=0.03), compared with interferon beta-1a (29.42±47.83 EUR) (Coeff=6.79; p=0.61), and peginterferon beta-1a (23.91±43.90 EUR).

Conclusion: Peginterferon beta-1a and interferon beta-1a sc have been used in relatively similar populations, while glatiramer acetate was preferred in older and more disabled patients. However, peginterferon beta-1a was associated with higher adherence and lower escalation rates towards more effective (and costly) DMTs.

A LONG TERM POST-MARKETING OBSERVATIONAL MONOCENTRIC STUDY OF A POPULATION OF PATIENTS TREATED WITH DIMETHYL FUMARATE

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Objective: To date, long-term data of efficacy and safety of Dimethyl Fumarate (DMF) in relapsing-remitting multiple sclerosis patients (RR-MS) in real-world practice are poor. The aim of this study was to analyze long-term effectiveness and safety of DMF in RR-MS patients and to identifying predictive factors of efficacy.

Material and Methods: 838 patients who started DMF between January 2014 and July 2020 at San Raffaele Hospital MS Center were included with a mean follow-up of 39.5 months (±25.2). We analyzed the results for protocol.

Results: Among 838 patients, 40% were naïve, 37% switched from first-line treatment for intolerance and 16% for inefficacy, 7% switched from second-line treatment. ARR decreased from 0.63 at baseline to 0.12 and 0.05 at first and second year respectively ($p< 0.0001$), then remained low for over 5 years. A 72% and 84% of patients were relapse free and progression free at 5 years respectively. T1-gadolinium-enhancing lesions decreased from 0.39 at baseline to 0.25 and to 0.10 at first and second year respectively ($p < 0.0001$) and then remained low. In the global population, the percentage of patients NEDA-3 at 12, 24, 36, 48 and 60 months were 67.9%, 55.8%, 44.1%, 34.3% and 29.4%. The most frequent side effects reported were flushing (57.2%) followed by GI discomfort (40.2%) and lymphophenia (36.4%). Of total, 30% discontinued DMF: 14% stopped DMF due to inefficacy, 13.4% for side effects/intolerance (5.25% for GI effects, 5.36% for persistent lymphopenia and 0,7% for flushing and 2.6% for patients' choice). Predictive factors of discontinuation for inefficacy were age, ARR in previous year, MRI activity at baseline and disease activity at rebaseline. In our center due to acquired clinical experience, the 2017 was a watershed for a better patient's selection with a decrease of discontinuation rate for inefficacy from 19.2% to 8%.

Discussion: To our knowledge our observational study is the study with the longest FU in real-word practice. Our data confirm long-term safety and efficacy of DMF and high persistence with the drug due to disease control and good quality of life.

Conclusions: Despite the actual debate in favour of the use of high efficacy over lower efficacy drugs since early phase of the disease, DMF can be considered as initial treatment for patients with low/moderate disease activity and without negative predictive factors due to its favorable benefit-risk profile. However in these patients, is important a close monitoring in order to make a vertical switch in case of sub-response.

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AN ITALIAN LONG TERM REAL LIFE PROSPECTIVE OBSERVATIONAL STUDY IN NAÏVE HIGHLY ACTIVE MULTIPLE SCLEROSIS PATIENTS TREATED WITH ALEMTUZUMAB: MEAN FOLLOW-UP OF 5 YEARS

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Objective: Alemtuzumab (ALEM) is an anti-CD52-monoclonal antibody approved for the treatment of active Multiple Sclerosis (MS) which showed higher response in the highly active (HA)subgroup of patients in clinical trials.

Aim: To evaluate long term efficacy and safety of ALEM-treatment in HA-naïve-patients.

Material and Methods: We conducted a multicenter prospective observational study in a cohort of ALEM-HA-naïve MS patients. Clinical

and radiological parameters were collected from patients' clinical records in 28 MS-Centers from October 2015 to August 2019.

Results:138 naïve patients:60,8% females, mean age 36,6(± 11,6) years, mean disease duration 18,45(± 24,9) months, mean follow-up (FU) 61,03 (35,2-89,77) months, median EDSS 3(0-6,5), ARR in the year preceding treatment 1,7 (± 0,9), mean number of brain T2/FLAIR-hyperintense lesions 29,8(± 20,8) and mean number of Gd-enhancing lesions 3,4(± 5,1). Regarding ALEM efficacy, we report data obtained after the first complete cycle of treatment because the presence of disease activity between the two courses is not indicative of a therapeutic failure. All 138 pts had at least 36 months of FU, 36 of 4 and 93 reached 5 years.71% (98/138) were relapse-free, ARR was 0,18 and the mean time to first relapse was 17,96(± 3,75) months;61,6% were MRI activity-free;78,3% were progression-free with median EDSS of 2,0(IQR 1-2);53,6% (74/138) was NEDA-3. Most of the patients who did not reach NEDA-3 had evidence of minimal disease activity. 8(5,7%) patients due to disease activity underwent a third cycle of ALEM while 15 patients started a new drug:7 shifted to ocrelizumab(3 due to disease activity while the remainings for safety/concern issues during COVID-19 pandemic), 4 to natalizumab(all of them due to choices during COVID-19);2 to modulator S1P-receptor due to disease progressive phase, one to rituximab and the last one underwent a-HSCT due to disease activity. Overall 74,4% had adverse events:70,1% infusion-reactions and 9,8% infections. Regarding secondary autoimmune diseases: 22,2 % of thyroid dysfunctions and 3 cases of immune-thrombocytopenia, agranulocytosis and vitiligo. Overall patients reported a very good quality of life. There were 10 pregnancies with healthy babies.

Discussion: Our study to our knowledge is the first to show long-FU data in ALEM-HA-naïve MS patients in a real-life setting. After ALEM-treatment a strong reduction of both relapse rate and MRI activity was achieved.

Conclusions: These results strengthen the assumption that the aggressive-naïve-patient is an ideal candidate for immune system resetting, likely due to young age, short disease duration, low disability and probably due to the absence of previous treatments altering the immune system. However, a larger number of patients and a longer FU is needed to confirm our data and evaluate whether an early induction therapy could be worthy in this specific population, balancing benefit-risk ratio.

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DID THE INTRODUCTION OF THE SARS-COV-2 VACCINE INFLUENCE THE CHOICES OF THERAPY IN PATIENTS WITH A NEW DIAGNOSIS OF MULTIPLE SCLEROSIS?

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Introduction: Since the beginning of the Sars-Cov-2 pandemic, several evidences have been gathered on the use of Disease Modifying Drugs (DMTs) in patients with Multiple Sclerosis (MS) [1]. As is well known, the pandemic has changed the management of MS as well as changed the previously applied therapeutic choice paradigms [2]. The introduction of the Sars-Cov-2 vaccine marked a turning point for MS patients, considered among "fragile patients" [3].

Aims: The objective of this study is to describe changes about the use of first-line DMTs in patients with a new diagnosis of MS, comparing the semester before and after the start of vaccination campaign for Sars-Cov-2.

Methods: The study included patients newly diagnosed with MS according to McDonald's 2017 criteria. The proportion of patients initiated into the use of Interferon Beta (IFN), Dimethylfumarate (DMF) and Teriflunamide (TERI) was defined as a proportion for the previous semester (October 2020- March 2021) and subsequent (April 2021 – September 2021) to the avaibility of Sars-Cov-2 vaccine. The determinants of the choice of first-line DMTs were evaluated through regression analysis.

Results: The study included 134 patients, including 40 (29.9%) male, average age of 38.3 ± 12.3 years, disease duration of 3.0 ± 4.6 years, average EDSS of 1.7 ± 1.1. Among these, 75 (56%) patients started a first-line DMTs in the semester before the start of vaccination campaign [IFN 13 (9.7%), TERI 6 (4.5%), GA 28 (20.9%), DMF 28 (20.9%)], while 59 (44%) in the following semester [IFN 4 (3%), TERI 11(8.2%), GA 12 (8.9%) and DMF 32 (23.9%)]. A reduction of 40% and 53% respectively in the use of GA and IFN was observed in the semester following the start of the vaccination campaign. In contrast, an increase of 29 % in the use of TERI and 6% in the use of DMF respectively was reported in the semester following the start of the vaccination campaign. The regression analysis shows the use of injection therapies (IFN and GA) being associated with female gender (p= 0.032) and with the previous semester to the availability of Sars-Cov-2 vaccine (p=0.006). In contrast, the use of TERI is associated with male gender (p=0.031) and with the following semester the introduction of the vaccine (p=0.05). About the use of DMF, a relationship with the post-introduction semester of the vaccine has been observed (p=0.037); beyond this, the relapse rate in the previous 2 years is the strongest determinant in the choice of this treatment (p=0.001).

Conclusions: Our data show how the start of the vaccination campaign for Sars-Cov-2 influenced the use of first-line immunotherapies in patients with new diagnosis of MS.

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COMPARISON OF FIRST AND SECOND LINE THERAPIES: THE EXPERIENCE OF THE PEDIATRIC MS CENTER OF THE BAMBINO GESÙ CHILDREN HOSPITAL

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Objectives: The primary objective of the study is to compare pediatric populations with MS being treated with I and II line drugs. The secondary objective is to identify any clinical, MRI or laboratory characteristics that may guide the choice of treatment.

Materials and Methods: A retrospective analysis was carried out of pediatric patients with Multiple Sclerosis who have received diagnoses from 2015 to date and who have started treatment with disease-modifying drugs. The clinical, laboratory and neuroradiological characteristics of the patients who received first and second line treatment were compared in the statistical analysis.

Results: The data of 55 patients with MS (F 62% vs M 38%) with a mean age at onset of 13.5 ± 3 years (range 4 to 17.7) were analyzed. The choice of therapy undergoes a trend reversal after 2018, the year of approval of the first second-line drug for the pediatric age. Before that year, 20 out of 23 underwent therapies with first-line drugs, while from 2018 the choice fell mainly for the second (27 patients vs 5 patients). In particular, patients with polyphocal and cerebellar symptoms, with lesions of the cerebellar peduncle, spinal cord, brainstem and corpus callosum and contrast enhancing lesions, undergo II-line therapy more often. The relapse rate is also significantly lower with second-line drugs (3%) than with first-line drugs (48%).

Discussion: Considering the impact of disease activity on brain atrophy, cognitive impairment and development of secondary progressive MS at a younger age, we would recommend treating pediatric MS as a highly active disease, favoring the early use of highly effective DMTs rather than injectable DMTs.

Conclusions: Early treatment and the criteria for choosing the most appropriate drug, based on clinical, laboratory and MRI characteristics at onset, represent an essential basis for greater therapeutic efficacy in pediatric-onset MS.

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EVALUATION OF PARAMAGNETIC RIM LESIONS AS A MARKER OF DISABILITY

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Background: In multiple sclerosis (MS) brain lesions with a paramagnetic rim (PRL) detected by brain magnetic resonance imaging (MRi) are considered a potential biomarker of chronic inflammatory active lesions and presence of >4 PRL/ patient seems to correlate with disability accumulation. In this study this correlation was evaluated in a large cohort of patients.

Methods: MS patients under treatment and with disease activity (n=119) were included (RR, n= 99; SP, n= 20). Each of them received one conventional MRi scan with 3D-EPI susceptibility weighted image (SWI) acquired with a 3T scanner for the detection of PRLs. MRi data were compared with the clinical characteristics of the patients by descriptive and multivariate analysis. Data were expressed as medians and ranges.

Results: Overall, the patients with PRL were 73/119 (61,3%), PRL number/patient = 3,3 (1-18), the RR 57/99 (57.6%) PRL number= 1,9 (0-18), the SP 16/20 (80%, p<0,05), PRL number = 2,8 (0-10). EDSS= 3.5 (0.0-8.5), disease duration 14,1 years (0-40), previous year ARR 0.11 (0-1), age 48,6 (23-69). Bivariate analysis between PRL presence and baseline clinical and demographic parameters showed association with EDSS that was confirmed by multivariate analysis indicating independently association, but not with other clinical/demographic characteristics as age ARR or disease duration. In addition, multiple linear regression analysis showed high correlation between EDSS and PRL number (r= 0,98; p= 0,001) in the RR patients, but not in the SP patients.

Conclusions: In RRMS, presence of PRLs correlates with disability. Noteworthy one single PRL seems sufficient to increase high EDSS development risk. Also of note is that disability - usually most strictly associated with spinal cord lesions showed strong correlation with a disease marker located in the brain as PRLs. No correlation instead was observed at the higher EDSS values observed in the SP patients despite a higher PRL number/patient in these patients, probably because of a ceiling effect.

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EFFECT OF AUTOIMMUNE COMORBIDITIES ON MULTIPLE SCLEROSIS DISEASE COURSE

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Aims: To assess the effect of autoimmune comorbidities (AC) in patients with relapsing-remitting Multiple Sclerosis (PwRRMS) on clinical and neuro-radiological disease activity and disability progression.

Materials and Methods: In this observational, retrospective, multicenter study we included PwRRMS affected and not by AC diagnosed before and/or at the MS onset. All consecutive PwRRMS [1], visited from July 1st 2020 to January 31th 2021 (T1), with disease duration ≤ 10 years from the onset of MS symptoms, belonging to 14 Italian MS Centers, were enrolled. We considered eligible as "cases" all patients suffering from ≥1 autoimmune diseases (without other comorbidities), not needing immunosuppressive/immunomodulatory therapies (e.g., type I DM, etc.), with a retrospective follow-up (FU) to the time of the visit of 36 months (T0). All PwRRMS visited in the same periods of 'cases', without AC and the same FU, were enrolled as Reference group.

Results: We enrolled 866 PwRRMS, of which 211 with and 655 without AC. PwRRMS and AC were older at MS diagnosis (36 vs. 31.7 yrs; p<0.001), mainly females (77.3% vs. 67.6%; p=0.010) and with a higher EDSS score at diagnosis (2 vs. 1.5; p<0.001). Thyroid diseases was the most common coexisting AC (50.7%), followed by rheumatologic (14.7%) and dermatologic (10.0%) disorders. The higher EDSS score at T0 (1.5 vs 2.0; p<0.001) persisted also at T1 (p=0.024) in cases. The progression index (EDSS score/disease duration) was higher among cases (2 vs 2.5; p=0.042). Focusing on pre-post differences in the two subgroups, a significant increase in the no. of clinical relapses (p=0.038) and in the EDSS score (p<0.001) was observed among Reference group. The interaction logistic regression models confirmed the significantly positive prognostic role of the interaction between a lower disease duration and the presence of AC (OR 0.92, 95% CI 0.86-0.97, p=0.005).

Discussion: Our data showed that, the presence of AC delays the MS diagnosis, favouring a higher EDSS score at diagnosis probably caused by the delay in starting therapy. Conversely, PwRRMS without AC showed a higher disease activity and disability progression at FU. To date, only few studies have evaluated if the burden of AC may influence the MS disease course, with controversial results [2]. Our data suggest a protective role of AC in the MS course.

Conclusions: The presence of AC delay the MS diagnosis but it is associated with a better MS disease course.

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DISCONTINUATION OF BOTULINUM TOXIN TREATMENT FOR SPASTICITY SYMPTOMS IN MULTIPLE SCLEROSIS

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Objectives: Botulinum toxin is an effective treatment for spasticity symptoms in patients with multiple sclerosis (MS). Despite its wide use, only few studies have explored long-term persistence. We aim to evaluate the rate of discontinuation of botulinum toxin treatment and correlation with MS, spasticity, and injection variables.

Methods: This retrospective study on 3-year prospectively collected data included 122 MS patients receiving botulinum toxin injection for spasticity. We collected MS clinical (disease duration, expanded disability status scale (EDSS), disease modifying treatment (DMT), and symbol digit modalities test (SDMT)), spasticity (modified Ashworth scale (MAS), concomitant treatments) and injection variables (formulation, dose, number of injections, interval between injections).

Results: 14 out of 122 patients discontinued botulinum toxin treatment after a mean time of 3.0±1.5 years. In the Cox regression model including MS variables, the probability of botulinum toxin discontinuation increased in patients with DMT change during follow-up (HR= 6.34; 95%Cl=2.47, 18.08; p<0.01), and with impaired SDMT (HR=1.20; 95%Cl=1.04, 1.96; p<0.01). In the model including spasticity variables, there were no associations with MAS or other spasticity treatments. In the model including injection variables, the probability of discontinuation decreased by 80% for each cumulative injection (HR=0.16; 95%Cl=0.05, 0.45; p<0.01), but increased by 1% for each additional day on the top of the 3-month interval between injections (HR=1.27; 95%Cl=1.07, 1.83; p<0.01).

Conclusion: Botulinum toxin discontinuation was associated with concomitant MS-related issues (e.g., treatment failure and DMT change), and presence of cognitive impairment, which should be accounted for when planning botulinum toxin injections. Interval between injections should be kept as short as feasible from regulatory and clinical perspectives, to maximise response across all spasticity symptoms and reduce discontinuation in the long term.

SPECIFICITY AND POSITIVE PREDICTIVE VALUE OF FIXED CELL-BASED ASSAY FOR MOG ANTIBODY TESTING: A SINGLE CENTER EXPERIENCE

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Objective: To determine the specificity and positive predictive value (PPV) of myelin oligodendrocyte glycoprotein (MOG)-IgG testing by fixed cell-based assay (CBA) in a single center cohort of patients with new-onset demyelinating disorders of the central nervous system (CNS).

Materials and methods: Serum samples from adult patients (age >18 years) with new onset CNS demyelinating disorders consecutively seen at the Neurology Unit of the University Hospital of Sassari between January 2021 and April 2022 were tested for MOG-IgG by commercial fixed CBA. Patients with positive test result but clinical-MRI phenotypes not consistent with MOG-IgG-associated disorder (MOGAD) were designated as having a false MOG-IgG positivity. Serum of patients who tested positive for MOG-IgG by fixed CBA were re-tested by live CBA at the Neuropathology Laboratory of the University of Verona.

Results: A total of 26 patients were tested for MOG-IgG by fixed CBA over 16 months; 2 (7%) patients tested positive. The first of the

two patients with MOG-IgG positivity had an isolated longitudinally extensive transverse myelitis and concomitant positivity for aquaporin-4 (AQP4) -IgG on serum. The clinical-MRI pheotype was considered consistent with MOGAD and MOG-IgG positivity was confirmed by live CBA. The second patient presented after two attacks of brain demyelination over 3 years in the context of multiple CNS lesions on MRI consistent with multiple sclerosis (MS), 2 cerebrospinal fluid (CSF) restricted oligoclonal bands and elevated IgG index (1.21). Based on the clinical-MRI phenotype, MOG-IgG positivity was considered a false positivity in the second patient. Live CBA did not confirm the positive test result. Overall, our findings translate into a specificity of fixed MOG-IgG testing of 96.1% and a PPV of 50%.

Discussion and conclusions: In our single center real-life cohort, fixed CBA for MOG-IgG showed a high specificity but a considerable risk for false positive results when performed indiscriminately on consecutive patients with new-onset CNS demyelinating disorders. Live CBA has a greater specificity than fixed.

PROFILING THE RISK OF SEVERE ADVERSE EVENTS DURING SEQUENCING THERAPIES IN PATIENTS WITH MULTIPLE SCLEROSIS: PRELIMINARY DATA FROM AN OBSERVATIONAL COHORT ANALYSIS BASED ON ITALIAN MULTIPLE SCLEROSIS REGISTRY

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This analysis aims to assess, during different therapeutic schemes of Disease-Modifying Therapies (DMTs) for a large cohort of Italian Multiple Sclerosis (MS) patients, the risk of Severe Adverse Events (SAEs). We included Relapsing (R) and Secondary Progressive (SP) patients with MS (pwMS), aged ≥18 years, treated with at least one DMT. We considered nine therapeutic sequences: 1°Line (Interferons/Glatiramer Acetate/Teriflunomide/Dimethyl Fumarate/Azathioprine); 2°Line Long (2°LineL) (continuous therapy: Fingolimod/Ocrelizumab/Rituximab/Natalizumab/Siponimod); 2°Line Short (2°LineS) (pulsy therapy: Alemtuzumab/Mitoxantrone/Cladribine/Cyclophosphamide/Methotrexate). The SAEs evaluated were: infections, grade III-IV lymphopenia and neoplasms, in according to MedDRA classification available on Web application of Registry. Data was extracted in January 2022. Baseline characteristics of the patients (number, percentage of males, age and EDSS at first DMT, time from onset to the first treatment start) are described as median and interquartile range, and percentage, as appropriate. The rates of SAEs are represented as events every 1000 patients. When the patients switched from one drug to another, the incidence of SAEs is assessed in each therapeutic period. From a sample of 50,039 subjects, the selected cohort included 22,237 patients. Age at first DMT ranged, among the different groups from 32.1 to 42.9 years, while the percentage of male patients from 27.6 to 36.7%. The time from onset to the first drug is between 12.8 (in patients switching from 2°LineL to 2°LineS) and 62.0 months (2°LineS). EDSS at first DMT prescription was lower in patients starting 1°Line and those switching from 1°Line to 2°LineL (2.0). The incidence of evaluated SAEs varied between the therapeutic schemes. Infections are more frequent in 2°Line treated patients than those in 1°Line (6.32 vs 46.56). Also neoplasm were more frequent in the 2°Line than in the 1°Line (9.57 vs 2.50). In patients switching from 1st to 2nd line, the incidence of SAEs was higher in the 2nd line period. Surprisingly, lymphopenia was reported more frequently in patients treated with 1°Line than those in 2°Line. These preliminary results are interesting for further analysis. Based on the mechanism of action of the different drugs, the unexpected findings related to lymphopenia are probably affected by the under reported data. Based on this exploratory analysis, a careful evaluation of the different SAEs during the therapeutic patient journey will be need to compare the different drug sequences using more appropriate complex models.

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FATIGUE IN MULTIPLE SCLEROSIS: AN ANALYSIS OF FLUCTUATIONS OF SPONTANEOUS EEG TOPOGRAPHIES

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Objectives: Fatigue affects approximately 80% of people with Multiple Sclerosis (PwMS). This symptom involves all aspects of patients' lives with a significant impact on their quality of life. Despite several studies have demonstrated an alteration of neural networks of the brain, the possible link between fatigue symptoms and the functioning of resting-state networks is largely unknown. Aim of this study is to investigate the differences of spontaneous fluctuation of EEG microstates (McSt) in a group of fatigued PwMS (patF-PwMS) compared with a group of non-fatigued PwMS (normoF-PwMS) and with patF and normoF healthy controls (HCs). McSt were evaluated across frequency bands.

Materials: A total of 44 PwM and 24 HCs were enrolled. EDSS>3 and cognitive impairment were posed as exclusion criteria. All participants underwent an administration of Modified Fatigue Impact scale (MFIS) and a 15-min resting-state high-density EEG recording (256ch).

Method: Each recording was filtered 1-30Hz, ICA-corrected for artifacts, down sampled to 256Hz and then filtered into the 5 traditional EEG frequency bands (delta, theta, alpha1, alpha2, beta). A set of voltage maps representing the EEG activity, across broadband and frequency bands, were detected by McSt analysis. Differences in the temporal dynamic of McSt between groups were assessed using parametric (T-test) or non-parametric (Mann-Whitney) statistical tests according to the normality test; alpha=0.05.

Results: No significant difference was found in the patF percentage among PwMS and HCs (26% and 17% respectively; p=0.373). A strong trend to higher values in MFIS total scores distribution was found for PwMS compared to HCs. PwMS had significantly higher values in the MFIS subscale of physical fatigue than HCs (p=0.039). We found a total of six McSt across participants. McSt-6 (related to salience network) showed a significantly decreased activity for broadband, theta and alpha1 in patF-PwMS than in normoF-PwMS. In HCs, McSt-1 (related to auditory network) was significantly increased for broadband and low frequencies in patF-HCs than in normo-HCs.

Discussion: Altered fluctuations of EEG topographies in microstate analysis were observed in participants experiencing pathological levels of fatigue regardless if they were PwMS or HCs. However, these alterations

in EEG topographies were different in nature: a decrease in McSt-6 activity, correlated to salience network characterized the patF-PwMS, while an increase in McSt-1 activity, related to auditory processing, was found in patF-HCs.

Conclusions: A better knowledge of the neural mechanisms underlying MS fatigue will lead in future to more effective treatment strategies.

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IMPACT OF CYTOMEGALOVIRUS ON IMMUNOPHENOTYPE OF NATURAL KILLER CELLS AND CD8+ T CELLS IN MULTIPLE SCLEROSIS

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Aims: Cytomegalovirus (CMV) causes a persistent infection which may have a multifaceted impact in multiple sclerosis (MS) [1]. However, its influence remains controversial [2]. Many studies reported the close association between CMV and expansion of Natural Killer (NK) cells expressing the activating receptor NKG2C, as well as the expansion with senescent CD8+ T-cell [3]. In the present study, we aimed to characterize the NK-cell and CD8+ T-cell immunophenotype to evaluate the potential influence of CMV on MS disease progression.

Materials: At the Neuroinfectious Unit of Policlinico Umberto I Hospital, untreated MS patients and Healthy Donors (HDs) were enrolled and the following parameters were evaluated: sex, age, disease duration and EDSS (Expanded Disability Status Scale).

Methods: Serum, plasma samples and peripheral blood mononuclear cells (PBMC) were collected. On serum and plasma samples, respectively, CMV serostatus and CMV DNA were evaluated. For a patient subgroup, PBMC were examined by flow cytometry to characterize NK- and CD8+ T-cell immunophenotype; by median fluorescence intensity (MFI), NKG2C expression levels on CD56dimCD57+ NK cells were evaluated. Correlations between immunophenotype and clinical parameters were also investigated.

Results: Overall, 74 MS patients (39 M/35 F) with median age [IQR] 51 [43-58], median disease duration 11 [6-19] and median EDSS score 5.0 [3.5-6.0] were enrolled. Results showed that 69% (51/74) of MS patients were CMV-seropositive and 16% (12/74) resulted positive for CMV DNA. A significantly higher expression levels of NKG2C (409[274-1304] vs 318[195.5-424] respectively, p=0.041) and a lower T cells percentage in MS compared to HD (68.9[62.3-71.3] vs 75.3[70.4-78.9] respectively, p=0.001) were observed. According to CMV serostatus, CMV seropositive MS patients showed a significantly higher expression levels of NKG2C (600.5[375.5-1597] vs 197[0-399] respectively, p=0.008), higher CD56dimCD57+ NK cells percentage (36.5[26.2-43.1] vs 20.0[10.3-30.1] respectively, p=0.021) and higher NKT cells percentage (1.6[0.8-3.7] vs 0.5[0.2-0.6] respectively, p=0.008) compared to CMV seronegative MS patients. NKG2C expression levels were significantly higher in CMV seropositive MS patients compared to CMV seropositive HD subjects (600.5 [375.5-1597] vs 320 [210-750] respectively, p=0.022). Moreover, NKG2C levels were positively correlated with EDSS (r=0.439, p=0.022) and disease duration (r=0.423, p=0.028).

Conclusions: We provide data supporting the CMV impact on NK phenotypic changes in MS. The NKG2C expression levels significantly higher in MS patients appear to be related to EDSS worsening, suggesting a CMV putative detrimental role on MS progression.

