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ABSTRACT

CHEMOTHERAPY INDUCED PERIPHERAL NEUROTOXICY: WHY SHOULD WE CARE?

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Chemotherapy Induced Peripheral Neurotoxicity (CIPN) is a long-lasting adverse event. CIPN causes sensory loss and neuropathic pain at limb extremities. It hampers quality of life (QoL) of cancer survivors and can have a negative impact on working abilities due to emerging disabilities (e.g., sensory ataxia). CIPN is still under-reported for methodological issues in its assessment, and its socio-economical costs were not extensively investigated. It is of highly relevance to accurately define the socio-economic burden related to this condition to plan future health care programs and a policy to manage CIPN. We are shedding light into CIPN-related socio-economic burden by combining 2 working packages (WP) in a pilot research study. In WP1 we are enrolling (monocentric study) CIPN patients to accurately detect and grade neuropathy signs/symptoms to match these with QoL and socio-economic condition assessments. In WP2 we analysed a large, general administrative database from *Regione Lombardia* (data from all adult citizens in the 2000-2021 period). We have enrolled 20 patients in WP1 with a grade 1-2 CIPN (as assed via Total Neuropathy Score) and we have collected patient-level information related to the socio-economic burden. In WP2 we estimated the incidence of CIPN in the population of patients affected by cancer. Given that CIPN is not officially labelled in this administrative database, we used information about medical treatments to indirectly detect CIPN. To avoid confounding factors, we considered only patients affected by cancer and without other comorbidities potentially leading to neuropathy. We will compare the results of the analysis of WP2 dataset with WP1 data to discuss the robustness of the CIPN estimate adopted in WP1; this in order to discuss the health system and the out-of-pocket costs of CIPN. Preliminary WP2 results showed that, among the 2 million of patients treated for cancer focusing on 2019, 52 thousands do not present other comorbidities leading to neuropathy (mean age: 61 y.o.; 46% male). The public health expenditure to treat them was about 960 euro/person. Of these, 23% of them received CIPN-related medical treatments which account for 5% of the total expense. Therefore, a specific prevention and management of CIPN could help reducing the health expenditure and improve the medical outcomes. We are extending WP1 in an international multicenter study and deepening further WP2 analysis to reach a comprehensive understanding of CIPN socio-economic impact. Funding: Bicocca starting grant (UNIMIB).

STUDYING THE CAUDAL NERVE ANATOMY AND PHYSIOLOGY TO REFINE DETECTION OF PERIPHERAL NERVE DAMAGE IN RODENT MODELS.

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Animal models of peripheral neuropathy (PN) give the advantage of combining detailed neurophysiological and morphological observations. In particular, the rat caudal nerve is an easy site to be tested both with neurophysiology and neuropathology, and it is of specific interest in case of length dependent processes. However, the site of testing is crucial and different information can be detected at different levels; main published protocols test the nerve in one or, maximum, in 2 different sites. We aimed at refining our experimental approach increasing the set of measures we routinely perform both with histopathology and nerve conduction study (NCS). To refine our experimental setting, we selected a solid model of moderate-severe PN, related to paclitaxel (PTX) chronic administration.

Variables were collected from a control (vehicle [VEH] treated, n=8) and a PTX treated group (PTX 10 mg/Kg, 1qw4ws, n=8). NCS were performed at baseline and at end of treatment with a newly devised montage. Caudal nerve sensory nerve