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THE ROLE OF PALLIATIVE CARE IN THE REVISION OF THE PDTA COMPANY MULTIPLE SCLEROSIS AUSL FIDENZA, PARMA, ITALY

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Back in 1996 the American Academy of Neurology Ethics and Humanities Sub-Commettee recommended that "since many patients with neurological diseases die after a long course of illness during which the neurologist represents the clinical figure of reference, it is imperative that neurologists understand and apply the principles of palliative medicine" (AAN 2016). An estimate of CP needs in Multiple Sclerosis (MS) can be defined on the basis of its prevalence, approximately 109,000 (Battaglia 2017): MS is an example of a highly complex chronic neurodegenerative disease, whose optimal organizational model resides in the PDTA. The PDTA represents the multidisciplinary response to the disease. The Neurology Unit of Fidenza represents the AUSL reference center for MS and as such has an independent PDTA, born in 2011/2012 and updated in 2018 as well as modified in 2021 with the inclusion of ethical-legal considerations and guidelines for early care in the field of Palliative Care, in light of the needs and rights of the MS person, well defined and protected by the Association Italian SM (AISM) in the 2020 agenda. The effort was to try to decline the different moments / stages of the disease in which the CP can enter the field, defining the possible setting of action, based on the concept of DISABILITY with 4 levels A, B, C, and D (EDSS 0-2.5 / 3-5.5 / 6-7.5 / 8-9.5) and different levels of complexity of the disease: level I (low, palliative approach), level II (low-complex, palliative approach / shared care), level III (complex-very complex / shared care) and level IV (high complexity / specialist palliative care). By crossing these objective data, I tried to define the different areas, IV levels, the last of which can be defined as SM END STAGE:LEVEL IV of disability, enticement, sick person and family with severe psychological, social, spiritual suffering, pain control requiring high doses of analgesics, need for enteral feeding (PEG, SNG) for

dysphagia / malnutrition, presence of dyspnoea or hypoventilation with C.V. <50% or pneumonia from aspiration, loss of motor functions in at least two parts of the body, difficulty in verbal communication,

asthenia, cognitive disorders, recurrent infections. The revision of the PDTA was carried out in the dual capacity of neurologist and palliative care practitioner, in the light of the recent II level Master obtained

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IMPACT OF MENOPAUSE ON BRAIN ATROPHY IN MULTIPLE SCLEROSIS: A PRELIMINARY MRI STUDY

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Objectives: While the effect of pregnancy on disease activity is well described in literature, the role of menopause in influencing multiple sclerosis (MS) trajectory represents a controversial issue. Recent evidence shown a significant association between menopause and MS progression, however the impact of hormonal changes on MRI findings is still little explored [1]. This study aims at investigating possible role of menopause in influencing MS course under a clinical and radiological perspectives. In particular, results on the association between menopause and brain atrophy in terms of whole brain volume (WBV), white matter volume (WMV), gray matter volume (GMV), and cortex volume are presented.

Materials: The study included women over 40 years of age diagnosed with MS according to McDonald's criteria and recruited from Multiple Sclerosis Centre, Cagliari, Italy. Demographic and clinical characteristics were collected and each patient was interweaved on menopause status. Presence of disease activity on the past two years was defined on clinical relapse rate and neuroradiological changes in terms of new T2 lesions and/or presence of gadolinium-enhancing lesions on MRI scan. Data on WBV, WMV, GMV, and cortex volume using the SIENAX software were also sought.

Method: This is an observational nested case-control study. Menopausal and non-menopausal MS patients were compared for clinical and radiological characteristics. Multiple linear regression analysis was used to examine the association between brain volumes, included as dependent variables in the model, and the menopausal status, while controlling for demographic (age) and clinical variables (disease duration and EDSS score).

Results: A sample of 70 MS patients with a mean EDSS score of 3.7 ± 2.1 was included in the analysis. 48 (68.8%) patients were menopausal with a mean age at menopause onset of 49.2 ± 4.3 years. Mean age of non-menopausal women was 46 ± 4.3 years. When compared for clinical relapses, menopausal patients reported reduced rate than the non-menopausal group ($p<0.05$). Moreover, WBV was lower in menopausal patients ($p=0.036$) evaluated by T-test; in line, multivariate analysis showed a significant association between reduced GMV and menopausal status ($p=0.026$).

Discussion: Strong evidence shows that estrogens play a neuroprotective role on brain microenvironment and an anti-inflammatory effect linked to its modulating action on the immune system [2]. Our preliminary results suggest that menopause could promote brain atrophy and a subsequent shift into a more progressive phase of the disease.

Conclusion: Menopause may represent a negative prognostic factor for MS progression.

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SEROPREVALENCE AND SEROCONVERSION OF JCV ANTIBODIES IN NATALIZUMAB-TREATED MS PATIENTS

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Objectives: Progressive multifocal leukoencephalopathy (PML) is a highly disabling disease of the central nervous system (CNS) caused by John Cunningam virus (JCV). Natalizumab-treated multiple sclerosis (MS) patients represent a high-risk category [1]. The worldwide estimated anti-JCV antibody prevalence in MS patients is 57.1% [2]. STRATIFY JCV™ (Focus Diagnostics, Cypress, CA) is used to detect anti-JCV antibodies and represents a risk stratification tool for PML in clinical practice. The present study aims to explore the frequency and timing of anti-JCV antibody seroconversion in natalizumab-treated multiple sclerosis (MS) patients and to explore possible determinants associated with baseline JCV status.

Materials: The study included a cohort of natalizumab-treated MS patients recruited at Multiple Sclerosis Centre, Cagliari, Italy and screened for anti-JCV antibodies by STRATIFY JCV™ test. Data on anti-JCV antibody screening at baseline and at semiannual determinations from patients who carried out natalizumab for at least one year were included. Demographic and clinical characteristics as well as prior expositions to immunosuppressors were also sought.

Method: This is an observational retrospective cohort study. Multiple regression analysis was used to examine the association between JCV seroconversion and clinical MS features, included as dependent variables, while controlling for demographic (sex, age) variables. Paralleling, multiple regression analysis was used to examine the association between natalizumab discontinuation with baseline JCV Ab status and JCV seroconversion, which were included in the model as dependent variables, while controlling for demographic and clinical variables.

Results: The study included 221 MS patients and 116 (52.65%) had a baseline JCV+ status. An association between JCV+ status with age (p 0.005), disease duration (p 0.05) and duration of natalizumab exposure (p 0.005) was reported. 24/105 (22.8%) JCV- patients seroconverted over time and 90% in the first 3 years. Regression analysis showed an association between JCV seroconversion and previous exposure to immunosuppressors (p 0.024). Finally, an association between discontinuation of natalizumab and JCV + baseline (p 0.001) and JCV seroconversion during treatment (0.001) was observed.

Discussion: Our results show that previous exposure to immunosuppressants, an important determinant in PML risk stratification, may also

influence seroconversion over time. In addition, both baseline anti-JCV status and seroconversion over time may influence the choice of natalizumab treatment.

Conclusion: Previous exposure to immunosuppressants, baseline anti JCV status and the timing of seroconversion are important prognostic determinants for the choice and duration of natalizumab treatment in MS patients.

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OCRELIZUMAB USE IN THE REAL WORLD: EXPERIENCE IN A LARGE SARDINIAN COHORT

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Objectives: Ocrelizumab (OCR), acting by depletion of the CD20+ B cells, is shown to be a highly effectiveness drug on disease inflammatory activity and progression for both relapsing-remitting (RR), active progressive and primary progressive multiple sclerosis (MS) patients [1]. The present study aimed to evaluate in the real world setting the trend in OCR use over the last 5 years, including the two-year period of the pandemic, also exploring possible predictors of therapeutic response according the NEDA 3 criteria (No Evidence of Disease Activity) [2].

Methods: Demographic and clinical features of progressive (P) and relapsing remitting (RR) patients exposed to OCR, categorized as naive or switchers from I° and II° line DMTs, were analysed. NEDA-3 status at 24 months was evaluated for RR patients by the three assessment components (no clinical relapses, no Expanded Disability Status Scale progression, no radiological activity). Determinants of therapeutic response were also explored by using regression analysis.

Results: The sample included 285 MS patients, of which 260 (91.2%) were RR and 25 PMS (8.8%). RR patients were categorized as naive (34;13.1%) and switchers from I° (140;53.8%) and II° line (86;33,1%) disease modifying treatment (DMTs). An increase of OCR use boh in PP and RR patients from 2017 were observed, included in the last two years, despite the SARSCov 2 pandemic. NEDA-3 status was calculated for 83 RR patients after 24 months of OCR treatment and achieved in 68 (83,1%) of these. Analyzing the predictors of response to OCR, a lower baseline age both in naïve (p=0.01) and switchers (p=0,03), and in switchers a lower MS duration (p=0.016) with lower latency to start OCR (p=0.05) were associated with achievement of the NEDA-3.

Conclusions: Our real-world experience confirms Ocrelizumab as highly effectiveness drug for naïve, vertical and horizontal switchers. Age and MS duration were confirmed as factors influencing treatment response, in line with current literature data indicating that "early is better than late treatment, but late is better than never" [3].

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CHARACTERIZATION OF THE TOLERABILITY PROFILE OF THE BNT162B2 VACCINE IN PATIENTS WITH MULTIPLE SCLEROSIS

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Introduction: Vaccination against SARS-coV-2 was strongly recommended for patients with multiple sclerosis (MS) as soon as this vaccine was available, regardless of the treatment with disease-modifying therapies (DMTs). [1] Both the nature of the disease and the mechanism of action of DMTs has led to the insertion of people with MS in priority groups for the vaccination. From April to July 2021 a vaccination hub dedicated to people with MS was created in the Regional Centre for diagnosis and treatment of Multiple Sclerosis the Binaghi Hospital in Cagliari. This contributed to the faster immunization of patients with MS and allowed to collect data about the safety and tolerability profile of vaccination against SARS-coV-2.

Objective: To analyze the frequency of adverse drug reactions (ADRs) following the administration of the BNT162b2 vaccine (Comirnaty) in people with MS; to describe the possible relationships of ADRs with demographics and MS clinical characteristics.

Materials and methods: The study included MS patients which received the BNT162b2 vaccine at the hub vaccination site of the MS Centre of the University of Cagliari. Demographical (age, sex) and clinical (EDSS, DMT) data were also recorded. A questionnaire designed ad hoc was administered to each patient in order to assess any side effects following vaccination.

Results: The study included 397 patients, of these 128 (32,2%) were male. The mean age was 49.7 years (± 15.3 SD), the mean EDSS score was 2.2 (± 2.3 SD). The frequency of ADRs after first and second dose were, respectively: pain at the injection site 64.7% and 38.6%, fatigue 33.5% and 31.5%, headache 20.1% and 14.4%, muscle/articular pain 20.4% and 17.3%, chills 10.1% and 14.2%. 2.5% of the patients reported new onset of neurological symptoms following the vaccination. No severe ADRs were reported. A logistic regression analysis performed to study the association of ADRs severity with clinical and demographic factors, showing that an older age (p=0.001) and female sex (p=0.032) were associated with a more pronounced perception of the ADRs. An association with ADRs perception and the use of interferon beta (p=0.04) was also reported.

Conclusions: The study showed a good safety and tolerability profile of the BNT162b2 vaccine in patients with MS. It is reasonable to postpone the administration of interferon for a few days in order not to increase vaccine related side effects.

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HIPPOCAMPAL ATROPHY IN PATIENTS WITH EARLY MULTIPLE SCLEROSIS AND ITS CORRELATION TO MEMORY IMPAIRMENT

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Introduction and Aims: Hippocampal atrophy represents a relevant measure in multiple sclerosis (MS), particularly in association with memory impairment. Studies on the structural and functional correlates of hippocampal damage and its subfields in the early disease course are lacking. To assess regional hippocampal atrophy in a large multicenter dataset of early MS and to investigate the association of hippocampal abnormalities with memory impairment using a voxel-based approach.

Materials and Methods: From the Italian Neuroimaging Network Initiative (INNI) dataset, we selected volumetric 3D-T1W brain images acquired at 3T on i) 219 early (disease duration <5y) Relapsing-Remitting (RR) MS patients (150F, 34y +10, EDSS: 1.5 [1-2]) who underwent Selective Reminding Test (SRT) and Spatial Recall Test (SPART) and ii) 246 age and sex-matched healthy controls (HC) (133F, 34y+9). Left and right hippocampal binarized masks were obtained following the EADC-ADNI protocol. Voxel-based analysis (VBM) was performed to select regionally atrophied hippocampal areas in RRMS and to select, within the regional areas significantly atrophied in RRMS, the voxels correlating with clinical scores. Finally in a post-hoc analysis projecting back hippocampal clinically significant regions in the native space, the correlations between volumes stratified for subfields (as obtained by using FreeSurfer) and clinical scores was further evaluated. Significant results ($p<0.05$, in VBM corrected for multiple comparisons) are reported.

Results: Early RRMS showed lower volumes in the whole, right and left ($p<0.001$ for all) hippocampi compared to HC. In RRMS, lower volume of the right hippocampus correlated with SRT and SPART performance ($p<0,01$, corrected). Spearman analysis demonstrated a selective involvement of right hippocampal subfields. Specifically, atrophy of right cornus ammonis (CA1) and tail correlated with SRT impairment ($r=0.28$ for both). CA1 atrophy also correlated with SPART ($r=0.27$) ($p=0.01$l). No correlation was found between memory impairment with other subfields of right hyppocampus and with left hippocampal subfields.

Discussion and Conclusions: Hippocampal atrophy represents an early event in RRMS. The relationship between atrophy of the right hippocampal subfields (mostly CA1) and impairment of verbal and spatial processing tests suggests that deficits in the memory processes are relevant since the early phase of the MS.

CLINICAL AND ECONOMIC BURDEN OF COMORBIDITIES IN MULTIPLE SCLEROSIS

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Introduction: Comorbid conditions are common in persons with multiple sclerosis (pwMS) and can lead to poorer outcomes negatively impacting on MS course, delay of diagnosis, progression of disability, treatment management and adherence. Existing literature has examined the economic cost of MS [1], however, evidence is lacking on the specific contribution of comorbidities to this burden. The aim of the study was to quantify the clinical and economic burden of comorbidities in pwMS, providing estimates based on a bottom-up approach related to main component of costs (health, non-health care cost and productivity loss).

Methods: The study is a retrospective study carried out in two Northern Italy areas (Pavia and Genoa). The presence of main comorbidities was investigated through an anonymous self-assessment questionnaires. Costs were compared between pwMS with at least one comorbidity vs. pwMS without comorbidity. Adjusted incremental costs associated with comorbidities were reported using general linear models with log-link and gamma distributions or two-part models (for cost components > 5% zero values). Models were controlled for age, sex, educational and disability levels; robust sandwich-type variance estimator was used to account for clustering within MS Centers.

Results: Six hundred pwMS were included in the analysis. 51.0% had ≥1 comorbidity. Hypertension (21.0%), depression (15.7%) and anxiety (11.7%) were the most prevalent comorbidities. The average annual total cost per patient was 18,500€ and 14,533 € for those with ≥1 comorbidity and without comorbidity, respectively. The total cost remained significantly greater when at least one comorbidity was present, with an incremental cost amounted to 3,311 € after controlling for age, sex, educational and disability levels (<0.001). The main components of costs resulted increased in comorbidity group, being incremental costs significant for health care costs and productivity loss (1,077 €, $p<0.001$ and 333 €, $p=0.046$, respectively) after controlling for potential confounders.

Conclusion: Presence of comorbidities increases the complexity of patient management and have health, social, and economic consequences for pwMS. These data can provide a more complete picture for the economic implications in MS to health and non-health care providers and policy makers.

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PROGRESSION INDEPENDENT OF RELAPSE ACTIVITY IN PEDIATRIC-ONSET MULTIPLE SCLEROSIS

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Objective: Disability accrual in Multiple Sclerosis (MS) can occur as relapse-associated worsening (RAW) or progression independent of relapse activity (PIRA). We evaluated the proportion of PIRA in paediatric-onset (PO)MS patients, as compared with that occurring in adult-onset (AO)MS patients.

Materials and Methods: Clinically isolated syndrome and relapsing-remitting (RR)MS patients assessed within one year from onset and with follow-up ≥5 years (n=5169) were extracted from the Italian MS Registry and grouped by age at onset in POMS (<18 years, n=323) and AOMS (>18 years, n=4846). Confirmed disability accrual (CDA) was defined by an increase in Expanded Disability Status Scale (EDSS) score confirmed at 6 month and classified per temporal association with relapses. Predictors of PIRA and RAW were assessed using multivariable Cox regression models.

Results: Over a follow-up period of 12.2±6.1 years, PIRA accounted for 44.8% of CDA events in POMS and 61.7% in AOMS (p<0.001). Focusing on the first 5 years of follow-up, PIRA accounted for 43.1% of CDA events in POMS and 55.2% in AOMS (p=0.045). In both cohorts, PIRA was associated with longer disease duration (POMS: HR 3.43;95CI 1.18-10.02, p= 0.024; AOMS: HR 1.51, 95CI 1.23-1.85, p < 0.001). In AOMS PIRA was also associated with lower EDSS (HR 0.89;95CI 0.86-0.94, p<0.001), lower number of relapses before the event (HR 0.93;95CI 0.9-0.95, p<0.001), RR course (HR 1.45;95CI:1.29-1.63, p<0.001) and older age (HR 1.03;95CI:1.02-1.03, p<0.001). As for RAW events, in both cohorts they were associated with younger age (POMS: HR 0.86;95CI:0.78-0.95, p=0.004; AOMS: HR 0.99,95CI:0.98-0.99, p=0.020). In POMS RAW was also associated with female sex (HR 2.2,95CI:1.29–3.89, p=0.005) and longer disease duration (HR 2.72,95CI:1.03-7.19, p=0.043); in AOMS with RR course (HR 1.52;95CI:1.31-1.77, p<0.001), lower EDSS (HR 0.92;95CI:0.87-0.98, p=0.005), higher number of relapses before CDA (HR 1.07;95CI:1.05-1.09, p<0.001). In both cohorts, longer exposure to disease modifying drugs (DMDs) reduced the risk of PIRA and RAW (p<0.001).

Discussion/Conclusion: PIRA is less frequent in POMS than in AOMS. However, a substantial proportion of POMS patients can experience PIRA events, even during the early phase of the disease. Notably, in either group, treatment with DMDs was effective in reducing the risk of both PIRA and RAW.

SILENT PROGRESSION AND "HIDDEN" SYMPTOMS IN RELAPSING-ONSET MULTIPLE SCLEROSIS PATIENTS

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Objectives: Recent evidence demonstrates progression independent of relapse activity (PIRA) starting from the early stage of relapsing-onset multiple sclerosis (MS). To better characterize early PIRA events, we assessed whether PIRA can involve different functional systems (FS) on the Expanded Disability Status Scale (EDSS) as compared with relapse associated worsening (RAW) at first confirmed disability accumulation (CDA) event.

Materials and methods: Relapsing-onset MS patients with follow-up >/= 5 years (n=16,130) were extracted from the Italian MS Registry. CDA was defined by an increase in EDSS score confirmed at 6 months and classified per temporal association with relapses. EDSS-FS involved in PIRA and RAW events at first CDA were compared using logistic multivariable regression analyses.

Results: Over a follow-up of 11.8 + 5.4 years, a total of 8,998 (55.8%) patients experienced at least one CDA. PIRA (n=6,162) accounted for 68.5% of first CDA events. Data on EDSS-FS were available in 6,394 patients. Seventy-nine percent of CDA involved 2 or more FS, without differences between PIRA (79.3%) and RAW (79.6%, p=0.782). In the multivariable analyses (adjusting for sex, age, EDSS, disease course, disease duration, type of onset), PIRA involved more frequently bowel and bladder functions (OR=1.29; 95%CI 1.15-1.44; p<0.001) and cerebral functions (OR=1.54; 95%CI 1.32-1.79; p<0.001). On the other hand, RAW involved more frequently pyramidal (OR=1.13; 95%CI 1.01-1.27; p=0.040) and sensory functions (OR=1.16; 95%CI 1.04-1.29; p=0.006).

Discussion/conclusion: In a large, real-world relapsing-onset MS cohort, PIRA was mainly associated with worsening of "hidden "symptoms, such as bowel and bladder functions, cognition and fatigue. Accurate monitoring of these functions and symptoms from the early stage of MS can improve the detection of "silent progression". The analysis on different EDSS-FS involvement in multiple RAW-PIRA events is ongoing.

FETAL EXPOSURE WITH PONESIMOD TREATMENT ACROSS CLINICAL DEVELOPMENT STUDIES

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Targets: Multiple Sclerosis (MS) is 3 times more common in women than in men, typically diagnosed between the childbearing ages of 20-50 Limited data are available for the class of S1P receptor modulators in pregnant women. Based on animal studies, adverse effects on embryofetal development and teratogenicity have been noted. Women of childbearing potential should use effective contraception to avoid pregnancy during treatment with S1P receptor modulators, and for certain period following discontinuation (based on the respective half-lives and clearance periods). We report the outcomes of pregnancies occurring in the ponesimod (PON) clinical development program, despite study protocols requiring a negative pregnancy test at enrollment and use of reliable contraception by women of childbearing potential

Materials: The analysis included women exposed to PON during pregnancy in the PON clinical development program.

Method: Pregnancy outcomes were evaluated in women exposed to PON during pregnancy across all phase 2 and 3 studies including long-term safety extensions.

Results: Across all studies, including 1062 women, 20 pregnancies with fetal exposure to PON during the first trimester were reported as of September 2021. Nineteen pregnancies were reported in patients with MS (n=990, receiving PON 20 mg (n=17) or other doses (n=2). Of the 20 pregnancies, outcomes were reported in 18 with 6 normal newborns, 8 induced abortions (no indication of fetal toxicity in 5 cases, benign hydatidiform mole in 1 case, unknown in 2 cases), and 4 spontaneous abortions; outcomes not reported in 2 pregnancies (pregnancy ongoing and lost to follow-up [1 each]). Among the 12 cases of abortion, fetal abnormalities were reported as unknown in 11, and the remaining one case was a benign hydatidiform mole. All pregnancy cases were assessed by the investigator as not related to study treatment, except for 1 case of benign hydatidiform mole and 1 case of spontaneous abortion.

Discussion: The proportion of spontaneous abortions in patients with MS (3/19, 15.8%) was within range of that reported for the general population (14.2%-20.9%) and the unexposed MS population (4.3%-21.2%). Based on the limited clinical data, there is no evidence of teratogenicity with PON treatment. Recognizing the importance of collecting more information on pregnancy exposure, a multinational Pregnancy Outcomes Enhanced Monitoring (POEM) program has been established to record prospective data on pregnancy outcomes in women exposed to PON.

Conclusions: Women of childbearing potential should use effective contraception to avoid pregnancy during PON treatment and for 1 week after discontinuation.

PONESIMOD IN RELAPSING FORMS OF MULTIPLE SCLEROSIS – LONG-TERM POOLED SAFETY RESULTS FROM THE CLINICAL DEVELOPMENT PROGRAM

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Targets: Ponesimod is an orally active highly selective modulator of the sphingosine-1-phosphate receptor 1 (S1P1) approved in multiple countries for the treatment of relapsing forms of multiple sclerosis (RMS). The Phase 2 and 3 clinical development program of ponesimod monotherapy in MS includes two completed double-blind, controlled studies (AC-058B201 and AC-058B301/OPTIMUM) and two ongoing long-term extensions (LTE) studies (AC-058B202 and AC-058B303/OPTIMUM-LT). This safety analysis was undertaken to provide a comprehensive safety perspective of ponesimod in RMS and to characterize the overall safety profile of ponesimod 20 mg in a large and robust 'long-term' pooled dataset.

Materials: This analysis focuses only on patients in the ponesimod 20mg arm.

Method: The long-term pool included patients who received ≥1 dose of ponesimod in the completed double-blind studies or their ongoing LTE studies (data collected up to and including 18 March 2020).

Results: A total of 1148 patients treated with ponesimod 20 mg were included in this analysis. The total mean exposure to ponesimod in the 20-mg arm was 2.834 years (3253.21 patient years). Of these, 855 (74.5%) patients were receiving ongoing ponesimod 20 -mg treatment as of March 2020. The incidence of treatment-emergent adverse events (TEAEs) and serious AEs (SAEs) was 87.1% and 11.1%, respectively. Most TEAEs were mild or moderate in intensity. TEAEs classified as severe were reported in 8.8% of patients in the ponesimod 20 -mg arm. TEAEs leading to discontinuation occurred in 8.9% of patients. One death was reported (sudden death in a patient with multiple cardiovascular factors and history of peripheral vascular disease and vascular surgery - not considered related to ponesimod treatment). The most frequently reported (≥10% of patients) TEAEs by preferred term for the ponesimod 20-mg arm were nasopharyngitis (19.7%), alanine aminotransferase increased (17.9%), headache (13.0%), and upper respiratory tract infection (11.0%). In the 20-mg arm, the most frequent SAEs (>1.5%) by system organ class were infections and infestations (2.2%) and nervous system disorders (1.7%). Overall, the incidence of malignancies was low with 0.3% of patients in the ponesimod 20 mg arm reporting basal cell carcinoma and one patient, malignant melanoma. There were no cases of

progressive multifocal leukoencephalopathy, cryptococcal meningitis infection or any other opportunistic infections with fatal outcome.

Discussion: The safety profile, including the pattern and nature of TEAEs, was consistent with TEAEs reported from the individual clinical trials as reflected within the product labelling.

Conclusions: No unexpected safety findings were identified in this analysis.

COGNITIVE RESERVE MODULATES THE IMPACT OF FRONTAL LOBE DAMAGE ON EXECUTIVE FUNCTIONING IN MULTIPLE SCLEROSIS

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Objectives: Early-life enriching experiences may influence frontal lobe maturation and may preserve executive function (EF) integrity in multiple sclerosis (MS). In this study, we investigated the interaction between cognitive reserve, frontal gray matter (GM) atrophy and white matter (WM) tract microstructural abnormalities and their associations with EF in MS patients.

Material and Methods: Frontal GM volumes, lesional volume, fractional anisotropy, mean diffusivity, intracellular volume fraction and orientation dispersion index of frontal WM tracts were quantified in 93 MS patients and 27 matched healthy controls (HC). Cognitive reserve index (CRI), Wisconsin Card Sorting Test (WCST) and Word List Generation (WLG) of the Rao's battery were assessed. Interaction of structural MRI measures and CRI on cognitive performance were explored.

Results: MS patients vs HC showed diffuse frontal GM atrophy and WM tract microstructural abnormalities ($p \leq 0.046$) and worse performances in categories and total errors of WCST and WLG ($p \leq 0.034$). In MS, higher CRI was correlated with better WLG performance, WCST-categories, frontal gyri volumes and diffusivity measures of frontal WM tracts (r from -0.212 to 0.455; $p \leq 0.046$). The combination of demographic, clinical and MRI measures of frontal lobe structural damage significantly explained EF (WLG: $R2=0.44$; $p=0.022$; WCST categories: $R2=0.33$; $p=0.010$). Higher CRI explained a further portion of variance in WLG (WLG: $R2=0.50$; $p=0.002$; $\Delta R2=0.07$; $p=0.003$).

Discussion: In MS, CRI is associated with higher frontal GM volumes and better frontal WM tract microstructural integrity. CRI may contribute to preserve semantic verbal fluency and cognitive flexibility, possibly moderating the effect of frontal lobe structural damage on cognitive performance.

Conclusions: The application of a multiparametric MRI approach may contribute to disentangle the mechanisms underlying the beneficial role of cognitive reserve in limiting the detrimental effects of brain structural damage in MS patients.

MULTIPLE SCLEROSIS AND PULMONARY LANGERHANS CELL HISTIOCYTOSIS: MULTIFACTORIAL ASSOCIATION?

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Background: There is no evidence about the relationship between Multiple Sclerosis (MS) and Langerhans cell histiocytosis (LCH). Some reports relate fingolimod treatment and hemophagocytic lymphohistiocytosis (HLH). There are strong evidences of an association between cigarette smoking and Langerhans cell histiocytosis. We observed a relapsing remitting MS patient treated with subsequent drugs (interferon beta, natalizumab and fingolimod) with tobacco smoking habit who developed pulmonary Langerhans cell histiocytosis.

Case report: The neurological history of our patient started in 1997 (at 21 years old) with dizzy syndrome and subsequently with access to our MS Center in 2000 when MS diagnosis was made (according to clinical, neuroradiological and liquoral findings). She was reluctant to start a Disease Modifying Drug (DMD), so Interferon beta therapy was started only in 2003, with partial response. (EDSS 2). In May 2012 natalizumab was started with good efficacy. The therapy was discontinuated in August 2014 for the JCV test stratify positivity. Fingolimod therapy was initiated in October 2014 after an extensive screening. She had a disease activity good control, but complained a slow progression of weakness to the right leg (EDSS3). In January 2019 a routine chest x-ray showed interstitial disease. An extended infectious and pneumological diagnostic path with a lung biopsy was made with the final diagnosis of Pulmonary Langerhans cell histiocytosis. Fingolimod therapy was stopped in April 2019 and the patient was invited to quit smoking. After a therapeutic delay due to COVID-19 pandemic, MS reactivation treated with steroids and a first line bridge treatment for the patient refusal to initiate high efficacy Disease Modifying Drugs therapy, she underwent cladribine therapy with good control of MS and stability of the pulmonary involvement.

Discussion: Pulmonary Langerhans cell histiocytosis is a rare disorder characterized by granulomatous proliferation of histiocytes forming granulomas within lung parenchyma, in strong association with tobacco smoking. Smoking cessation is considered to be critical in management, but has variable effects on outcome. No drug therapy has been validated. No association with multiple sclerosis is reported. Cladribine down-regulates histiocyte proliferation and has been successful in curbing multi-system PLCH.

Conclusions: The clinical practice real word is frequently challenged by unusual comorbility without the availability of comprehensive guidelines. Our case sets an example of a rare condition that needs interdisciplinary work to manage the therapeutical problems. The association between MS and cigarette smoking needs an extensive diagnostic workup with pneumological studies.

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DOUBLE INVERSION RECOVERY IDENTIFIES ASYMPTOMATIC OPTIC NEURITIS

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Background: The evidence of asymptomatic optic neuritis (aON) is not considered in the criteria of lesion dissemination for the diagnosis of Multiple Sclerosis (MS).

Objective: To evaluate whether a specific cut-off value of Macular Ganglion Cell Layer (mGCL) volume could be applied, in association with brain MRI and/or Visual Evoked Potentials (VEP) parameters, to identify aON.

Methods: 110 MS patients and 38 healthy controls (HC) were consecutively included in this study. All subjects performed optical coherence tomography (OCT), while double inversion recovery (DIR) sequence and visual evoked potentials (VEP) were performed in 84 patients with no clinical history of optic neuritis (ON-).

Results: mGCL volume strongly associated with the evidence of optic nerve lesion on DIR (O.R.: 13.1 x1010, p<0.0001). When the identified cut-off value (1.035 mm3) was applied to ON-, 16 pathological eyes were identified, while DIR and VEP disclosed pathological changes in 11 and 39 optic nerves respectively. mGCL volume significantly associated with pathological DIR (p=0.041) but not with VEPs (p=0.075). Finally, a correlation was observed between mGCL volume and ipsilateral thalamus and LGN volumes (□: 0.012, p=0.018).

Conclusions: DIR sequence was more specific than VEP and OCT, in the identification of asymptomatic optic nerve lesions.

IN PATIENTS WITH MULTIPLE SCLEROSIS RETINAL HYPER-REFLECTIVE FOCI ASSOCIATES WITH CORTICAL PATHOLOGY

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Objective: To evaluate the presence and numbers of Hyper-Reflecting Foci (HRF), considered clusters of activated and proliferating retinal microglia, and their association with clinical and radiological disease parameters in relapsing remitting MS (RRMS), as well as to explore the origin of HRF analysing the concentration of 86 CSF cytokines in RRMS and Other Not Inflammatory Neurological Disorders (ONIND).

Methods: OCT and 3T-MRI (including 3D-T1, FLAIR and DIR sequences) at baseline was obtained in 80 RRMS, closed to the disease onset (mean: 6.3±5.1 months), and then were clinically and radiologically followed for a mean of about 4 years, evaluating the condition of No Evidence of Disease Activity (NEDA), further subdivided into clinical (cNEDA) and radiological (rNEDA). Patients with symptmatic or asymptomatic optic neuritis (defined clinically or by OCT/MRI findings) were excluded from the study. A subgroup of RRMS (19 patients) and 15 ONIND underwent also CSF examination of 69 cytokines.

Results: HRF number was higher in the Inner Nuclear Layer (INL) of RRMS patients compared with HC (19.55±5.65 vs 13.84±2.57, p<0.001) and associated with INL volume (beta: 1.21, p<0.001). INL HRF count strongly correlated with GM lesion volume (p=0.008). Survival analysis revealed a significant association between INL HRF and both NEDA (p=0.017) and rNEDA (p=0.002). INL HRF count correlated with many monocyte-derived cytokines (namely, IL-22, IL-34, IL-35, CXCL-2, CXCL-10, and CXCL-13). Multivariate analysis confirmed a strong association (r2: 0.47) with both CXCL-2 (Beta: -0.965, p=0.0052) and CXCL-13 (Beta: 0.241, p=0.018). This latter cytokine increased in RRMS with high HRF count compared with NIND and RRMS with low HRF count. Finally, both HRF count (r: 0.8, p<0.005) and cortical lesions volume (r: 0.5, p<0.05) strongly associated with CXCL-13/CXCL-2 ratio.

Interpretation: We found a strong association between retinal microglia proliferation and cortical pathology in RRMS, a finding suggesting a possible underlying common immunopathological mechanism. Furthermore, microglia activation at baseline was observed to predict subsequent inflammatory events, indicating HRF might be a candidate prognostic biomarker worthy of further investigation. Finally, the association between monocyte derived cytokines and INL HRF suggest that these parameter could mark in vivo retinal microglia activation.

A TELENEUROPSYCHOLOGY PROTOCOL FOR THE COGNITIVE ASSESSMENT OF PEOPLE WITH MULTIPLE SCLEROSIS

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Objective: To compare the administration of neuropsychological tests by teleneuropsychology (TeleNP) and face-to-face (F-F) to determine the feasibility and reliability of TeleNP in people with MS.

Materials: Thirty people with MS and 30 healthy controls (HC) underwent both F-F and remote neuropsychological testing (via videoconferencing) sessions in a counterbalanced cross-over design, at 4 weeks. The testing included the Montreal Cognitive Assessment (MoCA) tapping global cognitive functioning and Rao's Brief Repeatable Battery [1].

Methods: The neuropsychological performance scores were compared by performing a repeated-measures analysis of variance with Group (i.e., MS and HC) and Assessment Modalities (i.e., F-F or TeleNP) as independent variables. Moreover, the intraclass correlation coefficient (ICC) was calculated to assess reliability across modalities and criterion validity.

Results: The analysis of variance revealed a significant effect of Group (F=5.835; p<0.001); a significant effect of the Assessment Modalities (F=3.942; p<0.001), but not a significant Group X Assessment Modalities interaction effect (F=1.052, p=0.419). Specifically, people with MS performed significantly worse than HC in test tapping processing speed (Paced Auditory Serial Number Test; PASAT3; F=10.05; p=0.002) and verbal fluency (Word List Generation; WGL; F=49.415; p<0.001). Finally, statistically significant differences in the modality of administration emerged for test tapping visuospatial learning (Spatial Recall Test; SPART; F=37.142; p<0.001) and long-term memory (Spatial Recall Test-delayed; D-SPART; F=14.658; p<0.001). ICCs analysis showed that almost all neuropsychological scores obtained by people with MS (range = 0.45 to 0.72) and HC (range = 0.37 to 0.97) were significant p< 0.001 suggesting good agreement across test administration modalities, except for tests assessing visuospatial learning (SPART; ICC: MS=0.09; HC= 0.11) and visuospatial long-term memory (D-SPART; ICC: MS=0.23; HC=0.22).

Discussion: For most of the neuropsychological tests, the performance assessed by TeleNP was highly consistent with F-F administration, except for the visuospatial ability. These results are in line with previous studies [2], which show that performance in tasks requiring a motor response is more influenced by the modality of administration.

Conclusions: These findings support the validity of TeleNP testing compared with F-F neuropsychological testing. Further studies on larger samples are necessary to confirm the generalizability of these results.

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THERAPEUTIC ADHERENCE AND QUALITY OF CARE OF MS PATIENTS DURING COVID-19 PANDEMIC: RESULTS OF AN ITALIAN MULTICENTER PATIENT-CENTERED SURVEY (COVIMPSAT)

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Background and aims: Multiple Sclerosis (MS) Centers experienced a significant disruption of their clinical activities during the first waves of COVID-19 pandemic. As part of a national multicenter survey (COVId Ms Patients SATisfaction survey – COVIMPSAT), we collected i) the opinion on quality of care (QoC) received by people with MS (pwMS) from MS Centers (MSC), and ii) data on therapeutic adherence and discontinuation, during the lockdown period (March-May 2020) in Italy.

Materials and methods: In April-May 2021, 16 Italian MSC compiled and sent a digital (35-item) survey to their patients. Statistical analyses were performed with SPSS, version 25.

Results: 1670 pwMS (67.3% women) completed the survey. Most of them (89.9%) were on disease-modifying therapies (DMTs). The most used DMTs were dimethyl fumarate (18.6%), ocrelizumab (14.4%) and natalizumab (13.9%). During the lockdown period, 88% did not modify their DMT regimen, while 11% reported a change in DMT intake, with a reduction in 7.8% and a drug discontinuation in only 4.2% cases. Almost 9 out of 10 pwMS (89.1%) were able to get in contact with their MSC without difficulties. Thirty-six percent of pwMS contacted their MSC for getting information about COVID-19, while 30% were directly contacted from the MSC personnel to provide information on MS and COVID-19 and preventive behaviours. More than half of the patients (63.5%) performed their check-up visits at the MSC with the same schedule as the pre-pandemic period, while 36.5% of pwMS voluntary skipped follow-up visits mainly because of fear of getting COVID-19 infection (46%) and the sensation of feeling well without an absolute/urgent need of a check-up visit (16.8%). Interestingly, although only 1.3% of pwMS underwent a teleneurology follow-up visit, 80% of patients suggested to invest more in telemedicine programs in order to expand contact channels with MSC. The overall opinion of pwMS on MSC during the pandemic period in Italy was more than positive, with 32% of pwMS declaring a significant increase in trust in their MSC.

Discussion and Conclusions: Italian pwMS judged globally well the activity, accessibility and information received by their MSC during the first wave of COVID-19 pandemic. Only 1 out of 10 pwMS underwent a change in their DMT regimen, showing a high drug adherence. Our data also demonstrate that implementing telemedicine programs would further improve the QoC of patients, particularly those with higher disability or living far from the MSC.

NEUROBIOLOGICAL INSIGHTS IN MULTIPLE SCLEROSIS FROM TEARS-DERIVED EXTRACELLULAR VESICLES

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An improved understanding of multiple sclerosis (MS) neurobiology parallels the search for novel biomarkers of disease. Extracellular vesicles (EVs) are a heterogenous group of membrane-bound vesicles, which mediate intercellular communication. Their concentration in tears is approximately 100-fold higher than in plasma, suggesting that EVs from tears are a promising source of liquid biopsy [1]. Previous work has demonstrated a higher number of neuronal- and microglial-derived EVs in tears of MS patients compared to healthy controls (HCs) [2]. A recently optimized innovative "SORT-omics" workflow offers the possibility to subtype cellular specific EVs with an appropriate panel of antibodies and then to perform proteomic characterization of sorted EVs [3]. Here, employing this technique, we sorted and counted EVs from tears of 12 MS patients and 12 HCs, and found a significantly lower count of leukocyte-derived EVs (Leuko EVs) ($p < 0.05$) and higher count of microglial-derived EVs in MS patients. Then, we focused on Leuko EVs, since peripheral immune cell diapedesis across the blood-brain barrier is an early event in MS, which triggers a cascade of subsequent inflammatory events. We compared the proteome of 140,000 Leuko EVs from 23 MS patients (age 41.9±11.6; M/F= 3/20; mean disease duration 12.7±10.3 years; median EDSS= 3.5; range: 1-7; patients with ≥ 1 relapse in the previous year= 7; patients on disease modifying treatment= 20) and 10 HCs (age 31.4±4.42; M/F= 4/6). Functional proteomic analysis revealed that migration of endothelial cells function was significantly upregulated via Leuko EVs proteins by transforming growth factor beta-1 (TGFβ1) as activated upstream regulator in tears of MS

patients. TGFβ1 has potent T-cell inhibiting activities and plays an important role in limiting autoimmune inflammation. We also revealed an activation of the angiogenesis function in MS Leuko EVs, which may reflect the mutual relation between chronic inflammation and angiogenesis. Indeed, different immune cells are able to secrete angiogenic cytokines, which promote growth, migration and activation of endothelial cells. Neuropathological studies have demonstrated endothelial cells proliferation in acute and chronic demyelinating lesions, as well as in normal-appearing white matter of MS patients. If this angiogenic response contributes to disease progression or, alternatively, to remission after relapses remains to be elucidated. Overall, our results suggest that Leuko EVs offer a non-invasive source of neurobiologically relevant information, which may improve our understanding of disease pathophysiology.

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FUNCTIONAL CONNECTIVITY MODIFICATIONS IN MONOAMINERGIC CIRCUITS OCCUR IN FATIGUED MS PATIENTS TREATED WITH FAMPRIDINE AND AMANTADINE

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Objective: Fatigue is a common and disabling symptom in multiple sclerosis (MS). Different pharmacological agents have been tested for treating MS fatigue, with no clear evidence supporting their efficacy. Symptomatic treatments for fatigue rely on drugs reinforcing monoaminergic synaptic transmission. Therefore, monoaminergic network abnormalities may have a role in fatigue pathogenesis. Here, we investigated changes over time of fatigue severity and concomitant modifications of resting state (RS) functional connectivity (FC) abnormalities in monoaminergic networks in 45 fatigued MS patients after different symptomatic treatments.

Methods: MS patients were randomly, blindly assigned to treatment with fampridine (n=15), amantadine (n=15) or placebo (n=15) and underwent clinical, neuropsychological and 3T RS fMRI at baseline (T0) and after four weeks (W4) of treatment. Fifteen matched healthy controls (HC) were acquired twice. Dopamine-, noradrenaline- and serotonin-dependent RS FC patterns were derived by independent component analysis (ICA), constrained to PET atlases for dopamine, noradrenaline and serotonin transporters, previously obtained in HC. Changes in modified fatigue impact scale (MFIS) score and monoaminergic-dependent RS FC were assessed.

Results: MS patients showed baseline abnormalities vs HC in all three networks, with decreased monoamine-related RS FC in temporal, occipital, insular and cerebellar regions, and increased RS FC in frontal, parietal and subcortical areas. At W4, MFIS scores decreased in all patients' groups, with no time-by-treatment interaction. At W4, fampridine and amantadine patients showed increased dopamine- and noradrenaline-dependent RS FC in the insular cortex, as well as increased serotonin-dependent RS FC in the precuneus/posterior cingulate cortex. Amantadine patients also showed increased dopamine- and noradrenaline-dependent RS FC in the anterior cingulate cortex (ACC). Conversely, placebo patients mostly showed increased noradrenaline-dependent RS FC in the precuneus and middle cingulate cortex. In fampridine and placebo groups, there were trends towards significant correlations between RS FC modifications and MFIS improvements (r=-0.49:-0.52, p=0.07-0.08).

Discussion: At T0, fatigued MS patients presented diffuse dysregulation of monoaminergic networks. At W4, amelioration of MFIS scores in fampridine and amantadine patients was accompanied by increased monoamine-related RS FC in regions having a role in the pathogenesis of central fatigue, such as the insula and ACC, which are part of the interoceptive system. Increased RS FC in placebo patients was mainly located in associative sensory and motor regions.

Conclusions: Fatigue improved in all MS groups. Concomitant monoaminergic-dependent RS FC modifications were found in insular, ACC and parietal regions for fampridine and amantadine MS patients, and in medial parietal regions for placebo patients.

CORRELATIONS BETWEEN CSF CYTOKINES, SLEEP MACROSTRUCTURE AND CYCLIC ALTERNATING PATTERN IN DE NOVO RELAPSING-REMITTING MULTIPLE SCLEROSIS: A CONTROLLED POLYSOMNOGRAPHIC STUDY

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Study objectives: To evaluate subjective and objective sleep measures in de novo relapsing remitting multiple sclerosis (RRMS) compared with healthy controls and CSF cytokines (CK) in RRMS.

Methods: Twenty-one patients affected by RR-MS underwent CSF levels of CK, overnight polysomnography and subjective evaluation of sleep and sleepiness. Twenty-one healthy controls (HC) underwent subjective scales and overnight polysomnography. Scoring and analysis of sleep macrostructure and cyclic alternating pattern (CAP) parameters were performed. Partial correlation adjusted for age, gender, disease duration was performed between CK and sleep variables.

Results: We found higher sleep period time (SPT), time in bed (TIB), REM sleep latency, N3 percentage; wakefulness after sleep onset (WASO), stage shifts/h (SS); lower sleep efficiency (SE) and REM sleep percentage (REM%) in RRMS vs HC. RRMS with OSA showed higher SPT; TIB, REM sleep latency; WASO; SS; lower SE and REM% when compared to HC.RRMS without OSA demonstrated higher N3%, WASO; lower REM% and SE. Regarding CAP, higher CAP time, CAP rate, CAP rate in N1 and N2, A3%, A,A1,A2 and A3 mean duration, A1 and A3 indices; lower A2%, phase B mean duration were evident in RRMS vs HC.OSA-MS showed higher CAP rate, CAP time, CAP rate in N1 and N2, A3%;A, A1, A2 and A3 mean duration, A3 index; lower B mean duration. RRMS without OSA revealed higher CAP rate, CAP time, CAP rate in N2; A, A1, A2 and A3 mean duration, A1 and A3 indices; lower phase B duration. N3% was positively related with IL6,

REM% negatively with IL8, lower REM latency and number of awakenings with IL2 and less stage shift/h with IL2, IL6, IL15 and IL1ra. We also demonstrated a positive correlation of A, A1, A2 mean duration with IL2, IL12 and IL15; of A3 mean duration with IL6, IL12, IL15 and IL1ra; of B phase mean duration with IL1b and IL10; of cycles duration with IL12, IL15 and IL10; a negative correlation CAP sequences duration and cycles per sequences with IL1b and IL10.

Conclusions: De novo RRMS is associated with sleep fragmentation as shown by CAP analysis more evident in RRMS with OSA. Inflammatory cytokines may influence sleep homeostasis by adaptive mechanisms in a vicious circle where sleep fragmentation may also modulate CK release.

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NEUTROPENIA COMPLICATING RITUXIMAB AND OCRELIZUMAB TREATMENT IN PATIENTS WITH MULTIPLE SCLEROSIS: A RETROSPECTIVE CASE SERIES AND A SYSTEMATIC REVIEW OF REPORTED CASES

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Aim: To evaluate clinical features and management of neutropenia complicating anti-CD20 treatment in patients with Multiple Sclerosis (PwMS).

Materials: We retrospectively identified in our center 3 PwMS who developed neutropenia during treatment with CD20 depleting drugs, which was not better explained by other medical conditions, and we performed a systematic review of the literature following the PRISMA guidelines. A PubMed/Medline research was performed with the queries "ocrelizumab AND neutropenia" and "rituximab AND multiple sclerosis AND neutropenia" (last update February, 3rd 2022). After screening, 13 records (16 patients) were included in the qualitative synthesis.

Methods: Clinical, demographic and data related to neutropenia development, management and CD20 rechallenge obtained through the retrospective evaluation and through the systematic review were analyzed together.

Results: A total of 19 patients were included (3 from our clinical experience, 16 from the systematic review). Median age was 38 years (25-69) and nearly 70% were female. Eleven patients developed neutropenia during ocrelizumab treatment, 8 during rituximab treatment. Disease course was described in 16 patients: 9 of them were affected by relapsing remitting multiple sclerosis (MS), 3 by primary progressive MS, and 4 by secondary progressive MS. Neutropenia occurred after a median of 2 (1-7) infusions and after 9.5 (1-42) months from the first infusion. Median time from the last infusion was 90 days (2-156). About 70% of patients were symptomatic and most were treated with G-CSF and antibiotics. No relapses after G-CSF were reported. In those patients who did not suspend anti-CD20 (68.8%), neutropenia reoccurred in 18.2% of cases.

Discussion: As neutropenia is an infrequent complication of treatment with CD20 depleting agents and the administration of granulocyte-colony stimulating factor (G-CSF) has been previously associated with an increased relapse risk in PwMS, the management of this side effect is still matter of debate.

Conclusion: Our data suggest that neutropenia may develop in patients with both relapsing and progressive disease courses, relatively early during treatment with anti-CD20 (after a median of 2 infusions). Late onset neutropenia (>4 weeks from the last infusion) encompassed most of the cases. The administration of G-CSF was not associated with relapses, suggesting that its use may be safe in PwMS. As in some cases neutropenia occurred or reoccurred after switching from RTX to OCR and viceversa, switching among anti-CD20 depleting agents, which are different in terms of humanization of monoclonal antibodies, seems not to be useful to prevent the reoccurrence of neutropenia.

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ASSESSING TREATMENT RESPONSE TO ORAL DRUGS FOR MULTIPLE SCLEROSIS IN REAL WORLD SETTING: A MAGNIMS STUDY

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Introduction: The assessment of treatment response, currently based on the integration of clinical and magnetic resonance imaging (MRI) measures, is necessary in patients with relapsing-remitting multiple sclerosis (RRMS) on disease-modifying therapies (DMTs). However, previous studies have reported response to injectable DMTs. So far we do not know if, we can use the same tools to predict response to oral DMTs.

Objective and Aims: To explore the significance of clinical and MRI measures, alone and combined into the MAGNIMS score, to evaluate response to oral DMTs.

Methods: A multicenter clinical dataset was collected within the MAGNIMS network from 12 centers across Europe. We retrospectively evaluated data of RRMS patients who started dimethyl fumarate (DMF), fingolimod (FNG) or teriflunomide (TNF) according to the following criteria: treatment-naive or switching from injectable DMTs; at least 1 year treatment duration; brain MRI scan collected at baseline and year 1; at least 3 years of clinical follow-up. We explored the association between one-year clinical and MRI activity and (i) the risk of confirmed disability worsening (defined on the basis of the Expanded Disability Status Scale [EDSS]); (ii) the switch to another treatment for efficacy reason by Cox regression adjusted for baseline demographic, clinical and MRI variables.

Results: Data from 1.200 patients (69% women; mean ± SD age 39.3 ±10.7 years; median EDSS score 1.5 [range 0 to 7.0]; 34.8% treatment naïve) were collected. Of them, 598 were treated with DMF, 308 with FNG and 294 with TNF. Between year 1 and year 3, 13.3% of the patients experienced confirmed disability worsening, 20% switched to another DMTs due to lack of efficacy and 11% had one or more relapses. In the whole cohort, confirmed disability worsening at year was predicted by the occurrence of relapses in the first year (HR=2.11, p<0.001) and the fulfillment of MAGNIMS score 1 and 2 (HR=2.06, p=0.001; HR= 2.56, p=0.018 respectively). Patients experiencing relapses during the first year as well as those with 3 or more new T2 lesions at year 1 MRI scan, had a higher probability to switch to other DMTs (HR= 1.52, p=0.015; HR=2.21, p<0.001).

Conclusions: In a multicenter study we report that early relapses and MRI activity in the first year of treatment with oral DMT are associated with an increased risk of short-term confirmed disability worsening and treatment failure in patients treated with oral DMTs.

SPINAL CORD RESERVE AND DISABILITY WORSENING OVER TIME IN PATIENTS WITH MULTIPLE SCLEROSIS

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Background: Spinal cord volume is a strong predictor of physical impairment and progression over time in Multiple Sclerosis (MS). Mirroring the concept of "brain reserve", spinal cord reserve has been recently found to be associated with perceived disability, but its value in predicting clinical worsening has not been explored yet.

Objectives and Aims: To evaluate how (i) spinal cord reserve is related to measures of objective disability and (i) how it impacts on disability worsening over time, in patients with MS (PwMS).

Materials and Methods: As a part of an ongoing study, we collected clinical [9-hole peg test (9HPT), 25-foot walking test (25FWT), Expanded Disability Status Scale (EDSS)] and Magnetic Resonance Imaging (MRI) data (3D T1W Brain scan covering C2-C3) of 100 PwMS [F: 74; mean age 36.7 ± 8.3; EDSS 2. 0 (range: 0-6.0)] at baseline. Of them, 92 underwent clinical follow-up (FU) (median: 3 years). Clinical worsening at FU was defined according to the EDSS-Plus. A cohort of 41 matched healthy controls (HC) [F:28; mean age 32.8 ± 6.5] underwent the same MRI protocol. Spinal cord and canal areas (SCA and SCaA) were obtained with Jim 7 software at C2/C3 level. Spinal cord parenchymal fraction (SCPF) was computed as SCA/SCaA. Differences between groups were investigated controlling for age and sex via ANCOVA. Linear and binary logistic regression were used to test (i) the association of spinal cord reserve with clinical measures at baseline (adjusted for SCPF, age and sex and (ii) its value in predicting disability worsening at FU (further adjusted for FU duration, relapse rate and baseline EDSS), respectively.

Results: PwMS showed lower SCA and SCPF compared to HC (SCA: 59.65 ± 9.3 vs 66.5 ± 5.7 mm 2, p=0.001; SCPF: 0.31 ± 0.5 vs 0.34 ±0.3, p=0.004), while no differences in SCaA were detected (191.0 ± 32.6 vs 194.6 ± 26.35, p=0.9). At baseline, SCaA was associated with EDSS (ß=-0.29, p=0.01; adj R2= 0.235, F=8.2, p<0.001) and 9HPT (ß=-0.37, p<0.01; adj R 2= 0.201, F=7.3, p<0.001). Approximately 39% of patients showed disability worsening at FU. PwMS showing a higher SCaA at baseline had a lower probability of developing future clinical worsening (OR=0.97, 95% CI 0.96-0.99, p=0.01).

Conclusion: A larger spinal canal area, as proxy of higher spinal cord reserve, might extert a protective effect against the expression and short-term evolution of motor disability in MS. Further studies with longer follow-up and larger sample are needed to better explore this new concept.

TEMPORAL EVOLUTION OF HUMORAL AND T-CELL SPECIFIC IMMUNE RESPONSE TO COVID-19 MRNA VACCINE IN MULTIPLE SCLEROSIS

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Background: Although a full course of vaccine against Sars-Cov-2 is effective in most patients with MS (PwMS), the duration of the protection and the efficacy of a booster dose remain poorly explored, especially across different disease modifying treatments (DMTs).

Aims: To characterize humoral and T-cell immune response along time and following third dose of COVID-19 vaccination in PwMS.

Methods: From an established cohort evaluated at baseline (T0), PwMS were recruited after 24 weeks (T1) from the first cycle of mRNA vaccine and 4 weeks after third dose (T2). At each timepoint we evaluated the serological response by measuring the anti-Region-Binding-Domain (RBD). Cell-mediated response was analyzed by computing interferon (IFN)-γ in response to spike peptides.

Results: The baseline cohort consisted of 134 PwMS [mean age 46.6 ±10.8 years; F:92; mean disease duration 15.1±9.4 years; 26.9% ocrelizumab (OCR) 30.6% fingolimod (FTY), 16.4% cladribine (CLA), 26.1%IFN-ß-1a (IFNB)]. Of them, 109 were reassessed at T1, 78 at T2 and 64 completed all evaluations. In the whole cohort there was a significant reduction (p<0.0001) in anti-RBD rate from T0 [76% positive, median 52.8 BAU/ml Interquartile Range (IQR) 1150.9] to T1 (57.8% positive, median 13.2 BAU/ml IQR 95.98] and a significant 20- and 5-fold increase in median titer at T2 (75% positive, median 272.3 BAU/ml IQR 4212.3) from T1 and T0 respectively (p<0.0001). Median IFN-γ

level at T2 was significantly higher than those evaluated at T1 ($p<0.0001$) and T0 ($p=0.009$). These latter results were consistent across all DMTs. At T1 the highest detectable anti-RBD response was found in CLA (100%, median 87.7 BAU/ml IQR 22) and IFNB (93.5%; median 126.3 BAU/ml IQR 149.2) cohort, while PwMS treated with FTY and OCR showed 60% (median 8.25 BAU/ml IQR 34.3) and 21% (median 0.8 BAU/ml IQR 6) rate of anti-RBD response respectively. At T2 100% PwMS showed positive anti-RBD response except those treated with OCR (23.8% positive, median 0.6 BAU/ml IQR 4.1). IFN-γ-S-specific T-cell response was reduced in FTY cohort at both T1 and T2 (3.3 % positive, median 0.8 pg/ml IQR 3.1 and 0.6 pg/ml IQR 2.4 respectively).

Conclusions: A third dose of COVID-19 vaccine reinforces both humoral and cell-mediated immune response in PwMS on DMTs. Despite vaccination, PwMS treated with OCR and FTY show lower humoral and T-cell specific immune response respectively, suggesting the need of specific treatment to halt COVID-19 in case of infection.

LATE-ONSET MULTIPLE SCLEROSIS (LOMS) AFTER FIRST DOSE MRNA COVID VACCINE

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Introduction: Multiple sclerosis (MS) affects young adults commonly between 20 to 40 years old, but early and late onset MS have been described. LOMS is defined by an onset after the age of 50 and it accounts for about 5% of cases. Increasing cases of disease reactivation after COVID 19 or mRNA COVID vaccine administration are described but there are no clear data about a new disease onset.

Objectives: We report a 61 year old female receiving LOMS diagnosis after SARS-COV2 vaccination.

Case: On April '21, one month after first dose SARS-COV-2 mRNA vaccination, a 61 years old female complained generalyzed asthenia and fever. Laboratory tests and chest CT scan were normal. Two weeks later she developed hypostenia and dysesthesias in the right limbs with gait disturbances, and urinary retention. No cognitive and cranial nerve damn was observed. Magnetic resonance imaging (MRI) revealed a gadolinium enhancing lesion in C3-C4 and multiple non enhancing vascular shaped brain hyperintensities. Autoimmune and thrombophilic screening were negative, so were anti-aquaporin-4 and anti-myelin oligodendrocyte glycoprotein antibody. Cerebrospinal fluid was normal and meningitis CSF oligoclonal bands were pending and CSF panel was negative for bacteria and viruses. After methylprednisolone she partial recovered in strength while sensory symptoms remained unchanged. She was discharged with a diagnosis of post-vaccine mielitis. Five days later she was newly admitted for acute urinary retention and a new MRI showed a new gadolinium enhancing lesion in C1; CSF oligoclonal bands (IgG) were present. A second course of steroid leads to a significant improvement and subsequent stabilization. A follow up MRI scan 5 months later showed dissemination in time and diagnosis turned into MS: first-line MS treatment has been started. To date no further clinical or radiological reactivations have been observed.

Discussion: the role of viral infections in developing autoimmune response in genetically predisposed people is well understood. mRNA vaccines leads to T and B cells response as viral infections do, so they could also play a role in autoimmunity. Only few cases of newly diagnosed MS after Covid mRNA vaccine exposition have been reported. In our case, the latency between vaccine administration and the beginning of symptoms suggests a putative role of vaccine immune stimulation on the genesis of the disease; anyhow no data suggest a latent disorder: nor symptoms, nor age neither radiological characteristic.

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BALANCE DISORDERS IN EARLY MULTIPLE SCLEROSIS PATIENTS: ROBOTIC AND CLINICAL EVALUATION

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Objectives: Purpose of this study was to evaluate whether a robotic system (Hunova®) can represent a valid tool in the initial functional evaluation of persons with multiple sclerosis (PwMS), analysing the postural alterations in a sample of subjects with mild disabilities, in the absence of imbalance at clinical evaluation, performed with the standardized Berg Balance Scale (BBS).

Materials and methods: 31 adult PwMS and mild disability were recruited. The Expanded Disability Status Scale (EDSS) score was ≤ 3.5, and the maximum score on the BBS was 56. All subjects under went robotic evaluation and standard clinical evaluation (10 Meter Walk Testing Form, Activity Balance Confidence (ABC), BBS, Modified Fatigue Impact Scale, Timed Up and Go (TUG). The sample population included: 8 males and 23 females, average age 45.4, mean disease duration 9.4 years, mean EDSS score 2.7, ABC 80.8%, mean TUG time 7.4, disease modifying or symptomatic treatment in 81%. Using the "Receiver Operating Characteristic" (ROC) curves, the diagnostic accuracy of the different indicators analysed was evaluated, and data were compared to the reference values stratified for age groups.

Results: Relevant adaptive and reactive components of the equilibrium were assessed through the robotic test. Statistical analysis was carried out on the results that differed from normal values. The analysis of the ROC curves, in particular the "Area Under Curve" (AUC), highlight as the most accurate indicators: the amount of movement of the trunk with the eyes open and closed (respectively 19.35% and 35.48%), the area of the sway with eyes closed in static balance (61.29%), the amount of trunk movement in passive balance (35.48%), the forward stabilization time in the "Reactive Balance (77.42%) and the duration of the" Five times Sit to Stand test "(5TST) (45.16%). The result of the AUC of static balance with open eyes (6 subjects in total), due to the small normal range with decimal variations, resulted significant.

Discussion: The choice to recruit in the study only subjects who had a normal score on the BBS allowed to demonstrate a greater sensitivity of the robotic device in identifying subtle impairment.

Conclusion: Evaluation of stabilometric indicators has proved to be useful in identifying alterations in postural control already in an undisturbed standing position, even in subjects who clinically don't have

neuro-motor and balance dysfunctions, with a normal score at BBS. The robotic device therefore represents a reliable tool for assessing postural alterations in mild forms of MS.

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INTEGRATION OF THE EXPANDED DISABILITY STATUS SCALE WITH AMBULATION, VISUAL AND COGNITIVE TESTS, IMPROVES ASSESSMENT OF DISABILITY

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Introduction: The Expanded Disability Status Scale (EDSS) is usually calculated through a neurological examination with self-reported performance. This may lead to incorrect assessment of several Functional Scores (FS), prominently visual and cerebral FSs, and ambulation. Aim of our study was to estimate the difference between EDSS scores obtained during routine visits, or after specific visual, cognitive and ambulation tests.

Methods: We enrolled 670 Multiple Sclerosis (MS) patients that underwent a routine visit with EDSS calculation. Then, patients underwent a tes with a Digital Acuity System (DAS) using the Landolt's C-target digital eye optotype table, ambulation evaluation with an odometer, and neurocognitive assessment with the Brief International Cognitive assessment for MS (BICAMS). We calculated a new integrated EDSS (iEDSS) using the refined values of the FS. EDSS and iEDSS were compared in terms of absolute values and in terms of change caused by the addition of recalculated FSs.

Results: Addition of DAS to the Visual FS led to a different score in 453 patients (67.6%), the addition of BICAMS to the Cerebral FS changed the score in 322 patients (48.1%), and the same was true for Ambulation in 307 patients (45.8%). FSs were all significantly higher after additional evaluations: visual FS (+1.169; 95%CI 1.077, 1.262; p<0.001), cerebral FS (+0.727; 95%CI 0.653, 0.801; p<0.001), ambulation score (+0.822 (95% CI 0.705,0.939; p<0.001). Mean iEDSS was higher than EDSS (+0.658; CI +0.558, +0.755, p<0.001). Instrumental measurement of the Visual FS led to a worse EDSS score in 30.1%, the addition of BICAMS to the Cerebral FS worsened the EDSS score in 11.6% patients, better estimation of the Ambulation score worsened EDSS in 34% of our patients. The integration of all the three measures in the iEDSS worsened the original EDSS score in 59.4% of cases.

Conclusions: Accurate measurement of visual, cognitive and ambulation results in a better calculated EDSS in almost two-thirds of cases. This should lead to a more thorough evaluation of critical patients, i.e. patients in the transition or progressive phase.

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VALIDATION OF AN IPAD VERSION OF THE BRIEF INTERNATIONAL COGNITIVE ASSESSMENT FOR MULTIPLE SCLEROSIS (BICAMS)

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Background: The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) is the most widely used screening tool for cognitive impairment in Multiple Sclerosis (MS). However, the administration and scoring procedures of the paper version are time consuming and prone to errors. Aim of our study was to develop a tablet version of BICAMS (iBICAMS), and to assess its reliability compared to the paper version.

Methods: We administered both BICAMS and iBICAMS to 139 MS patients in two different sessions. We compared scores on both versions using a paired t-test. We used a repeated measures ANOVA to test the impact of rater, order of administration and test-retest time on test-retest performances. We used the Intraclass Correlation Coefficient (ICC) to assess the reliability between BICAMS and iBICAMS.

Results: All three sub-tests of the BICAMS (SDMT, CVLT-II and BVMT-R) were different between the paper and the tablet versions. Order of administration influenced test-retest performances at the SDMT (p<0.001), CVLT- II (p<0.001) and BVMT-R (p<0.001). Intraclass coefficient correlation (ICC) revealed a high level of agreement between the paper BICAMS and the iPad version for all three tests: SDMT (0.92), CVLT-II (0.83) and BVMT-R (0.82).

Conclusions: Results suggest that using the iBICAMS guarantees a better adherence to standardized procedures in both administration and scoring phase of tests. The high reliability between the two versions and the inherent advantages of automated scoring, favor the iBICAMS as the most appropriate method.

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EFFECTIVENESS AND PATIENTS SATISFACTION OF NABIXIMOLS (SATIVEX®) ON MULTIPLE SCLEROSIS SPASTICITY IN A REAL-LIFE SWISS MULTICENTER STUDY

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Background: Nabiximols, a cannabinoid-based oromucosal spray, is approved for patients with moderate to severe multiple sclerosis spasticity (MSS) resistant to other antispastic medications. No data on effectiveness and patients satisfaction in Swiss MS patients have been reported so far.

Objective/Methods: To investigate the effectiveness, tolerability and satisfaction of nabiximols in a real-world multicentric Swiss cohort (with stable doses of other antispastic medications allowed). The following data were collected at treatment start (baseline) and 12 weeks thereafter: Modified Ashworth scale (MAS), scores at numerical rating scales ranging from 0 (absent) to 10 (considerable) for effect on spasticity (sNRS), pain (pNRS), gait (gNRS), urinary symptoms (uNRS), tolerability (tNRS) as assessed by the treating neurologist and overall treatment satisfaction (OTS) as assessed by the patient.

Results: Ninety-five patients (43 relapsing remitting, 37 secondary progressive and 15 primary progressive MS; median age=53 [25-86]; female 69%; median EDSS 5 [2-8.5], concomitant antispastic treatments in 72% of patients) were included. From baseline to week 12, median MAS score decreased from 3.0 to 2.0 ($p < 0.001$). Mean scores of the each NRS also significantly decreased (sNRS -1.81; pNRS -2.36; gNRS -0.88; uNRS: -1.93; all $p<0.001$). At week 12, median tNRS and OTS scores were 9/10 and 8/10, respectively, and 78% of patients continued to use nabiximols at the average dose of six sprays/day.

Conclusion: Our Swiss, multicentric, observational study supports previous finding of nabiximols being an effective and well-tolerated treatment option for resistant MSS and spasticity-related symptoms (pain, bladder dysfunction and gait).

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SAFETY AND EFFICACY OF CLADRIBINE THERAPY FOLLOWING A TREATMENT WITH ANTI-CD20 COMPOUNDS IN RELAPSING MULTIPLE SCLEROSIS PATIENTS: A PILOT STUDY

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Background: Prolonged therapy with ocrelizumab and rituximab, two anti-CD20 monoclonal antibodies used in multiple sclerosis (MS), can lead to hypogammaglobulinemia and increased risk of infections. Cladribine, an MS immune reconstitution therapy, has not be associated with hypogammaglobulinemia so far.

Objective: To investigate IgG and IgM serum concentration changes up 12 months after switching to cladribine in patients previously treated with anti-CD20 compared to continued anti-CD20. Secondary aims were measures of effectiveness (EDSS, clinical relapses, new T2 lesions) and safety.

Methods: This is a prospective observational monocenter study including MS patients treated with anti-CD20 antibodies for ≥18 months. Patients with a ≥10% reduction of IgG and/or IgM or recurrent infections were switched to cladribine (CLAD-group). IgG and IgM concentrations, effectiveness and safety measures in CLAD-group were compared with those of patients continuing on anti-CD20 (CD20-group).

Results: Forty-five patients were included (median age=46.5 [36-54.5]; females=27 [60%]). Fifteen (33%) patients were switched to cladribine, 30 (67%) continued on anti-CD20. At baseline, IgG concentrations were similar between CLAD-group and CD20-group (8.2 [6.3-10.3] vs 8.7 [7.6-10.2] g/L, p=0.455). IgG (β=-0.03, p=0.048) and IgM (β=-0.004, p=0.030) concentration decreased over 1 year-follow-up, with no difference between groups (interaction p=0.850 and p=0.153 respectively). No patients in each groups experienced relapses or MRI progression. One patient in each group had worsening EDSS over follow-up. The number of severe adverse events was 2 in the CD20-group (both cases of inflammatory-bowel disease) and 1 in the CLAD-group (pelvic infection).

Conclusions: Rate of IgG and IgM decline following a switch to cladribine after anti CD20 treatment is similar to that observed in patients continuing anti CD20. Both treatment approaches are associated with low disease activity and similarly benign adverse event profile.

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VACCINATIONS IN PATIENTS WITH MULTIPLE SCLEROSIS: A REAL-WORLD, SINGLE-CENTER, EXPERIENCE

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Aim: Describing safety and timing-proposal in vaccinating patients with multiple sclerosis (pw-MS) to orient a proper vaccinations' schedule.

Materials and methods: Vaccination schedules were costumed according to national recommendations, clinical-/serological data, ongoing disease modifying drugs (DMDs) or therapy-start urgency. Disease-activity within 3 months stated the need of an accelerated cycle. Two different vaccines could be administered together and between the different administrations a 15-days-interval was recommended. Minimum 2 weeks from last inactivated-vaccine-administration to new therapy-start were required, 4-6 if live-attenuated. The essential immunization program's core included 4 vaccines (meningococcal-B, pneumococcal-conjugated, Haemophilus-influenzae-B and meningococcal-ACWY vaccines). Adverse events (AEs) were monitored during the vaccination-cycle; clinical relapses or magnetic resonance imaging (MRI)-activity were monitored at 3-/6-months after cycle-ending.

Results: One-hundred-ninety-five patients across 2017-2021 were enrolled. One-hundred-twenty-four patients (63.6%) were addressed to vaccination before a therapy-start/-switch and 108 of them (87.1%) effectively started the protocol before DMDs start without any significant deferral. The remaining 71 (36.4%) underwent vaccination during an ongoing-therapy. Regarding AEs during the cycle, 2 (1.0%) patients presented clinical-relapses while 1 (0.5%) MRI-activity. Both patients having clinical-relapse were clinically active within 3-months before immunization. Three and 6 months after the completion of the program, 2 patients (1, 0.5%, and 1, 0.5%, respectively; 1.0% globally) presented a relapse and 8 (4, 2.05%, and 4, 2.05%, respectively; 4.10% globally) had MRI-activity; 6 out of these last 8 patients (75.0%) with MRI-activity were already active 3-months before immunization-start. The median (95% confidence interval) time for therapy-switch was 65 (32) days. The core vaccination-cycles had a duration of 40.5 (42) days. Thanks to the growing expertise, we observed a progressive reduction in the time to vaccination-completion, reaching a median of 27 (22) in 2020.

Discussion: Despite the fundamental role of vaccines in preventing serious infections in at-risk patients [1], solid data regarding the achievement of a complete immunization in pw-MS are missing [2]. Moreover, real-life data regarding vaccinations' planning in pw-MS receiving DMDs is missing, especially in terms of starting a new therapy because of disease-activity. This might represent a challenging issue in the context of massive vaccination protocols as those linked to severe acute respiratory syndrome coronavirus [2]. Our real-world study prompts confidence in individualized vaccination-schedule increasing awareness in vaccinating pw-MS within a DMDs-switch.

Conclusions: Our study confirmed the optimal tolerance-safety profile of vaccination in pw-MS. A vaccination-cycle of 27 days might be considerate adequate in order to vaccinate pw-MS without interfering with DMDs-start.

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HIGH CORTICAL LESION LOAD AT DIAGNOSIS PREDICTS CONVERSION TO SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS AND LONG-TERM DISABILITY ACCUMULATION

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Objectives: Cortical pathology has been suggested as a major driver of multiple sclerosis (MS) disability accumulation, evident since early disease phases and associated with a severe disease course. [1] Further studies have demonstrated the role of cortical lesions in progressive patients and accumulation of disability after 30 years. [2] However a long term evaluation of the predictive value of cortical lesions at the beginning of the disease was still missing.

Materials and Methods: We evaluated 199 MS patients who underwent a brain MRI at the time of diagnosis (T0) and after two years (T2), which included assessment of cortical lesion number (CL) with Double Inversion Recovery sequences, and a spinal cord MRI at T0. All patients underwent regular clinical follow-up (17.0 ± 3.2 years). Time of conversion to SPMS, Expanded Disability Status Scale (EDSS) of 4.0 and 6.0 were recorded as outcomes.

Results: At the end of follow-up, 39 (19.6%) patients had a diagnosis of SPMS, 54 (27.1%) and 28 (14.0%) reached an EDSS of 4.0 or 6.0, respectively. Patients with SPMS had increased baseline CLN (6.28 ± 3.7 vs 1.2 ± 2.3, p<0.001), CL volume (657.7 ± 404.2mm3 vs 114.7 ± 236.5 mm3, $p < 0.001$) and increased new CL number at T2 MRI (2.18 ± 1.79 vs 0.21 ± 0.7, $p < 0.001$) compared to patients with RRMS. Multivariate Cox Regression confirmed that a higher CL number (classes ≥ 3, HR 12.2 [CI 3.55- 41.8], $p < 0.001$), and presence of spinal cord lesions (HR 2.3 [CI 1.08- 4.8], $p = 0.003$) were significantly associated with SPMS conversion. Furthermore, accumulation of new CLs in the first two years after a diagnosis of MS predicted earlier conversion to SPMS (HR 1.3 [CI 1.1-1.5], $p < 0.001$), as well as the earlier reachment of disability milestones such as EDSS 4 (HR 1.28 [CI 1.09-1.51], $p = 0.002$) and EDSS 6 (HR 1.39 [CI 1.12-1.73], $p = 0.003$). ROC curve analysis estimated the optimal cut-off values of 3 for CLs according to the risk of developing SPMS.

Discussion and conclusions: Early accumulation of focal cortical damage is a predictor of evolution in SPMS and of more rapid disability accumulation. Moreover, we pinpointed the higher risk of converting to SPMS in those patients with 3 or more cortical lesions at diagnosis, being the best predictor of progression among the tested variables. This has relevant clinical implications and should be taken into account in the management of MS patients since the early disease stages.

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A CROSS-SECTIONAL STUDY INVESTIGATING CLINICAL FACTORS RELATED TO FATIGUE IN MS

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Introduction: Physical fatigue is one of the most disabling symptoms in people with Multiple Sclerosis (pwMS), while there is no conclusive knowledge of either triggers or modifying factors. There is evidence that demographic and clinical variables may have an impact on fatigue in pwMS. A relatively new fatigue assessment, the Fatigue Symptoms and Impacts Questionnaire-Relapsing Multiple Sclerosis (FSIQ-RMS), allows to define better than previous assessments the impact of fatigue in pwMS.

Objects: Aim of our study was to investigate whether demographic and clinical variables may influence the development of fatigue in MS.

Materials: PwMS, aged 18-70 years, underwent a 90-minute interview. Recruitment took place at MS centers of Sant'Andrea and Policlinico Umberto I hospitals in Rome. The physical fatigue symptom was evaluated using the FSIQ-RMS, validated and culturally adapted in Italian, which consists of a double scoring: the first investigates the perception of fatigue relative to previous 24 hours, the second referring to previous 7 days evaluates the impact of fatigue on the ability to perform activities of daily life.

Methods: Gender, education, body mass index (BMI), level of disability measured by the Expanded Disability Status Scale (EDSS), working status, physiotherapy and disease modifying therapies (DMTs) were evaluated and related with fatigue in pwMS. Student t-test or analysis of variance (ANOVA) were used analysing both 24-hours and 7-days FSIQ-RMS scores.

Results: We enrolled 178 patients (132 female), 83% with relapsing MS, and 17% with secondary progressive MS. FSIQ-RMS, both 24-hours and 7-days, was strongly correlated with BMI, with underweight subjects showing a greater level of fatigue ($p<0.001$). Moreover, both FSIQ-RMS scores correlated with a greater level of disability, as assessed by EDSS ($p<0.01$). Finally, greater fatigue level at the 7-days FSIQ-RMS was seen in not-working status and not-exercising physiotherapy ($p<0.01$).

Discussion: We observed an inverse correlation between physiotherapy and perceived fatigue level. This can be an important starting point for future studies investigating both short and long-term effects of the physiotherapy intervention useful to impact the fatigue symptom in MS.

Conclusions: These results underline the importance of normal weight and physiotherapy in mitigating fatigue symptoms in MS.

THE EFFECT OF CLADRIBINE VERSUS FINGOLIMOD ON CLINICAL AND MRI MEASURES IN RELAPSING REMITTING MULTIPLE SCLEROSIS

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Aims: To compare the impact of CLAD (I course) and FINGO on clinical outcome measures, new T2/gadolinium enhancing lesions, brain volumes, white-matter microstructure and cortical lesions in a cohort of RRMS patients.

Materials: A total of 31 patients were included in the analysis, [16 CLAD and 15 FINGO; females: 67.6%; mean age, disease duration, ARR previous year: 41.3+2.8, 12.5+1.8 years, 0.5+0.2; median (range) EDSS: 1.5 (0-4.5); no differences in terms of age, gender, disease duration, ARR and baseline EDSS, 9HPT, T25Fw and balance impairment were found between the two groups]. In this ongoing study, RRMS patients underwent 3T-MRI at the time of treatment start and at 12-months follow-up (FU).

Methods: We used EDSS, ARR, 9HPT, T25Fw as clinical outcome measures. NIH toolbox standing balance test was used to quantify balance impairment. Changes in percentage-brain-volume-change (PBVC) and multi-compartment spherical-mean-technique (SMT) diffusion metrics of the normal-appearing-white-matter (NAWM) were evaluated with repeated measures ANCOVA.

Results: At 1-year FU, 1 patient in CLAD group and 1 patient in FINGO group showed a clinical relapse. No differences in terms of 9HPT-D, 9HPT-ND and T25FW were observed both in CLAD and FINGO group at 1-year FU (for CLAD baseline vs 1-year FU: 22±2.7 vs 21.5±5.5, 5.1±0.9 vs 5.1±1.7 respectively; for FINGO baseline vs 1-year FU: 22.1±2.9 vs 22.7±5.5, 23.5±4.5 vs 24.8±6.3, 5.2±1.4 vs 7±4 respectively). No significant differences were found in terms of balance impairment at 1-year FU both in CLAD and FINGO group (theta value for CLAD baseline vs 1-year FU:0,401±0,4 vs 0,605 ± 0,539; theta value for FINGO baseline vs 1-year FU: 0,592±0,462 vs 0,684±0,476). 4/16 (25%) in CLAD group had new T2/gadolinium-enhancing lesions vs and 5/18 (27.8%) in FINGO group. No differences were noted in terms of PBVC (-1%CLAD vs -0.8% FINGO) and SMT metrics of the NAWM between the two groups. Cortical lesions number did not differ between baseline and 1-year FU both in CLAD and FINGO group.

Discussion: Cladribrine and fingolimod showed their efficacy in treating RRMS in clinical trials. However, data about their comparison in the real clinical practice are still scarce.

Conclusions: We did not observe a superiority of fingolimod vs cladribine (I course) in terms of clinical and MRI measures at 1-year FU in our cohort of RRMS patients.

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CEREBROSPINAL FLUID B CELL AND NEUROAXONAL DAMAGE BIOMARKERS: CORRELATION WITH RELAPSES AND LONG-TERM DISABILITY IN MULTIPLE SCLEROSIS

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Introduction: It is of great importance to commence a high-efficacy drug at onset in those Multiple Sclerosis (MS) patients who are at greater risk of a more severe disease course before potentially irreversible damage occurs. Currently, several biomarkers informing on MS pathophysiology, with prognostic properties, can be measured at onset in cerebrospinal fluid (CSF).

Objective: Aim of the study was to assess the long-term prognostic role of multiple CSF biomarkers of B cell activation and of neuroaxonal

damage, measured at disease onset, in a longitudinal cohort of MS patients.

Methods: The following biomarkers were measured on CSF, collected for diagnostic purposes and stored at -80°C: neurofilament light chain (NFL), tau protein, chitinase-3-like 1 protein (CHI3L1), CXCL13. Furthermore, IgG and IgM oligoclonal bands (OCB) were sought and kappa index (CSF/serum kappa free light chains divided by CSF/serum albumin) calculated. Biomarkers were correlated with the risk of reaching disability milestones (Expanded disability status scale (EDSS) of 2,3,4 and 6 and a secondary progressive course), with the time to a relapse, the number of total relapses and with the use of a second-line treatment (SLT) during follow-up.

Results: Ninety-six patients (61F, 35M, mean age: 34 ± 11 years) were followed up for a median of 135 months (IQR: 100-162). Over this period 34 patients reached an EDSS of 2, 12 of 3, 8 of 4 and only 1 of 6; 4 transitioned to a secondary progressive form and 25 initiated a SLT. EDSS at last follow-up correlated with NFL (rho: 0.3, p=0.004) and CHI3L1 levels (rho=0.3, p=0.004). Baseline CSF NFL and CHI3L1 levels increased the risk of reaching an EDSS of at least 2 (p=0.018 and p=0.038, respectively), but only NFL of reaching an EDSS of at least 3 (p=0.037). CXCL13 and CHI3L1 (rho: 0.3, p<001 and 0.005, respectively) correlated with the number of relapses during follow-up and the time to a first relapse was influenced by high values (> median value) of CXCL13 (>14pg/ml) (p=0.043). NFL levels greater than 1000ng/L influenced the risk of initiating SLT (OR 3.9, 95%CI: 1.5-10.7, p=0.007) and the time to its initiation (p=0.003).

Conclusion: CXCL13 was associated with an early occurrence of relapses and with the total number of relapses, while NFL was associated with long-term disability and predicted the use of SLT during the disease course. This information can be useful during personalized treatment choices at disease onset.

CONSTRUCTION OF A RESOURCE FOR ADVANCE CARE PLANNING IN MULTIPLE SCLEROSIS (CONCURE-SM): RESULTS OF COGNITIVE DEBRIEFING WITH USERS

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Background and Objectives: Advance care planning (ACP) promotes discussion between patients, healthcare professionals (HPs) and, if the patient wishes, family members to ensure that future care will be consistent with the values disclosed, especially at the end of life. A recently published guideline on palliative care in people with progressive multiple sclerosis (PwPMS) [1] and a recent scoping review on ACP in neurodegenerative disorders [2] found no evidence on ACP in this condition. ConCure-SM is a multiphase project designed to set up and evaluate the effectiveness of an ACP intervention for pwPMS in Italy. The intervention consists of a training program on ACP for MS healthcare professionals (HPs) and the use of a fillable booklet during the ACP conversations. In 2020, we translated the booklet of the "Health Quality & Safety Commission's New Zealand National ACP Programme" and adapted it to the MS context and Italian legislation. Here we report the results of booklet appraisal by users and the ensuing revisions.

Methods: Multicenter, qualitative study consisting of 2 rounds. In round 1, we held cognitive interviews with 10 PwPMS and 3 significant others (SOs), and a focus group with 12 HPs (7 neurologists, 3 psychologists, one nurse, and one physiotherapist). In round 2, the booklet was revised and re-appraised by 2 PwPMS and one SO, selected from the most informative in round 1. Participants received the booklet 1-2 weeks before interview/focus group. We analysed the interviews using the framework method, and the focus group using thematic analysis.

Results: Interview analysis yielded three overarching themes: comprehensibility/clarity, content acceptability/emotional impact, and suggestions for improvement. Focus group analysis identified two themes: content importance/clarity, and challenges to ACP implementation. Participants to round 2 confirmed that the revised booklet was improved in clarity of contents, layout and images. They emphasized the importance of using the booklet together with the referring physician.

Conclusions: User's appraisal of the ACP booklet was key to improve its comprehensibility and clarity; we also ascertained common misunderstandings about the role of the HP in this process. HPs highlighted the main barriers to implementing ACP, which were in line with the most recent literature in other settings. The revised booklet is currently being used in a multicenter Italian pilot and feasibility study [3].

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ACTIVITY AND EFFICACY OF RADIAL SHOCK WAVE THERAPY IN REDUCING SPASTICITY IN PEOPLE WITH MULTIPLE SCLEROSIS

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Aims: The study aims to evaluate the efficacy of radial shock wave therapy RSWT in treating spasticity in people with Multiple Sclerosis (PwMS) and the effect on spasticity patterns at surface Electromyography (sEMG).

Materials: Inclusion criteria: MS diagnosis, age>18, MAS≥1. Assessments: Modified Ashworth Scale (MAS), Medical Research Council (MRC), Numeric Rating Scale (NRS) for spasticity, NRS for pain, sEMG (stretch reflex), Timed Up and Go test (TUG), Timed 25 Foot Walking Test (T25-FWT), Global Perceived Effect (GPE).

Methods: The sEMG spasticity patterns [1] evaluated before and after the treatment were the following: activity in dynamic phase (DSR-alone); activity in dynamic and static phase (DSR+SSR); spastic dystonia (SD), activity in dynamic and static phase (SD+DSR+SSR); SD and activity in dynamic phase (SD+DSR); noEMG activity. Treatment consisted of 4-session, 1-week interval. Each session: 2000 shots, frequency of 4 Hz, pressure of 1.5 Bars.

Results: A total of 16 PwMS were recruited (5F/11M, mean age 50.38 [SD= 7.39] years, mean EDSS 5.31 [SD=1.28], mean disease duration 11.31 [SD=7.59] years, 7 relapsing-remitting MS, 5 secondary progressive MS and 4 primary progressive MS course). Muscles treated were: 12 right plantar flexors, 9 left plantar flexors and 1 right knee extensor. Muscles sEMG patterns before RSWT: 16 DSR-alone, 29 DSR+SSR, 21 SD+DSR+SSR. Muscles sEMG patterns after RSWT: 24 DSR-alone, 21 DSR+SSR, 18 SD+DSR+SSR, 3 noEMG activity. Activity measured at DSR during stretch reflex before RSWT was 21.56 [SD=12.88] uV, while it was 17.42 [SD=14.45] uV after treatment, and resulted statistically different between the two time points. Regarding evaluation measures performed, scorse before RSWT were: T25-FWT 12.89 [SD=9.03] s, TUG 19.65 [SD=15.91] s, MAS 1.59 [SD=0.36], MRC 4.5 [SD=0.9], NRS pain 0.73 [SD=2.39], NRS spasticity 3.32 [SD=3.86]. After RSWT: T25-FWT 12.78 [SD=8.51] s, TUG 18.15 [SD=13.59] s, MAS 1.48 [SD=0.72], MRC 4.59 [SD=0.94], NRS pain 0.00 [SD=0.00], NRS spasticity 2.68 [SD=2.86]. Mean GPE for subjective perception was 5.13 [SD=0.96]; 11 subjects perceived a subjective benefit (GPE≥5).

Discussion: Spasticity is frequent in PwMS. Based on spasticity patterns described by Puce et. Al 2021 [1], patterns changes after RSWT were reported. Among clinical evaluations performed and sEMG assessment, only DSR changes significantly after treatment.

Conclusion: RSWT is a new approach to treat spasticity in PwMS and sEMG could be a useful tool to assess treatment effect.

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EVALUATION OF WORK DIFFICULTIES IN MS SUBJECTS AND ITS ASSOCIATION WITH SOCIO-DEMOGRAPHIC FACTORS AND PERFORMANCE MEASURES

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Aims: The study aimed at investigating the frequency of work-related difficulties in workers with MS using the Multiple Sclerosis Questionnaire for Job Difficulties (MSQ-Job) and to evaluate its correlation with objective and subjective performance measures.

Materials: Subjects were assessed through MSQ-Job, Work Productivity and Activity Impairment Questionnaire(WPAI), Timed Up and Go test(TUG), 2-Minutes Walking Test(2MWT), Timed 25-Foot Walk(T25-FW), 9-Hole Peg Test(9-HPT), Hand Grip Strength test(HGS), Modified Fatigue Impact Scale(MFIS-21), Symbol Digit Modalities Test(SDMT), Beck Depression Inventory(BDI-II), Multiple Sclerosis Quality of Life-29(MSQoL-29), Expanded Disability Status Scale(EDSS).

Methods: The study involved 2 Italian centres. Inclusion criteria: diagnosis of MS, age< 65, employed, stable disease course. Subjects were assessed through objective and subjective measures. The sample was stratified based on the MSQ-Job cut-off and divided into 2 groups: with job difficulties (wJD) and without job difficulties (woJD). Differences among the groups were evaluated.

Results: Seventy-five subjects were recruited: mean age 43.2(10.9) yrs, disease duration 9.92 (7.82) yrs, education 15.36(4.22) yrs, mean EDSS 3.6(2.38), disease course: 73.3 % RR, 12% PP and 14.7% SP. Regarding the occupational factors: 22.7% of the sample had reduced working hours and 14.7% had to change work role in the last 6 months. Results obtained at the clinical scales are as follow: MSQ-Job 13.81(11.38), WPAI:MS 22.74(25.67), SDMT 51.09(13.16), BDI-II 7.27(7.24), TUG 11.97(14.3) s, T25-FW 8.96(18.09) s, 2MWT 156.55(68.8) m, MSWS-12 27.83% (26.43), 9HPTdx 33.08(31.99) s, 9HPTsx 30.48(21.16) s, HGSR 26.77(10.05) Kg, HGSL 23.92(11.99) Kg, MFIS-21 20.39(17.1), MSQoL-29 67.9% (16.34). Twenty-seven subjects (36%) results at risk of job loss, based on MSQ-Job cut-off (wJD). The two groups statistically differ for: sex, WPAI:MS, HGS, MFIS, BDI-II and MSQoL-29.

Discussion: A previous study by Raggi et al. 2019 reported that among patients with multiple sclerosis, those who were older, with higher perceived disability and higher depression symptoms have more and more severe work-related difficulties. Whereas, our findings suggested that factor associated with job difficulties are sex, work productivity, handgrip strength, fatigue, depressive symptoms and quality of life.

Conclusion: Factors associated to a risk of job loss are female gender, low work productivity, low handgrip strength, higher level of fatigue both mental and physical, and presence of depressive symptoms and lower quality of life. It is worthy to note that clinical factors such as walking, balance and cognitive functions do not differ among subjects with and without job difficulties.

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INFLUENCE OF COGNITION AND FATIGUE ON THE CORRELATION BETWEEN OBJECTIVE AND SUBJECTIVE UPPER LIMB MEASURE IN PEOPLE WITH MULTIPLE SCLEROSIS

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Aims: The study aimed at evaluate the influence of cognition and fatigue on the correlations between objective and subjective upper limb measures in People with MS (PwMS).

Materials: Subjects were assessed trough 9-Hole Peg Test (9HPT), Box and Block test (BBT), Hand Grip Strength (HGS), Manual Ability Measure-36 (MAM-36), Modified Fatigue Impact Scale (MFIS) and Symbol Digit Modalities Test(SDMT).

Methods: The multicentre study included 5 Italian neurological centres. Subjects were included with age>18 years and confirmed diagnosis of Multiple Sclerosis (MS) and assessed through clinical scales. Spearman correlation was used to assess correlation in the whole sample and stratifying based on MFIS and SDMT cut-off.

Results: Sample consisted of 200 PwMS: 132 females; mean age of 51.66(13.60) years; mean disease duration of 14.75(10.91) years; 105 relapsing-remitting, 39 primary progressive, 56 secondary progressive disease course, mean EDSS of 4.89 (1.92). Scores obtained at the test were: 9HPT-R 36.41(30.24) s, 9HPT-L 40.86(37.35) s, BBT-R 45.48(15.87) blocks, BBT-L 44.70(15.39) blocks, HGS-R 20.01(9.91), HGS-L 18.11(8.94), SDMT 38.02(14.07), MFIS 33.01(18.43). Fatigue showed correlations with left-9HPT (L:r=0.167, p<0.05), with BBT (R: r=-0.208, p<0.01; L:r=-0.216, p<0.01) and HGS (R:r=-0.178, p<0.05; L:r=-0.228, p<0.01) on both arms, and with MAM36 (r=-0.490, p<0.01). SDMT correlated with MAM-36 (r=0.170, p<0.05), BBT for both arms (R:r=0.214, p<0.01; L:r=0.261, p<0.01), and 9HPT on both arms (R: r=-0.235, p<0.01; L: r=-0.307, p<0.01). No correlations emerged between HGS and SDMT. Correlation between the MAM-36 and objective upper limb (UL) measures showed minor variations based on the level of cognitive impairment and fatigue. On both arms, correlations between 9HPT and MAM36 were significantly stronger among patients without cognitive impairment (SMDT>48) (i: R: r=-0.310, p=0.000; L:r=-0.271, p=0.01; n-i: R: r=-0.592, p=0.000; L:r=-0.531, p=0.000; p-value<0.001). There were no significant differences across the groups in the correlation between the MAM-36, HGS and BBT. Stratifying the sample based on MFIS cut-off (MFIS>38) no significant differences across the groups in the correlation between MAM-36 and objective UL measures were observed.

Discussion: Small correlations between 9HPT, BBT, HGS and MAM-36 has been reported previously [1]. The present study reported the correlation between 9HPT, BBT, HGS, MAM-36 and MFIS and SDMT, moreover correlation among objective and subjective UL measure were reported in subject with and without fatigue and with and without cognitive dysfunction.

Conclusion: Although cognitive function were evaluated only using SDMT, cognition, but not fatigue, may influence correlation between objective and subjective UL measure.

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CSF IFN-GAMMA LEVELS ARE ASSOCIATED WITH DEPRESSIVE SYMPTOMS SEVERITY IN MULTIPLE SCLEROSIS

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Introduction: Psychiatric symptoms show a high prevalence in people with multiple sclerosis (pwMS). Depression may occur as the consequence of emotional reactions to the diagnosis of a chronic disease and it potentially disabling disease course [1]. Other biological mechanisms, such as circuit disconnection, neurotransmitters imbalance, neuro-inflammation, and synaptic dysfunction, might play a pathogenic role [2]. Interferon gamma (IFNγ), a potent pro-inflammatory cytokine has been hypothesized to play a role in the pathogenesis of depression [3].

Aim: To verify whether cerebrospinal fluid (CSF) levels of IFNγ at diagnosis are able to differentiate between pwMS with and without clinically relevant depression at follow-up.

Methods: The CSF levels of IFNγ in were tested in a cohort of 27 pwMS (relapsing-remitting phenotype, mean age 39.4±11.9 years, F:M 3:1) by means of an ultrasensitive assay (Simoa). Depression and anxiety were tested at follow-up by the use of BDI-II, STAI-Y1 and STAI-Y2.

Results: STAI-Y1, STAI-Y2 and BDI-II scores at follow-up (mean: 3.7 ± 2.3 years, median: 3.2 years, range: 0.1-7.8 years) were 41.7 ± 12.2, 41.2 ± 8.6, and 9.9 ± 6.1, respectively. Mean baseline CSF IFNγ levels were 0.169 ± 0.327 pg/mL (median: 0.095, range: 0.007-0.233 pg/mL). We did not find significant associations between CSF IFNγ and STAI-Y1 and STAI-Y2 scores. When categorizing pwMS according to follow-up BDI-II scores, we found that five patients (18.5%) had BDI-II scores ≥ 14, suggestive of clinically relevant depression. PwMS with BDI-II ≥ 14 had significantly higher baseline CSF levels of IFNγ (0.426 ± 0.653 vs 0.094 ± 0.082 pg/mL, p=0.02) compared to pwMS with BDI-II < 14.

Conclusions: Baseline CSF levels of IFNγ are higher among pwMS with more severe depressive symptoms at follow-up. Such findings suggest that IFNγ might be involved in the pathophysiology of affective symptoms in MS and deserve further studies.

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LOW SERUM VITAMIN D LEVELS ARE ASSOCIATED WITH COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS

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Objective: Cognitive impairment frequently affects people with multiple sclerosis (MS) possibly due to neurodegenerative mechanisms. Low vitamin D levels have been associated with cognitive features in different neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease), and, in MS, with motor disability and disease activity. We aim to investigate associations between vitamin D and cognitive status in MS.

Patients and Methods: In this cross-sectional study, we included 181 MS patients having serum 25-hydroxy-vitamin D measurements using Chemiluminescence ImmunoAssay, and cognitive assessment using the Brief International Cognitive Assessment for MS (BICAMS), which includes the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test II (CVLT-II) and Brief Visuospatial Memory Test-Revised (BVMT-R). Cognitive raw scores were age, sex and education-adjusted using Italian normative values. We collected demographic (age, sex), and clinical variables (disease duration, disease subtype, expanded disability status scale (EDSS), disease modifying treatment (DMT), relapses in previous 12 months, steroid treatment in previous 12 months, concomitant vitamin D supplementation, comorbidities).

Results: At univariate linear regression models, higher levels of vitamin D were associated with higher scores on SDMT (Coeff=0.93; 95%CI=0.81, 1.04; p<0.01), CVLT-II (Coeff=0.68; 95%CI=0.53, 0.83; p<0.01), and BVMT-R (Coeff=0.58; 95%CI=0.43, 0.73; p<0.01), with lower number of impaired BICAMS tests (Coeff=-9.63; 95%CI=-11.48, -7.79; p<0.01), and with lower EDSS (Coeff=-2.16; 95%CI=-3.57, -0.75; p<0.01). At multivariate linear regression models including all demographic, clinical and cognitive variables, EDSS was the only clinical correlate of vitamin D levels (Coeff=-2.14; 95%CI=-4.57, -0.71; p<0.01), while, among cognitive variables, SDMT (Coeff=0.73; 95%CI=0.58, 0.87; p<0.01) and CVLT-II (Coeff=0.14; 95%CI=0.01, 0.28; p=0.04) remained associated with vitamin D levels, but no association was found for BVMT-R (Coeff=0.10; 95%CI=-0.05, 0.26; p=0.19).

Conclusions: Higher vitamin D levels were associated with better performance in MS on multiple cognitive domains, including attention, information/processing speed and verbal memory. Vitamin D possibly affects neurodegenerative aspects of MS, as already seen for conventionally neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease). Future studies should consider longitudinal variations in cognitive function in relation to vitamin D supplementation.

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PREVENTIVE EXERCISE AND PHYSICAL REHABILITATION PROMOTE LTP-LIKE PLASTICITY EXPRESSION IN PATIENTS WITH MULTIPLE SCLEROSIS

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Objectives: Synaptic plasticity, and particularly long term potentiation (LTP), is a key physiological mechanism involved in clinical compensation of brain damage. Impaired LTP expression has been associated with worse disease course in patients with multiple sclerosis (MS) and represents a physiological hallmark of progressive MS [1]. Exercise and physical rehabilitation represent the main treatment options to promote synaptic plasticity and clinical recovery. Here we explored whether physical exercise (either preventive exercise or physical rehabilitation) is able to restore the expression of LTP-like plasticity in MS patients.

Methods: In a group of 46 newly diagnosed relapsing-remitting (RR) MS patients, we explored the impact of preventive exercise on LTP-like plasticity as assessed by the intermittent theta burst stimulation (iTBS) protocol. Patients were divided into two groups, sedentary and active, based on physical activity levels in the six months prior to diagnosis. In addition, in 16 patients with progressive MS (PMS), we evaluated the impact of an 8-week (6 days per week) inpatient rehabilitation program on LTP-like plasticity explored using the paired associative stimulation (PAS) protocol. Transcranial magnetic stimulation (TMS) was performed over the motor hot spot of the APB muscle for PAS [2]. iTBS [3] was applied to the FDI motor hot spot. At baseline, 15 MEPs of 0.5-1 mV peak-to-peak amplitude were recorded. Using the same stimulation intensity MEPs were recorded 5, 15, and 30 minutes after PAS or iTBS. MEP amplitudes were averaged at each time point and normalized to the baseline. Repeated measures ANOVA was applied to evaluate differences in TMS variables. Spearman's rho and Pearson correlations were used to test possible associations between TMS variables and clinical characteristics. p<0.05 were considered statistically significant.

Results: Preventive exercise in RR-MS patients was associated with increased expression of LTP-like plasticity. Specifically, the effect of iTBS was significantly higher in exercising patients compared with sedentary patients (p<0.05 at all time points). This association was significant even controlling for other clinical characteristics. In patients with PMS, a significant increase in the LTP-like effect induced by the PAS protocol was evidenced after 8 weeks of physical rehabilitation compared with baseline (p<0.05 at all time points).

Discussion and conclusions: Preventive exercise and physical rehabilitation may promote the expression of LTP-like synaptic plasticity in patients with RR-MS and PMS, with potential beneficial effects on disability accumulation.

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DIFFERENTIATING MS LESIONS WITH OR WITHOUT PARAMAGNETIC RIM WITH ADVANCED MRI

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Introduction and aims: In MS, paramagnetic rim lesions (PRLs) are thought to reflect chronic active inflammation mediated by microglia which may lead to a progressive neuronal damage and peripheral iron accumulation. PRLs microstructural characterization by advanced MRI

techniques may help to clarify their role in MS pathophysiology. Thus, we would to investigate if there are differences in microstructure between PRLs and no-PRL MS lesions detectable via diffusion MRI and/or quantitative susceptibility mapping (QSM).

Methods:78 RRMS patients were prospectively enrolled. WM lesions were stratified as PRLs and no-PRLs by visual inspection on GRE-phase images and QSM maps. Both PRLs and no-PRLs were further subdivided in two groups: FLAIR hyperintense/T1 isointense (isoT1) and FLAIR hyperintense / T1 hypointense (hypoT1) lesions. Within the lesions groups, differences in microstructure were studied with diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI) while intensity of paramagnetic signal was extrapolated from QSM. All measures were compared with Kruskal-Wallis and then Mann-Whitney Test accounting for age, sex, and lesion volume.

Results: out of 2819 lesions identified, 125 (4.4%) were PRLs. While all PRLs resulted hypoT1, 432 (15.3%) no-PRLs were isoT1 and 2262 (80.2%) were hypoT1. All DTI and NODDI parameters except for NODDI-isotropic volume fraction were significantly different between PRLs and isoT1 no-PRLs, and between no-PRLs hypoT1 and isoT1 ($p<0.001$ for all parameters). Statistically significant lower FA (p:0.005) and higher MD (p:0.034) and RD (p:0.005) together with higher ICVF (p:0.013) were found in PRLs compared to hypoT1 no-PRLs. Paramagnetic signal was significantly higher in PRLs than in both hypoT1 and isoT1 no-PRLs (p: <0.001 for both groups).

Discussion and conclusions: Microstructural analysis with DTI and NODDI and paramagnetic signal quantification with QSM were able to distinguish PRLs from no-PRLs. Particularly, PRLs showed higher degree of axonal damage and increased paramagnetic signal in comparison not only with isoT1 but also with hypoT1-noPRL. Therefore, PRLs seemed to show a more destructive behaviour which may contribute to explain their association with disability accrual in MS.

SAFETY, IMMUNOGENICITY, EFFICACY, AND ACCEPTABILITY OF COVID-19 VACCINATION IN PEOPLE WITH MS

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Background: The recent global health crisis – due to COVID-19 pandemic - has led to the death of millions, in particular among fragile individuals. Accordingly, people affected by chronic diseases are at increased risk for higher mortality from COVID-19. In this complicated context, the introduction of effective vaccines was a crucial moment for the management of SARS-CoV2 infection. However, the immunization campaign has been hampered by some hesitancy, especially by some subgroup of people who questioned the safety of new vaccines. This led to a general sense of distrust. In this literature review, our aim was to investigate the main evidence about the safety and side effects, immunogenicity, efficacy, and willingness of the COVID-19 vaccine in patients with Multiple Sclerosis (pwMS).

Methods: We considered articles published from 2020 to 2022, searching electronically on PubMed and Google Scholar databases. We used a combination of the following keywords/terms: COVID-19, SARS-CoV-2, Multiple Sclerosis, Vaccine, Safety, Efficacy, Acceptability, Willingness, Immunogenicity, Side effects, Disease-modifying therapies, Humoral response, Cellular response.

Results: Due to massive information campaigns, the acceptability of SARS-CoV-2 vaccines has significantly increased in the last year, although a relevant cluster of pwMS is still doubtful about the safety of vaccination. Available evidence confirms the safety and effectiveness of the COVID-19 vaccination among vulnerable people. Nevertheless, lower-grade immunization has been recorded among MS patients undergoing specific pharmacological treatments, such as anti-CD20 therapies or sphingosine l-phosphate receptor modulators.

Discussion: A strong recommendation for COVID-19 immunization should be promoted in patients with MS. Regarding people treated with anti-CD20 therapies and sphingosine l-phosphate receptor modulators, a tailored approach should be realized to identify the appropriate timing for vaccine administration. Further studies are needed to understand the role of cellular immunity in COVID-19 vaccination and the possible usefulness of further booster jabs.

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PREGNANCY PLANNING AND MANAGEMENT FOR WOMEN WITH MULTIPLE SCLEROSIS: NEUROLOGIST' AND PATIENTS' PERSPECTIVES

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Aim: To describe how pregnancy planning and management have changed in the last 15 years from neurologist' and Multiple Sclerosis (MS) patients' perspectives.

Materials and methods: We retrospectively enrolled all female patients with RRMS, referring to the Neurology Clinic of the University Hospital "Policlinico G. Rodolico" of Catania, who started a pregnancy between January 2005-December 2021. We collected data about demographics, MS and pregnancy course, disease-modifying treatment (DMT). After dividing the observation time in two periods according to pregnancy onset (January 2005-December 2013; January 2014-December 2021), we compared data about pregnancies belonging to each group. Participants were asked to answer an online 37-item questionnaire about their perspectives on pregnancy planning and course.

Results: 190 patients with RRMS carried 253 pregnancies in the selected time period. Age at first pregnancy was higher in the second period (33.1±5.7 vs 30.9±4.6 y, p=0.004), while no differences in disease duration at pregnancy, number of pregnancies and pregnancy outcomes were observed. Women undergoing a pregnancy in the second period were more frequently treated with high-efficacy DMT ($\chi2=41.7$; $p<0.001$) and exhibited a minor tendency to discontinuation before or during pregnancy ($\chi2= 41.4$; $p<0.001$). A lower annualized relapse rate (ARR) was recorded in the second period in the year before (0.20±0.45 vs 0.38±0.65; p=0.01) and after pregnancy (0.15±0.47 vs 0.47±0.76; p<0.001), while EDSS scores were not significantly different between groups. Among 42 responders to our survey, 14 (33.3%) declared that MS affected the decision to plan a pregnancy, and 16 (38.1%) planned the pregnancy with the

neurologist, who suggested to postpone pregnancy in 9 cases (56.3%). The neurologist was the main source of information for all pregnancy-related issues for 29 (69.0%) patients, dealing with pregnancy planning (31, 73.8%), MS course during pregnancy (33, 78.6%) and post-partum (32, 76.2%), mode of delivery (17, 40.5%), use of anesthesia (19, 45.2%), lactation (22, 52.4%), genetic counseling (23, 54.8%). Comprehensively, patients' perception of pregnancy planning and management was not different in the two periods considered.

Discussion and conclusion: Neurologists have changed their approach to pregnancy planning and management over years, tending more often to administrate and to not discontinue highly effective DMT whenever practicable. Accordingly, MS patients were less inclined to have relapses before and after pregnancy. Differently, the patient-doctor communication, dealing with patients' needs for elucidation and psychological support, has not changed much over time, despite neurologists remains the main reference point for women with MS facing a pregnancy.

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SIPONIMOD PRESERVES RETINAL THICKNESS, A MARKER OF NEURODEGENERATION, IN PATIENTS WITH SPMS: FINDINGS FROM THE EXPAND OCT SUBSTUDY

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Objectives: The inner retinal layer of people with multiple sclerosis (MS) shows abnormal thinning over time, reflecting neuroaxonal loss, and has been associated with MS-related disability and brain atrophy. In the Phase 3 EXPAND trial, siponimod significantly reduced the risk of 3-/6-month (M) confirmed disability progression, MRI disease activity and brain atrophy compared with placebo.

Objective: To assess the impact of siponimod versus placebo on retinal thinning, as measured by optical coherence tomography (OCT), during the core phase of the EXPAND trial in patients with SPMS who participated in the OCT substudy.

Aim: To evaluate changes in retinal thickness (μm), including the retinal nerve fibre layer (RNFL) and combined ganglion cell and inner plexiform layers (GCIPL), in patients receiving siponimod or placebo.

Methods: Changes in OCT measurements from screening to M12 and M24 were compared between the two treatment groups using mixed models for repeated measures adjusted for treatment, age, sex and respective baseline OCT variables.

Results: The OCT substudy included 159 patients (siponimod, n=104; placebo, n=55). At baseline, mean age and EDSS score, and other clinical variables were similar, but patients in the siponimod group had higher MRI disease activity and lesion volume than the placebo group. The mean baseline RNFL and GCIPL thickness was lower in the siponimod group compared to placebo. RNFL thickness at M12 numerically favoured siponimod (0.39 vs −0.99; difference 1.37, p=0.099) but not at M24 (−0.05 vs. 0.48; difference=−0.54, p=0.642). However, fewer assessments were available for RNFL at M24 (m, number of eyes: siponimod, m=40; placebo, m=12) than M12 (siponimod, m=64; placebo, m=40). The between-group difference in GCIPL thinning was 0.21 (−2.55 vs −2.76; p=0.875) at M12 and 3.82 (−0.47 vs −4.29; p=0.01) at M24. Siponimod reduced retinal thinning vs placebo at M12 (change from baseline: 0.66 vs −1.86; difference=2.53, p=0.006) and M24 (−0.05 vs −2.3; difference=2.25, p=0.033). Changes of retinal thickness and GCIPL at the subfield areas also favoured siponimod over placebo.

Conclusions: These results, though obtained in a relatively small number of participants, support the sensitivity of OCT as a measure of tissue damage in progressive MS and are in line with previously reported beneficial effects of siponimod on other outcomes related to neurodegeneration in EXPAND (grey matter atrophy and magnetisation transfer ratio). EXPAND: ClinicalTrials.gov Identifier: NCT01665144 https://clinicaltrials.gov/ct2/show/NCT01665144

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IMPACT OF COVID-19 LOCKDOWN MEASURES ON MENTAL HEALTH IN MULTIPLE SCLEROSIS PATIENTS: THE ROLE OF REMOTE ASSESSMENT

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Objectives: Post-traumatic stress disorder (PTSD) has been reported in up to 15% of general population during and after the first wave of the COVID-19 pandemic. [1] The study aims to evaluate the presence of PTSD symptoms as effect of lockdown measures in people with MS (PwMS) using an e-health application specifically built for remote management of PwMS, SMcare2.0® application.

Methods: Between March 4, 2020 and July 5, 2020 (T0) PwMS who were using (n=290) the app filled in the Impact of Event Scale - Revised (IES-R) questionnaire to evaluate PTSD symptoms. The IES-R has 3 subscales, intrusion, hyperarousal, avoidance, and a total score ranges from 0 to 88, with a cut-off value of 33 defining the presence of PTSD

symptoms (PTSD+). Only PwMS who completed the questionnaire the first time were asked to answer again after lockdown abolishment (T1). Clinical and demographic data were extracted from the Italian MS register application and linked to the IES-R results. Baseline clinical characteristics of PwMS (classified on the basis of IES-R score) and the proportion of PTSD+, subscales and total score at T0 and T1 were compared.

Results: During the lockdown 90 PwMS (31% response rate) completed the IES-R (62 F; mean (SD) age 40.1(1.0) years; median (IQR) EDSS score 2.3 (1-8); mean disease duration (SD) 10.7 (0.7)). Mean (SD) baseline subscales values were: intrusion 15.9 (7.1), hyperarousal 10.7 (5.0), avoidance 15.4 (6.7). Mean (SD) total IES-R score was 42.0 (17.0), 63 (70%) patients scored above 33 and were identified as having recently developed PTSD symptoms. No significant difference was found between PTSD+ and PTSD- patients in terms of age, EDSS and disease duration. At T1 the IES-R scores were significantly reduced in comparison to T0 scores (intrusion 8.6 (8.9), hyperarousal 6.0 (5.8), avoidance 8.4 (8.5), total score 4.8 (1.9), p<0.0001). The number of PTSD+ patients was significantly reduced in comparison to T0 (16 (17.8%), p<0.0001).

Discussion: The COVID-19 pandemic has acted as a catalyst for the application of telemedicine in neurology, allowing to evaluate even psychiatric symptoms. Lockdown measures caused a significantly sustained negative impact on lifestyles: assessing PTSD signs in PwMS is fundamental because prolonged stress may play a crucial role on exacerbation of disease activity and deterioration of the quality of life in MS. [2-3]

Conclusions: Our study demonstrated that PwMS during and after lockdown manifested post-traumatic stress symptoms, highlighting the strategic role of E-data in remotely monitoring patients.

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PROGRESSION INDEPENDENT OF RELAPSE ACTIVITY (PIRA) IN RELAPSING-REMITTING MULTIPLE SCLEROSIS PATIENTS ON INJECTABLE VS ORAL FIRST LINE DISEASE MODIFYING THERAPIES: AN ITALIAN REGISTRY STUDY

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Objectives: To analyze the contribution of relapse-independent progression (PIRA) vs relapse-associated worsening (RAW) to overall confirmed disability progression (CDP) in a cohort of pwRRMS undergoing as first therapy injectable disease-modifying therapies-DMTs (interferons/glatiramer acetate-IFNs/GA) or oral ones (Teriflunomide and Dimethyl fumarate-TERI/DMF) in a real-world setting.

Materials and Methods: Data from the Italian MS register were analyzed. We investigated the rate of confirmed disability progression (CDP) overall and separately as RAW and PIRA. CDP was defined as an increase of EDSS by 1 step (0.5 step, if previous EDSS was ≥5.5; 1.5 steps if previous EDSS was 0) compared to the year before and confirmed one year later. PIRA was defined as no relapses since the start of DMT. We included pwRRMS starting the investigated DMTs between 2013 and 2019 with >2 years of follow-up. The risk of CDP, PIRA, and RAW was compared among the investigated DMTs using a multivariable regression model adjusted for baseline characteristics.

Results: We included 2660 patients [1510 (56.8%) IFNs, 656 (24.7%) GA, 142 (5.3%) TERI, 352 (13.2%) DMF, median (standard deviation) age 41.1 years (SD 11.2); 70.7% female; median baseline EDSS=1.5 (interquartile range 1.0-2.0); mean follow-up 39.5 (SD 25.2) months]. DMT groups were well balanced about potential confounders. In total, 1688/2660 patients had at least one relapse during follow-up. CDP was observed in 987 patients (22.7%). Overall, PIRA was observed in 393 pwRRMS: 16.9% of the IFNs, 14.5% of the GA, 10.6% of the TERI, and 8.0 % of the DIM. RAW was observed in 594 pwRRMS: 36.6 % of the IFNs,34% of the GA, 25% of the TERI, and 24.4% of the DIM. Adjusted regression analysis indicated a higher frequent occurrence of PIRA in pwRRMS treated with IFNs than those treated with TERI (HR 2.074, CI 1.178-3.653, p=.012) and DMF (HR 2.471, CI 1.627-3.754, p<.001]. Among patients with relapses, the occurrence of RAW was higher in pwRRMS treated with IFNs than those treated with DIM [HR 1.650, CI 1.001-2.719, p=.049].

Discussion: A relevant proportion of CDP in pwRRMS was not relapse-associated. Among patients without any relapses on DMT, the rate of disability progression was higher in IFNs than in TERI/DMF-treated pwRRMS. RAW was also higher in IFNs than DMF treated pwRRMS.

Conclusions: The analysis of the proportion of disability worsening due to non-inflammatory processes is fundamental in guiding therapeutic choice and studying disease trajectories.

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A QUANTITATIVE ANALYSIS OF RESILIENCE AND COPING STRATEGIES IN THE MOTHER WITH MULTIPLE SCLEROSIS

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Background: Psychological difficulties are common among people with MS (pwMS), particularly among women in childbearing age and pregnancy is still a prominent concern. The resilience and the coping strategies

play a fundamental role in modulating the psychologic impact of the disease. The present study aimed to evaluate the level of resilience and the effectiveness of adopted coping strategies in mothers and childless women with MS.

Methods: Fifty-two mothers and fifty childless women diagnosed with Relapsing-Remitting MS (RR-MS) received the Resilience Scale (RS), the Resilience Scale for Adults (RSA) and the Brief COPE.

Results: Mothers group was older than childless women group and there were also difference for marital status ($p<0.001$), educational age and occupation ($p<0.001$). The RS and RSA scores (overall and single factors) were no difference in the two groups. The Brief COPE showed that mothers mainly adopted "behavioral disengagement" ($p=0.01$), the "positive refreming" ($p=0.02$) and the "acceptance" ($p=0.04$) strategies.

Discussion: The motherhood is not associated with high resilience among women with MS but mothers showed greater heterogeneity in the use of coping strategies than childless women, preferring both avoidant and emotional strategies oriented.

Conclusions: Motherhood seems not to impact on resilience and on disease management. Mothers are more prone to "flexibility" in multiple life contexts. Our study suggests that specific psychological programs were needed to support women with MS, according to their maternal status.

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MANAGEMENT MODEL OF SARS-COV-2 VACCINATION IN A COHORT OF FRAGILE PATIENTS WITH MULTIPLE SCLEROSIS

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Background: Vaccination offers a crucial opportunity for reducing COVID-19 transmission and Vaccine Hesitancy (VH) is a major public health concern. The present study aimed to evaluate the effectiveness of our vaccination protocol to increase vaccine adherence in people with MS (pwMS). Furthermore we assessed their VH and its relationship with anxiety levels.

Methods: From April to June 2021 we administered the Health Anxiety Questionnaire (HAQ) to pwMS eligible for the COVID-19 vaccine (mRNA BNT162b2 vaccine - Pfizer/BioNTech) to estimate COVID-19 vaccine willingness and to assess the level of health anxiety.

Results: Out of 334 patients, 92.8% accepted to be vaccinated, while 7.2% was vaccine hesitant reporting distrustful (62%) or great concern about vaccine (38%). Overall, 149 vaccinated and 24 refusing patients were included in the statistical analysis. DMTs duration was significantly higher in the refusing patients (77.8 vs. 47.8 months; $p=0.03$). We found no differences regarding the HAQ scores between vaccinated and refusing patients.

Discussion: The rate of COVID-19 hesitancy was lower than general population and other studies on pwMS. VH was not readily explained by demographics, psychological distress and clinical condition, except the duration of taking DMTs. We suggest that he patients most longly treatment time are also those clinically more stable and therefore less concerned about risk of the vaccine effect to their disease condition.

Conclusions: Medical and psychological presence of the hospital team and educational efforts are the most important predictors to reduce the VH rate. We highlight the importance of patient-centered programs that are associated with major COVID-19 vaccine willingness.

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AMA-VACC: CLINICAL TRIAL ASSESSING THE IMMUNE RESPONSE TO SARS-COV-2 MRNA VACCINES IN SIPONIMOD TREATED PATIENTS WITH SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS

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Objectives: SARS-CoV-2 mRNA vaccines are a key factor fighting the COVID-19 pandemic across the globe. However, data are lacking on the efficacy of vaccination in patients with secondary progressive multiple sclerosis (SPMS) on disease-modifying therapies (DMTs) both over time and after a booster vaccination. We are aiming to understand the longitudinal cellular and humoral immune responses to SARS-CoV-2 mRNA vaccines depending on the timing of vaccination and SPMS treatment.

Materials: AMA-VACC is an open-label, three-cohort, prospective study in Germany with 41 multiple sclerosis patients currently treated with siponimod, any first-line DMT or without treatment at all in clinical routine. Cohort 1 receives SARS-CoV-2 mRNA vaccination while continuing their current siponimod treatment, cohort 2 interrupts siponimod treatment for the purpose of a full vaccination cycle and cohort 3 receives vaccination during continuous treatment with first-line DMTs (glatirameracetate, interferons, teriflunomide) or no current treatment in clinical routine.

Methods: Primary endpoint is the rate of patients achieving seroconversion assessed by detection of serum neutralizing antibodies one week after SARS-CoV-2 mRNA vaccination. Furthermore, development and maintenance of SARS-CoV-2 specific T-cells is evaluated in all patients. Both parameters are analyzed in week one and month one and six after initial vaccination cycle and one month after a potential booster vaccination.

Results: After a positive first interim analysis showing both SARS-CoV-2 neutralizing antibodies and T-cell responses one week after complete vaccination in siponimod patients data will be available in early

2022 for all patients at week one and later time points including first booster vaccinations. If possible, AMA- VACC results will be compared to findings from other clinical SARS-CoV-2 vaccination studies in patients with MS.

Conclusions: This analysis will provide first longitudinal data on the immune response after SARS-CoV-2 mRNA vaccination in siponimod treated SPMS patients and enable physicians and patients to make an informed decision on the coordination of SARS-CoV-2 mRNA vaccination and SPMS treatment.

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- AMA-VACC: ClinicalTrials.gov Identifier: NCT04792567
- https://clinicaltrials.gov/ct2/show/NCT04792567

SLEEP

EPIGENETIC CLOCKS SUGGEST ACCELERATED AGEING IN PATIENTS WITH ISOLATED REM SLEEP BEHAVIOR DISORDER

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Objectives and Background: Isolated REM Sleep Behavior Disorder (iRBD) is a well-recognized prodromal state of an underlying α-synucleinopathy, occurring several years before an overt neurodegenerative disorder can be fully manifest. Indeed, the presence of iRBD indicates already early ageing and neurodegeneration of specific brainstem nuclei. Epigenetic clocks are mathematical models that, starting from DNA methylation profiles, return an estimate of the age of an individual. The discrepancy between predicted epigenetic age and chronological age (i.e., the epigenetic age acceleration –EAA) has proven to be informative of biological age in several pathological conditions, including neurodegenerative diseases. To date, epigenetic clocks have not been evaluated in Rapid eye movement sleep Behavior Disorder (RBD). We aim to evaluate biological aging in iRBD to evaluate its value as a marker of neurodegeneration.

Materials: We compared epigenetic age between videopolysomnography (vPSG)-confirmed iRBD patients (iRBD_pos) and vPSG-negative controls (CTR_vPSG). We considered the following epigenetic clocks, based on distinct sets of CpG sites, which can be indicative of different aspects of biological age: 1) the pan-tissue Horvath's clock; 2) the blood-specific Hannum's clock; 3) the PhenoAge, developed considering clinical measures related to differences in healthspan and lifespan; 4) the GrimAge, developed considering plasma levels of 7 proteins and smoking pack-years, associated with mortality.

Methods: We calculated EAA for each epigenetic age estimate, obtaining the following values: Horvath-EAA, Hannum-EAA, PhenoAge-EAA and GrimAge-EAA. We also calculated two additional EAA measures derived from Horvath's clock: the intrinsic-EAA, that is independent from changes in blood cell composition, and the extrinsic-EAA, that is indicative of immunosenescence.

Results: We compared 28 iRBD_pos (23 males, age 67.92±7.20 years) and 57 CTR_vPSG (32 males, age 66.56±9.56 years). Compared to CTR_vPSG, iRBD_pos patients showed higher Horvath-EAA and intrinsic-EAA values when correcting for experimental batch (CTR_vPSG =0.42±4.78 iRBD_pos=3.74±5.57 p=0.04 and CTR_vPSG =-0.90±5.92 iRBD_pos=3.78±6.77 p=0.03 respectively). A similar trend was present also for most of the other EAA values, without reaching statistical significance. When sex was added as covariate, intrinsic-EAA values were confirmed as marginally significantly different between CTR_vPSG and iRBD_pos (p=0.05).

Discussion and Conclusions: Our results suggest the presence of an accelerated ageing process in iRBD patients in respect to controls. As previously demonstrated by Horvath and collaborators in Parkinson's Disease, we suppose that the accelerated ageing in these patients reflects the neurodegenerative process already occurring in the brainstem. Bigger cohorts and longitudinal evaluations will allow us to strengthen these data and to evaluate their predictive value.

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EFFECTS OF DARIDOREXANT ON SLEEP AND DAYTIME FUNCTIONING IN OLDER PATIENTS WITH INSOMNIA DISORDER

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Objective: Insomnia impacts older adults more than younger adults. Drugs that improve insomnia symptoms with limited safety risks are needed to treat this patient group. We report elderly subgroup analyses from a phase-3 registration trial with daridorexant.

Methods: In this multi-center, double-blind trial (NCT03545191), adult (18–64 years) and elderly (≥65 years) patients with insomnia were randomized (1:1:1) to receive oral daridorexant 25mg, 50mg or placebo every evening for three months. Month 3 endpoints were: change from baseline in polysomnography-measured wake-after-sleep-onset (WASO) and latency-to-persistent-sleep (LPS) (both primary endpoints), subjective total sleep time (sTST), and daytime functioning (Insomnia Daytime Symptoms and Impacts Questionnaire [IDSIQ] – sleepiness domain; with a lower score indicating improved daytime functioning). Safety endpoints included treatment emergent adverse events (TEAEs), AEs of special interest (AESI; symptoms related to excessive daytime sleepiness or complex sleep behavior, and suicidal ideation/self-injury) and withdrawal effects upon treatment cessation (assessed by the Benzodiazepine Withdrawal Symptom Questionnaire total score and relevant AEs).

Results: Of the 930 patients randomized, 364 (39.1%) were ≥65 years: daridorexant 25mg (n=121), 50mg (n=121) and placebo (n=122). In this subgroup, at Month 3, the placebo-corrected least-square mean of change from baseline [95%CL] for daridorexant 25 mg and 50 mg were: WASO -17.0 [-27.0, -7.0] and -19.6 [-29.5, -9.7] min; LPS -7.8 [-15.2, -0.4] and -14.9 [-22.3, -7.5] min; sTST 18.7 [4.1, 33.2] and 30.6 [16.1, 45.2] min;

IDSIQ sleepiness domain -0.6 [-2.2, 0.9] and -2.6 [-4.1, -1.0], all respectively. TEAEs were reported in 32.2%, 35.3%, and 31.1% of patients ≥65 years in the 25mg, 50mg and placebo groups, respectively. Falls (n=1, 1, 4 for 25 mg, 50mg, placebo, respectively) and dizziness (n=4, 1, 1 for 25 mg, 50 mg, placebo, respectively), both of particular interest in elderly, were least frequent in the 50mg group. Compared to placebo, somnolence was as frequent for 50mg daridorexant (n=6, 1, 1 for 25mg, 50mg, placebo, respectively) while fatigue was more frequent in both daridorexant groups (n=4, 3, 1 for 25mg, 50mg, placebo, respectively); the incidence did not appear dose related. AESI, of mild intensity, were reported in two patients ≥65 years (one per daridorexant group). There was no evidence of withdrawal symptoms.

Conclusions: Daridorexant is efficacious in older adults for improvements in sleep and daytime functioning. No safety concerns in this vulnerable population were identified. Acknowledgements: Funded by Idorsia Pharmaceuticals Ltd. Previously presented at 16th World Sleep Congress, Mar 11-16 2022, Rome, Italy

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SIPONIMOD IN SECONDARY PROGRESSIVE MS: ANY EFFECT ON SLEEP QUALITY?

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Objective: Siponimod has been recently approved as a disease modifying treatment for secondary progressive multiple sclerosis (SPMS). Multiple sclerosis (MS) patients may complain of sleep disorders which influence disease course and quality of life. In this study we aimed to assess sleep quality in MS patients before and after the introduction of treatment with siponimod.

Material and Methods: Ten secondary progressive MS patients due to start siponimod were enrolled. At baseline none of the patients were assuming DMTs. We performed a sleep assessment at baseline and at the first follow up visit after starting siponimod using a seven-day actigraphy recording and sleep rating scales. Patients who experienced flare ups of symptoms, infections, changes in their sleep pattern due to external factors (i.e. shift work) or significant changes in their concomitant medications before the second assessment were not included. Patients with known severe sleep apnea were not included since Siponimod should be used with caution in these subjects. The following scales were administered: Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Berlin questionnaire for obstructive sleep apnea (OSA), insomnia symptom questionnaire (ISQ), evaluation of criteria for restless leg syndrome (RLS) and RLS rating scale.

Results: Mean age in our sample was 52,5 years old and 33% of subjects were female. Mean EDSS was 5. At baseline screening one patient was complaining of insomnia and two patients met criteria for RLS. Mean PSQI at baseline was 6.6 and the mean sleep efficiency measured through actigraphy was 87%. The median time to follow up evaluation was 120 days (range 35-199). When assessed at follow-up we didn't find any statistically significant difference in rating scale scores and actigraphy parameters compared to before Siponimod introduction.

Discussion: We assessed sleep in a cohort of patients with SPMS treated with Siponimod. We compared rating scale scores and actigraphic parameters between two time points, before and after established treatment with the DMT. We excluded patients who experienced significant changes in their lifestyle, disease course, symptoms or medications before the follow up evaluation to try and isolate the effect of Siponimod. In our sample quality of sleep measured with rating scales and actigraphy did not differ between the two evaluations.

Conclusions: In our study the introduction of treatment with Siponimod did not alter the scores on sleep rating scales and on sleep actigraphic parameters of SPMS patients.

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CLINICAL AND POLYGRAPHIC VARIANTS ON AUTONOMIC PARAMETERS: A COMPLEX INFLUENCE

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Objective: As we know sleep exerts an important regulating function on autonomic parameters and sleep disorders may cause a dysregulation of the sympathetic-vagal balance which modulates heart rate and blood pressure during the night. Aim of this study was to evaluate the impact of clinical and polygraphic variants on autonomic function measured through noninvasive parameters such as heart rate variability (HRV) and pulse wave amplitude (AI).

Materials and Methods: We retrospectively analyzed results from polygraphic studies performed in the last three years at the Sleep Service Outpatient Unit, Ospedali Riuniti Ancona. We collected data on patients' demographic, clinical characteristics, scores on validated scales for restless leg syndrome (RLS) and insomnia. As for polygraphic parameters we considered respiratory parameters (apnea hypopnea index AHI, oxygen desaturation index ODI and other as usual), presence of periodic limb movements, the low frequency/high frequency ratio (LF/HF) component of HRV and AI. We divided the subjects in different group considering as a cut off the value of 2 for LF/HF ratio and a value of 30 for AI, as described in literature.

Results: We analyzed data of 98 patients, mean age was 58,8 ±13 and 71% were males. Clinical characteristics were represented as follows: 52% hypertension, 9.2% diabetes mellitus, 22.4% smokes cigarettes, 48% dyslipidemia, 59.2% mood stabilizer treatment, 25,5% RLS, 23,5% insomnia. The LF / HF <2 group was characterized by higher BMI, lower AHI, lower ODI, a higher prevalence of RLS and insomnia compared to the LF / HF> 2 group. AI <30 group was characterized by a higher prevalence of arterial hypertension, dyslipidemia and a greater tendency to use mood stabilizers compared to the AI> 30 group. A statistically significant moderate degree linear correlation was found between the continuous variable LF / HF and the ordinal variable "RLS

severity" (correlation coefficient 0.3; p <0.007) and between LF/HF and "severity insomnia" (correlation coefficient 0.3; p< 0.008).

Discussion: Our data suggest that the presence of certain conditions such as sleep apneas, RLS, insomnia can influence autonomic parameters, and this can vary depending on their severity. A correct stratification for sex, years of disease, BMI, sleep stages and other parameters should be done for a correct interpretation of data.

Conclusion: The systematic evaluation of autonomic parameters in polygraphy seems to be useful for a correct stratification of patients and their cardiovascular risk, and also to modulate treatment response.

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CEREBROSPINAL-FLUID BIOMARKERS OF NEURODEGENERATION AND BLOOD-BRAIN BARRIER DYSFUNCTION MAY BE USEFUL TO PREDICT THE PHENOCONVERSION TO ALPHA-SYNUCLEINOPATHIES IN PATIENTS WITH ISOLATED REM SLEEP BEHAVIOUR DISORDER

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Background: Isolated rapid eye movement (REM) sleep behaviour disorder (iRBD) is one of the most specific prodromal markers of neurodegenerative diseases, especially α-synucleinopathies. Cerebrospinal fluid (CSF) biomarkers represent appealing candidates for diagnosis and prognosis of α-synucleinopathies [1]. CSF levels of α-synuclein have been suggested as the main biomarker for predicting phenoconversion in patients with iRBD. Other CSF biomarkers have been considered to be measured in patients with α-synucleinopathies. In particular, CSF beta-amyloid42 (Aβ42) levels may predict the cognitive impairment in these patients [2]. Moreover, the deterioration of the blood-brain barrier (BBB) may be a further marker of neurodegeneration in α-synucleinopathies, and the quantification of the CSF/blood albumin ratio can represent a sign of BBB dysfunction [3]. This study aimed to assess CSF Aβ42, tau proteins and CSF/blood albumin ratio in iRBD patients compared to controls and ascertain whether these biomarkers may represent a marker of phenoconversion to alpha-synucleinopathies.

Materials and Methods: Patients and controls underwent between 2012-2016 a clinical and neurological assessment, including the Unified Parkinson Disease Rating scale – section III and the Mini-Mental State Examination (MMSE), as well as a lumbar puncture for CSF biomarkers analysis (Aβ42; total tau, and phosphorylated tau) and CSF/blood albumin ratio. All iRBD patients were followed until 2021 and then classified into patients who phenoconverted to α -synucleinopathies (iRBD converters, cRBD) and remained alpha-synucleinopathies disease-free (iRBD non-converters, ncRBD).

Results: Thirty-four iRBD patients (mean age 67.12±8.14; 82.4% male) and thirty-three controls (mean age 64.97±8.91; 66.7% male) were included. At follow-up, eight patients were ncRBD and twenty-three patients were cRBD: eleven converted to PD, ten to LDB and two to MSA. cRBD patients showed lower CSF Aβ42 levels and higher CSF/blood albumin ratio than controls. Moreover, both cRBD to Parkinson's disease (PD) and dementia with Lewy bodies (DLB) showed lower MMSE scores than controls at baseline. Considering the cRBD group, iRBD patients that converted to DLB had lower CSF Aβ42 levels than controls.

Conclusion: This CSF-based study showed that CSF Aβ42 levels may be used for predicting the cognitive decline in patients affected by iRBD and possibly developing DLB. Based on the BBB alteration, it seems that this CSF biomarker may be useful for predicting the conversion to α -synucleinopathies.

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LACTATE AS A BIOMARKER OF SLEEP AND WAKE: A CEREBROSPINAL FLUID-BASED STUDY IN PATIENTS WITH NARCOLEPSY OF TYPE 1 AND 2

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Background: Besides the quantification of orexin-A/hypocretin-1 levels for diagnostic purposes in narcolepsy, several cerebrospinal fluid (CSF) biomarkers have been evaluated, however with controversial results [1,2]. CSF lactate levels changes have been quantified in response to sleep and wake, and it was documented that following REM sleep and wake CSF lactate levels increase as the result of a more present neuronal activity, whereas following Non-REM sleep CSF lactate levels decrease3. Considering that narcolepsy causes a severe alteration of wake and REM sleep, the present study aimed at investigating CSF lactate levels in patients with narcolepsy compared to healthy controls, considering both patients with narcolepsy of type 1 (NT1) and type 2 (NT2). Moreover, this study would test whether CSF lactate levels are related to sleep and wake measurements in narcolepsy patients and controls.

Materials and Methods: Patients with narcolepsy were observed at the Sleep Medicine Center of the University Hospital of Rome "Tor Vergata". All patients underwent neurological examination, laboratory tests, polysomnography, multiple sleep latency test, brain MRI and lumbar puncture (LP) for CSF analysis. A diagnosis of NT1 or NT2 was defined according to the International Classification of Sleep Disorders – 3rd Edition. A group of controls was included in the analysis and underwent neurologic examination, brain MRI and LP for diagnostic purposes, which were ruled out after the diagnostic investigations.

Results: 23 patients with type 1 narcolepsy (43.5% male; 36.43 ± 11.89 years), 15 with type 2 narcolepsy (46.7% male; 37.8 ± 14.1 years), and 17 controls (58.8% male; 32.3 ± 8.4 years) were included. Patients with NT1 and NT2 had a lower lactate concentration than controls ($p \leq 0.001$), but did not differ from each other ($p = 0.701$). A positive correlation was also observed in patients with narcolepsy between lactate levels and stage 1 of Non-REM sleep (N1) (rho=0.409, p=0.020).

Conclusions: CSF lactate levels can change in response to sleep and wake, and higher lactate levels correlated with wake whereas lower lactate levels with non-REM sleep [3]. Narcolepsy patients frequently present the impairment in daytime vigilance and REM-related episodes. In this study, CSF lactate levels were reduced in patients with narcolepsy, and also correlated with the amount of N1. Notably, the reduction of lactate levels was present in both NT1 and NT2 patients, independently of the pathological reduction of CSF orexin levels. Further studies are needed to understand the role of CSF lactate measurement in narcolepsy and its relation to nocturnal sleep and diurnal sleepiness.

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SLEEP MACROSTRUCTURE AND MICROSTRUCTURE IN PSYCHOGENIC NON EPILEPTIC SEIZURES: COMPARISON BETWEEN PNES AND TEMPORAL LOBE EPILEPSY

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Rationale: Sleep complaints are commonly reported in patients with PNES (Psychogenic Non-epileptic Seizure) but few studies have addressed this issue. In addition, the lack of clear markers makes PNES diagnosis still difficult and often late. We investigated the differences in sleep macrostructure and microstructure (cycling alternating pattern CAP, sleep spindles, slow-oscillations SO and coupling) between documented PNES patients and temporal lobe epilepsy (TLE) patients with hippocampal sclerosis, with the aim of finding a neurophysiological marker for the PNES diagnosis.

Method: 13 patients with PNES and 13 patients with TLE were recruited and underwent two 48-h ambulatory polysomnography (A-PSG) monitoring sessions. Scoring and analysis of sleep macrostructure and sleep microstructure (cyclic alternating pattern CAP, fast and slow spindles and sloSO were performed.

Results: No differences were found in sleep macrostructure between the two groups of patients. PNES patients presented a higher CAP rate in N1, a lower in N3, a longer mean CAP duration of phase B and a higher number of CAP cycles compared to the TLE group. PNES patients had higher amplitude of frontal slow spindles and central fast spindles. PNES had also higher density, amplitude and rate of slow oscillation (SO) but shorter mean duration of Slow Oscillation (SO) on frontal and central regions. Coupling between SO and spindle was higher in PNES patients compared to TLE group.

Conclusion: Sleep macrostructure does not allow to distinguish between PNES and TLE patients. Cyclic Alternating Pattern TLE patients show higher sleep fragmentation as evidenced by CAP analysis Epilepsy seems to induce derailment from spindles generators and slow oscillation to paroxysms with possible link with cognitive impairment in TLE patients. Sleep microstrutcture may represent a neurophysiological marker that may help to distinguish PNES.

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EVALUATING THE RISKS OF WITHDRAWAL SYMPTOMS AND REBOUND INSOMNIA UPON DISCONTINUATION OF DARIDOREXANT IN PATIENTS WITH INSOMNIA DISORDER

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Objective: Abrupt discontinuation of sleep medications in patients with insomnia often causes withdrawal symptoms and rebound insomnia. In a Phase 3 program evaluating efficacy and safety of daridorexant on sleep and daytime functioning in patients with insomnia during three months of treatment, the risks of withdrawal symptoms and rebound insomnia were evaluated at treatment cessation.

Methods: In two randomized, double-blind, 3-month trials, adult (18–64 years) and elderly (≥65 years) patients with insomnia were assigned (1:1:1) to receive oral daridorexant 25 mg, 50 mg or placebo (Trial-1, NCT03545191) or 10 mg, 25 mg or placebo (Trial-2, NCT03575104) every evening. Each trial included a 7-day, single-blind, placebo run-out period following double-blind treatment to evaluate withdrawal symptoms and rebound insomnia. Withdrawal effects were assessed by the change in Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) total score, from last assessment on double-blind treatment to end of placebo run-out, and occurrence of relevant adverse events (AEs). Rebound insomnia was assessed objectively by change in wake-after-sleep-onset (WASO) and latency-to-persistent sleep (LPS) from baseline to first night of placebo run-out, and by subjective total-sleep-time (sTST) from baseline to end of run-out (mean of 7-days). Analyses included all patients who received ≥1 dose of placebo run-out treatment (Trial-1: N=852; Trial-2: N=851).

Results: No increase in mean BSWQ score from last assessment on double-blind treatment to end of placebo run-out was reported (Trial-1: 25 mg, -0.6±2.3; 50 mg, -0.6±2.3; placebo, -0.7±2.3; Trial-2: 10 mg, -0.5 ±2.6; 25 mg, -0.4±1.9; placebo, -0.4±1.4). No patients had a BWSQ score >20 at end of run-out. No AEs suggestive of withdrawal symptoms were reported. Mean WASO and LPS values (min) decreased from baseline to placebo run-out (WASO Trial-1: 25 mg, -8.6±55.5; 50 mg, -2.5±52.4; placebo, -20.4±45.8; Trial-2: 10 mg, -11.6±58.3; 25 mg, -5.1±57.9; placebo, -26.2±53.5; LPS Trial-1: 25 mg, -17.2±56.7; 50 mg, -15.0±55.8; placebo, -27.8±47.2; Trial-2: 10 mg, -17.3±67.2; 25 mg, -10.3±67.3; placebo, -18.3±63.8) while sTST values (min) increased (Trial-1: 25

mg, 43.3±53.8; 50 mg, 42.9±59.6; placebo, 42.3±52.7; Trial-2: 10 mg, 43.3±52.9; 25 mg, 46.8±55.4; placebo, 42.3±53.8) indicating absence of rebound effects.

Conclusions: Treatment with daridorexant for up to three months was not associated with any evidence of drug withdrawal or rebound insomnia upon abrupt discontinuation, indicating no safety concerns for patients should treatment be stopped.

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SLEEP QUALITY IN IN A COVID-19 REHABILITATION DEPARTMENT

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Objective: In hospitalized patients with COVID-19 infection, there was a need for a multidisciplinary rehabilitation approach, in particular in patients with prolonged bed rest and respiratory and neuromuscular sequelae. Most studies demonstrated a relationship between sleep disturbance and rehabilitation outcomes and therefore the importance of assessing sleep problems. It is also known that COVID-19 had a significant impact on sleep quality, with an increased insomnia prevalence. The aim of this study was to assess the sleep characteristics in a group of hospitalized patients with COVID-19 during rehabilitation treatments.

Methods: We analyzed data from patients admitted in the COVID-19 Rehabilitation Department. Sleep diaries and validated questionnaires were used to assess the quality of sleep during the hospitalization and after 3 months of follow-up. We also analyzed the actigraphy data in a sub-group of patients in order to evaluated objective sleep variables.

Results: We enrolled 57 patients (59.6% men), mean age 66.42±12.71 yrs. During the hospitalization patients reported poor sleep quality (PSQI score= 9.28±5.36) and subclinical insomnia (ISI score=9.84±6.83). Anxiety symptoms resulted mild (BAI score=7.93±7.4), as well as depressive symptoms (BDI-II score=10.47±10.20). All the SF-36 macro areas reported poor scores. Actigraphic monitoring performed in 20 patients showed data consistent with subjective findings (SL 18 min, TST 405 min, TIB 485 min, WASO 38 min, SE% 83.55). At 3-month follow-up, we assessed 33 patients. Improvements in sleep latency (SL FU 23.00±28.00; p=0.001), sleep quality (PSQI FU 7.00±5.25; p=0.033), insomnia severity (ISI FU 6.94±5.02; p=0.004), and anxiety (BAI FU 5.18±6.95; p=0.029) were observed. Patients have also been assessed with the Short Physical Performance Battery (SPPB). We observed negative correlations between SPPB and ISI (r= -0.454; p= 0.009), and BDI-II (r= -0.454; p= 0.009). In patients with persistent COVID-19 related symptoms at follow-up (n=18), poorer scores at PSQI, ISI, BDI-II, BAI, and SF-36 compared to patients without persistent symptoms were observed.

Discussion: Our results show poor sleep quality, insomnia disturbances, anxiety and depressive symptoms in patients during COVID-19 hospitalization. Actigraphic monitoring showed data consistent with sleep diaries. After a 3-months follow-up, some improvements have been observed, particularly in patients with an improvement in general functional performance. However, 54.5% of patients reported persistent symptoms, as reported in the literature.

Conclusion: Patients frequently showed sleep disturbances, poor quality of sleep, and psychological consequences also after 3 months of symptoms onset/hospitalization. Long-term studies on large cohorts are needed in order to assess multifactorial effects of COVID-19 consequences.

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EFFECTS OF SOLRIAMFETOL ON EXCESSIVE DAYTIME SLEEPINESS, SLEEP INERTIA AND DEPRESSIVE SYMPTOMS IN OSAS AND NARCOLEPSY: A REAL-LIFE SINGLE-CENTRE EXPERIENCE

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Objectives: Solriamfetol is an inhibitor of dopamine and norepinephrine reuptake, recently approved for the treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy and obstructive sleep apnoea syndrome (OSAS). Following its introduction in clinical practice, we aimed at evaluating the response to Solriamfetol in the management of EDS and its effects on sleep inertia and depressive symptoms in both groups.

Materials and methods: Patients with either narcolepsy or OSAS with an Epworth Sleepiness Scale (ESS) score greater than 10 were considered eligible for the treatment. Additionally, in OSAS patients, first-line treatment, such as positive airway pressure (PAP) or mandibular advancement device (MAD), had to be demonstrated to be performed with good adherence before starting pharmacological therapy and upon exclusion of other causes of EDS. EDS was assessed by ESS, sleep inertia by Sleep Inertia Questionnaire (SIQ) and depressive symptoms through the Beck Depression Inventory (BDI), in basal conditions and after 4 months of treatment. Statistical analysis was performed by means of Wilcoxon test. Statistical significance was set at $p < .05$.

Results: We consecutively enrolled a total of 9 patients (6 men, 3 women, mean age 47.8±17.2 y.o.), 5 with narcolepsy (type 1 or 2), 4 with severe OSAS. In OSAS patients, first-line treatment (PAP in 3 patients, MAD in one patient) resulted in significant reduction in the apnoea-hypopnea index but with persistence of residual sleepiness. As regards patients with narcolepsy, 2 were de novo diagnosis and the other 3 patients had previously tried other wakefulness-promoting agents, with incomplete clinical response. Upon prescription of Solriamfetol no other stimulant drug was co-administered. At 4 months follow-up, all participants demonstrated a significant reduction of ESS (16.2±2.6 vs 9.6±4.5,

p=.014) and of SIQ values (54.2±21.1 vs 40.7±13.5, p=.016). We also found a reduction of BDI score (9.5±6.8 vs 2.5±1.6, p=.134), even if without reaching statistical significance. The average maintenance dose of Solriamfetol was 46.8±18.7mg in OSAS and 112.5±37.5mg in narcolepsy group.

Discussion and conclusions: Solriamfetol is not only an effective and safe option for management of EDS in patients with narcolepsy and OSAS but it also shows a beneficial effect on sleep inertia and depressive symptoms. Greater samples and further studies are needed to confirm its long-term role and to verify possible effects on symptoms related to sleepiness and mood disorders.

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CAN THE SHORT-TERM USE OF CONTINUOUS POSITIVE AIRWAY PRESSURE RESTORE COGNITIVE DYSFUNCTIONS IN OBSTRUCTIVE SLEEP APNEA SYNDROME?

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Objective: Obstructive Sleep Apnea Syndrome (OSAS) significantly impacts cognitive functioning in affected individuals. Long-term use (>3months) of Continuous Positive Airway Pressure (CPAP) for the OSAS seems to have positive effects in restoring cognitive functioning. However, there is few evidence about the restorative short-term (<15days) effect. Here, we investigated if short-term use of CPAP may significantly improve cognitive functioning in OSAS.

Materials: Fifty-patients with a diagnosis of OSAS (AHI>5) were recruited at Sleep Medicine Units of IRCCS Istituto Auxologico Italiano Piancavallo of Verbania and San Luca of Milan.

Method: We measured the level of obesity (BMI>30kg/m2). Patients underwent Orexin-A and Histamine determination in blood (ELISA). Other neurodegeneration associated peptides measured were: serum neurofilament light chain (NFL, SIMOA), serum Amyloid beta 1-40 (Abeta 1-40) and Amyloid beta 1-42 (Abeta 1-42, ELISA), serum catecholamines (ELISA).Through standardized neuropsychological tests, we investigated: verbal learning and long-term memory, attention (i.e., alert, selective attention, processing speed), and executive functions (i.e., abstract and strategic reasoning, problem-solving, planning, set-shifting and inhibitory ability). For each individual we collected the numbers of days since the CPAP adaptation. We evaluated the predictive role of days of CPAP adaptation on the performance at the neuropsychological tests, considering demographics, the level of obesity (i.e., BMI), OSAS severity (i.e., AHI index), and psychological factors (anxiety and depression).

Results: In our sample, the mean number of days since CPAP adaptation was of 4.44 (SD=3.68; range =0-15). As days of CPAP adaptation increase, the level of velocity associated with executive control decreased [p=0.04] and long-term verbal memory span increased [p=0.04]. The level of obesity significantly impacted on the level of velocity in executive control [p=0.02] and selective attention [p=0.01]. Anxiety- and depressive symptoms did not significantly predict the cognitive performance.

Discussion: A short-term use of CPAP (0-15days) seemed to improve the cognitive performance in OSAS, encouraging the early use of ventilotherapy to restore precociously an efficient cognitive functioning.

Conclusion: We underlined the importance to assess the level of obesity, since it may worse the performance, especially in the frontal-executive domains.

SLEEP MICROSTRUCTURE IN PARKINSON'S DISEASE RELATED DEMENTIA: CYCLING ALTERNATING PATTERN (CAP) DISRUPTION REFLECTS NEURODEGENERATION PROGRESSION

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Objective: CAP has proven being decrease in Alzheimer's disease, and its disruption correlates to cognitive impairment progression. In Parkinson Disease (PD) CAP has been investigated only in patients without cognitive impairment, revealing to be increased in early stage of disease, but with a decrease of major A1 components. The main aim of this study was to evaluate CAP in PD patients with different degrees of cognitive impairment, in order to provide an objective measure of sleep microstructure disruption according with neurodegeneration progression.

Materials: Patients affected by PD with cognitive impairment were recruited at the Neurology Units of Hospital Auxologico Piancavallo of Verbania and C. Mondino Institute. PD diagnosis was based on International Movement Disorder diagnostic criteria. Patients underwent a complete neuropsychological assessment delivered by a neuropsychologist. MCI or dementia diagnosis was based on Mini Mental State Examination Scores (MMSE), used to classify patients in PD with mild cognitive impairment (PDMCI) or with dementia (PDD).

Method: All patients underwent an in-lab full-night Video-polysomnography (PSG). Conventional sleep analysis was performed on the basis of the guidelines defined by Terzano and colleagues for CAP. CAP scoring of each patient was revised by an evaluator of the Sleep Medicine Unit of Parma. CAP metrics were then compared to normal values in healthy sleepers.

Results: We recruited 16 PDMCI patients and 16 PDD patients, age and sex-matched(p=0,6). MMSE corrected for age and level of instruction was significantly lower in PDD compared to PDMCI (p<0,0001). CAP rate was significantly reduced in both groups compared to normative values, with a mild decrease in PDD (Median 24,77, IQR 19,2) compared to PDMCI (Median 30,58, IQR 15,17). The proportion of CAP A1 phase was also reduced in both groups compared to normative values, and the same trend of reduction in PDD (Median 1.85, IQR 0 – 6,15) compared to PDMCI (Median 4,4, IQR 0,35-15,35) was found.

Discussion: Despite the small sample size, CAP rate proved to be significantly lower in both groups compared to normative values reported in literature. Also, CAP A1 component, the one which is most deeply related to sleep-dependent cognitive processes, was deeply reduced. We found a trend of reduction according to dementia severity of both CAP and A1 rates, as reported in other neurodegenerative dementias.

Conclusion: CAP proved to decrease in PD with cognitive impairment and seemed to correlate with dementia severity. In this view, sleep microstructure disruption in PD could reflect neurodegeneration progression.

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THE RELATIONSHIP BETWEEN SLEEP QUALITY AND RATIO OF HOUSE SIZE/NUMBER OF PEOPLE IN CHRONIC MIGRAINEURS DURING COVID-19 LOCKDOWN

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Objectives: The COVID-19 pandemic led the governments to introduce a series of restrictive measures referred as “lockdown”. Lockdown represented a revolution for life of many people, it was a stressful condition which forced Italians to stay at home. The present study aimed to evaluate if ratio of house size/number of people (H/P) during first COVID-19 lockdown in Italy influenced sleep quality (SQ) in patients with chronic migraine (CM).

Methods: The study was based on an e-mail survey addressed to CM patients of our headache center. We evaluated SQ using the Pittsburgh Sleep Quality Index score (PSQI), the score ranges from 0 to 21, a higher score is associated with a worse condition. H/P was calculated dividing the square meters (sqm) of patients’ house by the number of people living in the house. HP was dichotomized by values ≤ or > 40 sqm per person.

Results: A total of ninety-two patients completed the survey. Fifty-eight patients (63%) had a H/P ≤40 sqm per person and they presented a PSQI score of 13,23 ± 6,18. Thirty-four patients (37%) reported a H/P > 40 sqm per person and their PSQI was 9,82 ± 4,58. A statistical difference was found with a p-value = 0,007.

Conclusions: H/P was associated with a poor SQ in our patients during COVID-19 lockdown. No data are present in literature concerning this point and we hypothesize that probably having a small space to share with the other family members during lockdown created more stressful conditions and problems with sleep repercussion.

THE COMBINATION OF REBOXETINE AND HYOSCINE BUTYLBROMIDE GREATLY IMPROVES COGNITION IN OBSTRUCTIVE SLEEP APNEA PATIENTS. AN OBSERVATIONAL REAL-WORLD 3-MONTHS FOLLOW-UP STUDY

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Background: Drugs with noradrenergic and antimuscarinic effects improve upper airway muscle function during sleep reducing obstructive sleep apnea (OSA) severity. The noradrenergic agent reboxetine (RBX) combined with the antimuscarinic hyoscine butylbromide (HNB) showed to improve upper airway function during sleep in healthy individuals and it is able to reduce OSA severity. However, whether these findings translate to the clinically relevant meanings are unknown.

Objectives: To evaluate the combination of RBX-HNB in improving cognition and vigilance in moderate to severe OSA patients who refused or were intolerant to CPAP treatment.

Materials: Forty-six patients with moderate-to-severe OSA received RBX (4 mg) plus HNB (5 mg) administered prior to sleep.

Methods: All patients received a complete baseline not attended home polysomnography according to AASM guidelines for staging OSA severity. Two extensive clinical evaluations including sleep quality measures, cognitive evaluation assessed by the Self-Administered Gerocognitive Exam (SAGE) and Deary-Liewald Reaction Times (DLRT) were performed at baseline and after 3-months. We used for comparisons either two-tailed, paired Student’s t tests for normally distributed data or Wilcoxon signed rank tests for non-normally distributed data. Data are expressed as means±SD or median and interquartile range as appropriate. Statistical significance is inferred at P<0.05.

Results: On May 31, 2022, 18 (39%) of the 46 included patients (30 males; mean age±SD: 68±13 years), completed the follow-up period. Patients had a mean body mass index (SD) of 30.4(6.3) Kg/m2; a mean neck circumference of 42(5) cm with a mean waist circumference of 102(36) cm. Mean Epworth sleepiness scale score (EPSS) was 7 (5). Median (interquartile range) baseline apnea-hypopnea index and Respiratory Disturbance Index were 30.6(35.4) and 40.6(33.0), respectively. After 3 months, RBX-HNB increased the total SAGE scoring by median value of 3 [95% confidence intervals (95%CI): 1 to 4; P=0.003) and significantly reduced simple (-109 msec; 95%CI: -34 to -183 msec; P=0.007) and complex (-200; 95%CI: -72 to 328, P=0.005) DLRT but not EPSS scoring (P=0.886). Three male patients (6.5%) experienced urinary hesitancy and dropped out.

Discussion: In people with predominantly moderate-to-severe OSA that did not tolerate or refused CPAP treatment, the combination of RBX-HNB improved cognition and vigilance without relevant side effects.

Conclusions: These new findings further highlight the importance of noradrenergic and muscarinic mechanisms on upper airway control

during sleep and the therapeutic potential to target these processes pharmacologically. Our results provide evidence supporting OSA pharmacologic therapy in many patients that find CPAP intolerable and therefore remain untreated.

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SEX-RELATED DIFFERENCES IN SYMPTOMS AND IMPAIRMENT IN PATIENTS WITH NARCOLEPSY: FINDINGS FROM THE TENAR PROJECT

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Objective: Recent pre-clinical findings suggest the existence of sex-related differences in narcolepsy. We aimed at comparing severity of symptoms and psychosocial impairment of female and male patients with narcolepsy.

Materials: One-hundred and six female and 102 male patients with narcolepsy (mean age of 33.9 and 34.1 years respectively) participating in the TENAR randomized controlled trial [1].

Methods: Secondary analysis of baseline data including: socio-demographics (educational level, sentimental, marital and occupational status), sleepiness (Epworth Sleepiness Scale, ESS), frequency and duration of cataplexy attacks, Narcolepsy Severity Scale (NSS), depressive symptoms (Beck Depression Inventory, BDI), and main narcolepsy-related problems.

Results: Female and male patients did not differ with regard to socio-demographics and cataplexy but, compared with male, female patients had significantly higher ESS (11.2 vs 9.4), NSS (22.3 vs 17.1), and BDI scores (11.7 vs 6.9). With the exclusion of cataplexy and of the item "relationships with the others", compared with male, female patients reported more frequently as a problem all the narcolepsy-related problems investigated: sleepiness (71.7% vs 46.1%), sleep attacks (45.3 vs 26.5), concentration and memory problems (65.1 vs 35.3 and 42.5 vs 27.5 respectively), and maintain the work pace and achieve goals (54.7 vs 23.5 and 40.6 vs 21.6 respectively).

Discussion: Female and male patients with narcolepsy reported differences concerning sleepiness severity and narcolepsy-related problems. There may be several explanations: women may have a higher perception of sleepiness and of its consequences; there may be a suboptimal management of sleepiness in women or differences in treatment; more depressive symptoms may influence the perception of sleepiness and of narcolepsy-related problems in women.

Conclusions: These findings suggest that narcolepsy may impair differently female and male patients. A better understanding of sex-related differences is needed to improve the management and care of people with narcolepsy.

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PATIENTS WITH NON-REM SLEEP PARASOMNIAS CAN PRESENT INSOMNIA AND NEUROPSYCHIATRIC SYMPTOMS: A QUESTIONNAIRE-BASED STUDY AND THE EFFECT OF 5-HYDROXYTRYPTOPHAN AND CROCUS SATIVUS L

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Background and Objectives: Non-REM sleep (NREM) parasomnias, defined as undesirable behavioral events emerging from NREM sleep, are common in the general population. As a rule, they occur more frequently in children than in adults. No longer considered to be invariably a sign of psychopathology, parasomnias are currently understood as clinical phenomena that can be associated or triggered by neuropsychiatric symptoms. The first aim of the present study is to evaluate neuropsychiatric symptoms in adult patients with NREM sleep parasomnias. The 5-hydroxytryptophan (5-HTP) is the intermediate metabolite of L-tryptophan in the production of serotonin and melatonin; Crocus sativus (C. sativus) possesses a number of medicinally important activities such as antidepressant and relaxant properties. The second aim of this study is to evaluate the effects of 5-HTP and C. sativus on neuropsychiatric symptoms in patients with NREM sleep parasomnias.

Methods: Adult patients with NREM sleep parasomnias visited at the Sleep Medicine Centre of the University Hospital of Rome Tor Vergata were included in this observation. All patients were diagnosed after performing a video-polysomnography following the ICSD-3 criteria. All patients performed at time of diagnoses and after 3-month of treatment a clinical interview about episodes of parasomnias, Pittsburgh Sleep Quality Index (PSQI) for evaluating sleep quality, Epworth Sleepiness Scale (ESS) for evaluating daytime sleepiness, Hospital Anxiety and Depression Scale (HADS) for investigating these neuropsychiatric symptoms, and Short Form health survey for assessing quality of life. Exclusion criteria for patients were concomitant sleep disorders, presence of neurologic/psychiatric disorders, shift-work, use of drugs active on the CNS. All patients were compared to a control group similar for age and sex, who were evaluated at the same Sleep Medicine Centre, and not affected by sleep disorders according to the ICSD-3 criteria.

Results: Eighteen patients were included in this observation and compared to a control group of 10 subjects. Patients with NREM sleep parasomnias showed higher scores of PSQI and HADS and a lower quality of life than controls. 5-HTP and C. sativus resulted effective in reducing the parasomnias episodes, although the questionnaires scores did not differ between baseline and follow-up.

Discussion and Conclusion: Adult patients with NREM sleep parasomnias frequently present with neuropsychiatric symptoms and sleep impairment, possibly affecting quality of life. Three-month treatment with 5-HTP and C. sativus resulted effective in treating parasomnias episodes, although further studies with longer follow-up can be useful to understand the possible effect on neuropsychiatric symptoms.

DEVELOPMENT, ASSESSMENT AND APPLICATION OF HOME AMBULATORY SLEEP POLYSOMNOGRAPHY IN SLEEP-RELATED MOTOR BEHAVIOURS

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Study Objectives: For most sleep behaviour-disorders, in-laboratory polysomnography (PSG) is currently considered the gold diagnostic standard. However, a crescent need for more handy diagnostic tools has been underlined by several literature evidence. In the study of nocturnal motor behaviours, video analysis along with EEG evaluation is still essential to perform a correct differential diagnosis. We aim to describe the experience of Bologna Sleep Centre in the evaluation of sleep-related motor behaviours by means of home-based video ambulatory recording.

Materials and methods: We analysed consecutive home-based video ambulatory recordings from April 2016 to May 2022 of patients afferent for different suspected sleep-related motor behaviours including REM and NREM parasomnias, sleep-related epilepsy, psychogenic non-epileptic seizures, undefined nocturnal paroxysmal episodes. Home-based video ambulatory recordings were performed by means of XLTEK Trex HD, Natus Medical Incorporated®, video-camera Handycam HDR-CX700, Sony, 12,3 Megapixel resolution. The patients were equipped in the sleep lab by expert sleep technicians, who also provided the instructions to carry on with the recording in the home setting.

Results: We included 275 consecutive home-based video ambulatory recordings of 208 patients. Overall, 85.1% of recordings were diagnostic (either confirming or excluding the clinical suspicion), while 14.9% of recordings were not diagnostic (insufficient evidence to confirm a diagnosis or technical problems). An accurate technical evaluation of quality of polygraphic tracings was performed on the first 50 recordings. The mean percentage of channels with artifact was 8%, mostly encountered in electro-oculogram and electrocardiographic leads.

Discussion and conclusions: Home-based PSG tracings showed a very good level of quality, with lack of artifacts in the 92% of channels. In addition, home-based recordings provided a good diagnostic accuracy, with lesser costs than an in-lab PSG. The recording in the patient's natural environment might increase the likelihood to capture the habitual episodes, necessary for a correct diagnostic interpretation. On the other hand, at variance with an in-lab PSG, eventual technical issues cannot be fixed and, when present, invalidate the exam.

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SPECTRAL ANALYSIS IN SIMPLE AND COMPLEX EPISODES OF ADULT PATIENTS WITH DISORDERS OF AROUSAL

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Study Objectives: Disorders of Arousal (DoA) are NREM parasomnias characterized by abnormal motor and complex behaviours arising from NREM sleep. During DoA episodes, an interplay of both deep sleep and wake EEG rhythms has been observed. A few EEG studies detected changes in EEG activity in the seconds preceding DoA episodes. The aims of this work were to characterize the topography of EEG spectral changes prior to DoA episodes and to compare the EEG activity preceding episodes of different behavioural complexity.

Materials and methods: We collected 103 consecutive video-polysomnographic recordings of 53 DoA adult patients. We classified DoA episodes according to three different motor patterns of increasing complexity, distinguished in simple arousal movements (SAMs), rising arousal movements (RAMs) and complex arousal movements (CAMs). For each episode we compared a 5-seconds window prior to the motor onset ("pre-event") and a time frame of 60 seconds from 2 to 3 minutes before the episodes ("baseline"). Subsequently, a between-group comparison was performed for the pre-event of simpler versus the more complex episodes.

Results: Spectral analysis over 325 DoA episodes showed an absolute significant increase prior to DoA episodes in all frequency bands excluding sigma, which showed a decrease. In normalized maps, the increase was relatively higher over the central/anterior areas for both slow and fast frequency bands. No significant differences were detected from the comparison between simpler and more complex episodes.

Discussion and conclusions: These results suggest that, prior to DoA episodes, deep sleep and wake-like EEG activity coexists over overlapping areas, implying an alteration of local sleep mechanisms starting before the episode onset. Simple and more complex episodes were preceded by a similar EEG activation, suggesting that a common mechanism possibly leads to their occurrence.

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DISORDERS OF AROUSAL IN OLDER ADULTS: A CHALLENGING DIAGNOSIS

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Objectives: We describe the characteristics of Disorders of Arousal (DoA) in elderly to ease the differential diagnosis with other sleep related complex motor behaviors in older patients, particularly with REM sleep behavior disorder (RBD).

Materials: 5 patients (4 males, 1 female) from 65 to 72 years of age, consecutive referred to our Sleep Unit, complaining of nocturnal motor behaviors with features suggestive of DoA.

Methods: All patients underwent a clinical evaluation and a 24-48h Video-Polysomnography (VPSG). Two patients repeated a 48h VPSG six months later.

Results: The nocturnal episodes began between 10 and 60 years of age and showed a fluctuating trend, triggered by stress and sleep deprivation. Three patients complained of diurnal consequences (excessive daytime sleepiness and fatigue). Three patients had positive family history of DoA and one of them had Parkinson's Disease diagnosed 38-years after the onset of nocturnal episodes. The events occurred mainly in the first third of the night and usually lasted less than a minute. During the nocturnal episodes the patients sudden raised head or trunk, seemed confused and could scream or speak. One patient reported prolonged episodes characterized by ambulation and violent behaviors. When questioned by the bed partner, all patients were confused. Two patients reported a subjective perception during the episodes and three patients could recall the nocturnal events the next morning. VPSG detected 25 DoA episodes at the baseline and 4 ones at the 6-month follow-up; all events arose from NREM sleep.

Discussion: DoA in the elderly have seldom been investigated as they often resolve by puberty. However, they could persist or appear in older patients, showing the typical motor manifestation and anamnestic features (a DoA positive family history, the episodes related confusion, the onset in the first third of the night and the presence of trigger factors). VPSG recording supports DoA diagnosis (showing the onset from NREM sleep alongside with REM sleep physiological muscle atonia) distinguishing DoA episodes from RBD ones.

Conclusions: DoA are a chronic condition with typical clinical features and motor manifestations regardless the age of onset. A detailed clinical interview could identify some hallmarks, but a VPSG recording is required to assess a definitive DoA diagnosis, mainly in older patients with neurodegenerative disorders.

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PLASMA BIOMARKERS OF INFLAMMATION AND NEURODEGENERATION IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME AND MILD COGNITIVE IMPAIRMENT

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Aim of the study: The impact of Obstructive Sleep Apnea Syndrome (OSAS) on cognitive decline has been widely evaluated but still debated and few studies include multimodal evaluation of neurodegeneration in OSAS. Our aim is to investigate clinical, polygraphic and plasmatic biomarkers differences in OSAS patients with or without Mild Cognitive Impairment (MCI).

Materials and Methods: In this monocentric, prospective, case-control study, we recruited 23 moderate-severe OSAS patients. Inclusion criteria were: age greater than 60 years, absence of OSAS treatment, complaints about subjective cognitive impairment, exclusion of major comorbidities. We performed an extensive neuropsychological evaluation and took a blood sample to assess plasma levels of neurodegeneration markers (Amyloid β 42, total tau and phosphorylated tau protein levels), oxidative state such as Hypoxia-Inducible Factor 1-α (HIF1-α) protein level, and inflammatory state (interleukin 8 protein level). We compared for any variables OSAS patients without MCI (OSAS-MCI) and those with MCI (OSAS+MCI).

Results: Our patients had a mean age of 69,6±4,3 years, seven (30,4%) were female. These patients suffered from moderate-severe OSAS: the mean Apnea-Hypopnea Index was of 39,4±13,8 per hour, Oxygen Desaturation Index was 38,5±17,3 per hour, mean oxygen saturation was 92,1±3,0 percent, percentage of time spent with an oxygen saturation below 90% (T90) was 21,8±22,6. Sixteen patients (16/23, 69,6%) were diagnosed as OSAS+MCI patients, with verbal memory (n=12/16, 75%) and visuo-spatial abilities (n=5/16, 31,3%) being the two most affected domains. Comparing the OSAS+MCI versus OSAS-MCI group we found a significantly increased T90 (26,5±25,2 vs 11,1 ±9,5, p=0,046) and significantly higher levels of HIF1-α (59,4±52,7 pg/ml vs 24,7±15,8 pg/ml, p=0,03) in the first ones. Demographic, polygraphic and laboratory data did not show other significant differences.

Discussion and conclusion: Chronic intermittent hypoxia (IH) can induce the expression of HIF 1-α, which is involved in inflammation pathways, in OSAS patients. Higher T90 in OSAS+MCI combined with higher levels of HIF 1-α in OSAS+MCI patients further corroborate the role of IH as a potential contributor of neurodegeneration. Longitudinal changes after OSAS treatment (e.g. Continuous Positive Airway Pressure) are needed to shed light on a likely causative role of OSAS in neurodegeneration.

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OSAREDS STUDY: EDS AND REDS AFTER CPAP TREATMENT IN ITALIAN PATIENTS WITH OSAS

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Introduction: Excessive Daytime Sleepiness (EDS) at diagnosis and residual EDS (rEDS) after continuous positive airway pressure (CPAP) frequencies in obstructive sleep apnea (OSA) patients showed a wide variability among studies.

Objective: The OSA-related rEDS prevalence in Italian patients (OSAREDS) study assessed the frequencies of EDS and of rEDS (Epworth Sleepiness Scale [ESS] score >10), after continuous positive airway pressure (CPAP) treatment, in patients with OSA followed up by 7 Italian Sleep Centres.

Methods: OSA patients' characteristics, symptoms, treatments and compliance to CPAP were retrospectively collected from medical records and analyzed.

Results: Among 2743 patients included in the final analysis, 836 (males: 75.6%, mean age±SD: 56.5±9.1 yrs, BMI: 31.2±4.7 kg/m2) had a baseline visit (V1) and a control visit (V2) after 3-12 months (median 8.0 months) of CPAP treatment. At V1, AHI (mean±SD) was 38.4±27.0 and ESS score 9.0±5.1. Prevalence of main symptoms was: EDS 40.7%, snoring 96.5%, fatigue 37.7% and insomnia 14.1%. Main comorbidities frequencies were: systemic hypertension 60.2%, type 2 diabetes 17.1%, arrythmias 7.3%. Percentages of CPAP acceptance at V1 and of adherence to CPAP at V2 were, respectively, 98.8% and 85.9% and median CPAP use duration was 6.0 h/night. At V2 visit, AHI was 5.7±7.6/h and mean ESS score was 4.7±3.7 ($p<0.01$ by t-test). Prevalence of rEDS was 6.6% (95% CI 4.9-8.3, $p<0.01$) in the whole population and 15.7% in OSAS patients with EDS at baseline. Prevalence of snoring decreased to 11.5%, and prevalence of fatigue and insomnia decreased to 11.7% and 4.3%, respectively ($p<0.0001$ for all).

Conclusions: In the OSAREDS study more than 40% of OSAS patients had EDS before CPAP and, after a 8 months median duration of this treatment, rEDS still affected at least 15% of patients.

ROLE OF DAYTIME CONTINUOUS POLYSOMNOGRAPHY IN THE DIAGNOSIS OF PEDIATRIC NARCOLEPSY TYPE 1: DAYTIME SLEEP IN NARCOLEPSY CHILDREN

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Objectives: Narcolepsy type 1 (NT1) is still largely underdiagnosed, especially in children for difficulties to obtain a reliable diagnostic evaluation. Sleep onset REM periods (SOREMPs) at nocturnal polysomnography (nPSG) followed by the multiple sleep latency test (MSLT), cataplexy, and cerebrospinal hypocretin-1 (CSF hcrt-1) deficiency are NT1 fingerprints. However, children's active collaboration is necessary to obtain reliable MSLT results. With this study we aimed to validate the daytime continuous polysomnography (D-PSG) as instrument for NT1 diagnosis in children.

Materials and methods: 202 consecutive patients were included and randomly divided in two groups (Group 1, n=133; and Group 2, n=67). D-PSG data (number of naps, total sleep time, number of SOREMPs) were tested against NT1 diagnosis with ROC curves in Group 1. The diagnostic performances of single and combined D-PSG parameters were tested in Group 1, validated in Group 2, and applied in the whole dataset.

Results: 63 with subjective excessive daytime sleepiness (sEDS), 112 with NT1 and 25 with other central nervous system hypersomnia (CNS HA) were included. In the group 1: D-SOREMPs, nNAP and D-TST presented progressive decreasing significant area at ROC curve analysis (0.91, p=6 E -16, 95% CI 0.86 - 0.96; 0.81, p=9 E-10, 95% CI 0.74 - 0.89; 0.70, p= 0.0001, 95% CI 0.60 - 0.79, respectively). At least 1 for D-SOREMP, 2 for n-NAPs, and more than 60 minutes for D-TST were the best cut offs. n-NAP and D-TST combined maintain a high sensitivity (with lower specificity), while at least 1 D-SOREMPs with either n-NAP or D-TST yield a high specificity with lower sensitivity. In the group 2: the D-SOREMP> or =1 and SOREMP > or = 2 showed a sensitivity at 82% (95% CI 65-93) and 77% (95% CI 67-88) and a specificity at 85% (69-95) at 97% (85-100) respectively. The combination of D-SOREMP > or = 1 or D-SOREMP = 0 but with D-TST > 60 min and nNap > or =2 showed a sensitivity at 88% (95% CI 77-96) and a specificity at 62%. The combination D-SOREMP > or = 1 and at least one of D-TST > 60 min or nNap > or = 2 showed a sensitivity at 84% (95% CI 67-94) and a specificity at 88%.

Discussion: D-PSG recording is an easy, useful and reliable tool for identifying NT1 children, then expand the diagnostic possibility also outside of the sleep laboratory (i.e. home settings) and for not collaborating patients.

EFFICACY OF LONG-TERM TREATMENT WITH DARIDOREXANT IN PATIENTS WITH INSOMNIA DISORDER ON SLEEP AND DAYTIME FUNCTIONING: A POST-HOC ANALYSIS

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Objective: Daridorexant, a dual orexin receptor antagonist recently approved for use in the US, improved night and daytime symptoms of insomnia disorder in two parallel, ph3, randomized, 12-week studies and maintained these improvements in a subsequent 40-week extension study. This post-hoc analysis of the extension study further explored long-term efficacy of daridorexant 50mg, compared with placebo and daridorexant 25mg.

Methods: This post-hoc analysis includes 392 patients (≥18 years) with insomnia disorder randomised (1:1:1) to daridorexant 50mg, 25mg or placebo and completed 12-weeks of double-blind treatment (NCT03545191) and subsequently entered the extension study (NCT03679884). In the double-blind extension study, patients originally randomized to daridorexant (50mg [n=137], 25mg [n=132]) remained on their respective treatments while patients originally randomized to placebo were re-randomized 1:1 to daridorexant 25mg (n=66) or placebo (n=57). The treatment period of the extension study was 40-weeks (12 months cumulative treatment overall). Exploratory efficacy endpoints: change from baseline over time in subjective total sleep time (sTST) and daytime functioning. The latter was assessed using the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ), comprising total score, and three domains: sleepiness, alert/cognition and mood (lower scores indicating improved daytime functioning).

Results: For patients who participated in the 12-week trial and continued into the extension study, changes in sTST from baseline (baseline of the confirmatory 12-week study) were increased and consistently larger with 50mg versus 25mg and placebo throughout the extension study. Mean (±SD) increase in sTST from baseline to end of extension study (Month 12) was 75.6minutes (±69.90) with daridorexant 50mg compared with 65.5minutes (±66.61) for daridorexant 25mg, and 52.8minutes (±75.90) for placebo. For IDSIQ total score and domain scores, reductions were also consistently larger with 50mg throughout the 12-month treatment period, with no clear distinction between daridorexant 25mg and placebo. For IDSIQ total score (range 0–140), mean (±SD) reduction from baseline to Month 12 were –27.3 (± 25.48) for daridorexant 50mg compared with –17.3 (25.79) for daridorexant 25 mg and –22.1 (25.88) for placebo. IDSIQ sleepiness, alert/cognition, and mood domain scores also improved over time and favored daridorexant 50mg.

Conclusions: This post-hoc analysis provides additional evidence for the long-term maintenance over 12 months of the favourable treatment effect of daridorexant 50 mg on both nighttime symptoms and daytime functioning, based on an increase in sTST and improvement in IDSIQ scores, in patients with insomnia disorder. Acknowledgements: Idorsia Pharmaceuticals. Previously presented at 16th World Sleep Congress, Mar 11-16 2022, Rome, Italy.

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"SONNO E SALUTE STUDY": SURVEY ON PREVALENCE AND MANAGEMENT OF INSOMNIA IN ITALIAN PATIENTS OLDER THAN 50 YEARS. RESULTS FROM THE "SONNO E SALUTE" STUDY

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Introduction: Insomnia affects one-third of the adult population and is associated with multiple medical conditions. We conducted an observational epidemiological survey to assess: (1) the prevalence of insomnia in an Italian group of patients aged over 50 years, presenting directly to the general physician (GP); (2) the association of insomnia with sleepiness and comorbidities and (3) the pharmacological treatment.

Methods: The study was carried out by GPs. Each GP was asked to enroll the first patient over 50 years old spontaneously presenting for any medical problems for five consecutive days. The Italian version of the Sleep Condition Indicator (SCI) was administered; daytime sleepiness was evaluated by a visual analogic scale (VAS). For every patient, GPs collected information regarding comorbidities and pharmacological treatment for insomnia and evaluated the severity of insomnia using the Clinical Global Impression Severity (CGI-S) scale.

Results: A total of 748 patients (mean age 65.12 ± 9.45 years) were enrolled by 149 GPs. Prevalence of insomnia was 55.3%. SCI, VAS and CGI-S scores were highly correlated between each other ($p<0.0001$). At general linear model analysis, the comorbidities more associated with the presence of insomnia were anxiety-depressive disorder ($p<0.001$), other psychiatric disorders ($p=0.017$), cardiovascular disorders ($p=0.006$) and dementia ($p=0.027$). A statistically significant correlation was found between SCI score and the use of: benzodiazepines ($p<0.001$), z-drugs ($p=0.012$), antidepressants ($p<0.001$) and melatonin prolonged release ($p<0.001$).

Conclusions: Insomnia affects half of Italian primary care patients over 50 years and is frequently associated with different medical conditions, sleepiness and use of multiple, often off-label, drugs.

MULTIMODAL AUTONOMIC NERVOUS DYNAMICS EVALUATION IN PATIENTS AFFECTED BY CHRONIC INSOMNIA: A CASE-CONTROL STUDY

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Background and aim: Chronic insomnia (CI) is the most common sleep disorder in the general population. Autonomic nervous system impairment is considered as one of the factors that leads to the hyperarousal state associated with sleep loss. Nevertheless, empirical evidence of dysautonomia in patients affected by CI remains unclear. [1] Our aim was to explore whether cardiovascular autonomic dynamics are impaired in patients with CI during wakefulness.

Methods: Eighteen de novo patients affected by CI according to Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) criteria and sixteen age and sex-matched healthy subjects were enrolled. They underwent to cardiovascular reflexes evaluation consisting in head-up tilt test (HUTT), Valsalva maneuver, deep breathing, hand grip and cold face test. Heart rate variability (HRV) in rest supine condition and during HUTT was analyzed in the frequency domain, using autoregressive (AR) algorithm.

Results: Patients showed increased mean systolic blood pressure (SBP) values ($p=0.05$) and decreased mean heart rate (HR) values ($p=0.046$) measured at 10 minutes after they were tilted-up (HUTT-10). The difference of systolic blood pressure at HUTT (Δ SBP) from supine resting condition values was significantly higher in CI than in controls ($p=0.007$). Moreover, the difference between resting and HUTT-10 HR (ΔHR) was significantly lower CI than healthy subjects ($p<0.01$). Spectral analysis of HRV showed no significant differences between CI and controls under supine resting conditions and during HUTT. Within-group analysis showed physiological changes in HRV during HUTT for both IC and controls.

Discussion and conclusion: Our study showed the presence of a pre-hypertensive systolic response in patients with chronic insomnia during HUTT. We hypothesize that this may be the expression of the well-known increased cardiovascular risk of CI. [2] However we found normal HRV changes during HUTT in both groups. Daytime HRV testing of patients with insomnia has been conducted in four studies with

contradictory results. Only one of these studies analyzed the postural modification in HRV and reported that patients with insomnia have attenuated or absent HRV responses to postural changes by monitoring HRV in sitting and standing positions [3]. We first studied autonomic control of cardiovascular reflexes and HRV under controlled conditions through the use of a battery of standardized tests. The normal HRV changes during HUTT in CI patients suggest physiological autonomic nervous system (ANS) dynamics during wakefulness. More studies are needed to further explain the ANS role in the complex genesis of CI.

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CIRCADIAN VARIATION OF MUSCLE ATONIA INDEX IN DIFFERENT LEVELS OF VIGILANCE AS A POSSIBLE MARKER OF NARCOLEPSY COMPARED TO OTHER HYPERSOMNIAS: AN MSLT BASED RETROSPECTIVE STUDY

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Study objectives: The diagnosis of narcolepsy is often complex and delayed, requiring extensive diagnostic tests and invasive procedures such as CSF orexin dosage. The complexity of the procedures and the complex clinical picture may induce substantial diagnostic delays. Our study aimed to evaluate circadian changes in muscle tone (atonia index) in different levels of vigilance during the multiple sleep latency test in patients with narcolepsy type 1 (NT1) and 2 (NT2) compared with other hypersomnias and evaluate its possible diagnostic value.

Methods: Twenty-nine patients with narcolepsy type 1 (11 M 18 F, mean age 34.9 years, SD 16.8) and sixteen with narcolepsy type 2 (10 M 6 F, mean age 34.9 years, SD 16.8) and 27 controls with other hypersomnias (14 M, 13 F mean age 45.1 years, SD 15.1). An evaluation of the muscle atonia index (AI) was carried out in different levels of vigilance (wake and REM sleep) in each nap and the entire MSLT of each group. The validity of AI in the identification of patients with narcolepsy (NT1 and NT2) was evaluated using Receiver Operating Characteristic (ROC) curves.

Results: AI during wakefulness (WAI) was significantly higher in both the narcolepsy groups (NT1 and NT2 $p < 0.001$) compared with the control hypersomniac group. AI during REM sleep (RAI) was lower in NT1 than NT2 ($p=0.03$). The analysis of the ROC curves returned high AUC values for WAI (NT1 0.88; Youden index >0.57 Sensitivity 79.3% Specificity 90%; NT2 0.89 Youden index >0.67 Sensitivity 87.5% Specificity 95%; NT1 and NT2 0.88 Youden index >0.57 Sensitivity 82.2% Specificity 90%) in discriminating subjects suffering from different central hypersomnias. RAI showed an AUC value of 0.7 (Youden index ≤0.7 Sensitivity 50% Specificity 87.5%), differentiating NT1 and NT2.

Conclusions: AI during wakefulness seems to be a promising electrophysiological marker of narcolepsy and suggests a vulnerable tendency to dissociative waking/sleep dysregulation absent in other forms of hypersomnia.

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CYCLIC ALTERNATING PATTERN IN TEMPORAL LOBE EPILEPSY WITH OR WITHOUT OBSTRUCTIVE SLEEP APNEA SYNDROME

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Introduction: To evaluate the differences of sleep macrostructure and cyclic alternating pattern in patients with temporal lobe epilepsy with (AHI≥5, TLE-OSA) or without OSA (AHI<5, TLE).

Materials and methods: People with temporal lobe epilepsy who underwent overnight polysomnography were retrospectively recruited. Twenty-four patients with TLE-OSA and nineteen patients with TLE were included in the study. Scoring and analysis of sleep macrostructure and cyclic alternating pattern (CAP) parameters were performed. TLE-OSA group was divided into 2 groups by OSAS severity ("milder" group AHI<20/h n=12, moderate-to-severe group AHI≥20 n=12).

Results: TLE-OSA group had statistically higher age and BMI than the TLE group while the remaining demographic and clinical variables were similar. Higher time in bed($p=0.049$), WASO ($p=0.02$) and a trend toward a lower REM sleep percentage ($p=0.07$) was evident in TLE-OSA vs TLE. The milder group compared to TLE controls had more WASO($p=0.04$). CAP analysis showed higher CAP rate in N1($p=0.02$), lower A2%($p=0.046$), higher A3%($p=0.005$), A3 index ($p=0.013$), shorter duration of A ($p=0.008$), A1 ($p=0.004$), A2 ($p=0.033$) and A3($p=0.046$) in TLE-OSA vs TLE. The milder group compared to TLE showed a shorter duration of A($p=0.03$), while the AHI≥20 vs TLE group a higher A3%($p=0.01$), shorter mean duration A1($p=0.03$). Partial correlation adjusted for age, gender and BMI showed a positive correlation between AHI and CAP rate in N1($r=0.34$ $p=0.03$), percentage of A3($r=0.46$ $p=0.003$), the index of A3 ($r=0.32$ $p=0.04$) and a negative correlation with the percentage of A2 ($r=-0.32$ $p=0.039$), with the mean duration of phase A($r=-0.31$ $p=0.04$), with the average duration of phase A1($r=-0.43$ $p=0.006$); a positive correlation of ODI with the percentage of A3($r=0.35$ $p=0.025$) and negative with the mean duration of A1($r=-0.37$ $p=0.018$). Finally, the severity of hypoventilation (T90) showed a direct relationship with the average duration of phase B ($r= 0.32$ $p = 0.04$).

Discussion Our study represents the first study to compare the alternating cyclic pattern in TLE patients with and without OSAS and demonstrates more fragmented sleep in TLE-OSA also evident in "milder" group. CAP alteration in the group with OSAS involves failure of adaptive mechanisms and maladaptive arousal processes (A3) more evident in more severe OSAS. Severity of OSAS showed a marked relationship with cortical arousal while hypoventilation correlated with increasing phase B

duration, a more vulnerable phase to upper airway collapse and attenuation of biochemical and neural mechanisms in ventilator impulse control.

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DEFINITION OF SLEEP MACRO AND MICROSTRUCTURE OF PATIENTS WITH A SELECTIVE STROKE OF THE BASAL GANGLIA CONSEQUENT TO SUCCESSFUL MECHANICAL THROMBECTOMY: AN OBSERVATIONAL, COHORT STUDY

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Study Objectives: The primary endpoint of the study was to describe sleep architecture in patients with selective ischemic basal ganglia lesions. The secondary study aim was to determine whereas sleep parameters could predict the prognosis of patients with a basal ganglia stroke.

Materials and Methods: We included in this observational, cohort study consecutive adult patients admitted to the Stroke Unit (SU) of our hospital from July 2021 to May 2022, who underwent mechanical thrombectomy for a M1 occlusion leading to successful recanalization, defined as a thrombolysis in cerebral infarction score≥2c, and who presented a selective basal ganglia lesion (BG group). Exclusion criteria were: Unstable conditions, extended cortical strokes, previous diagnosis of sleep disorder, neurological and/or psychiatric diseases, and use of medication with a primary effect on the central nervous system at the time of registration. Each BG subject was age- and sex-matched with a patient who underwent polysomnography during the same time period for loss of consciousness and/or suspected sleep-related breathing disorders. The same exclusion criteria were applied to the control group (CG). All BG patients underwent polysomnography during their SU stay within 10 days from the ischemic event. Statistical comparisons were performed through Mann-Whitney U-test and by means of binary logistic regression or linear regression.

Results: Forty-five patients were enrolled in BG group: Median age was 77 (IQR: 67-84) years, and 40% were men. BG patients presented significantly lower percentage of Rapid Eye Movement (REM) sleep ($p<0.001$) and Cyclic alternating pattern (CAP) rate ($p=0.009$) than controls. In the logistic regression, only the percentage of REM sleep differed significantly between groups. Within the 40 BG subjects whose 3-months modified Rankin Scale (mRS) were available, 65% presented a good outcome (mRS≤2). Percentage of REM sleep ($p=0.001$) and CAP rate ($p<0.001$) were significantly higher in subjects with a good outcome compared to those with mRS>2. Multivariate analysis confirmed these findings.

Discussion and conclusion: A reduction of REM and an altered NREM microstructure characterize sleep of patients with a selective basal ganglia lesion. Reduced REM sleep and a low CAP rate are related to a poor 3-months stroke outcome. Animal models suggest a prominent role of basal ganglia in modulating nREM and REM sleep [1]. Moreover, a low CAP rate has been associated to a poor prognosis in comatose patients [2]. Our study highlights that basal ganglia play a pivotal role in human sleep modulation.

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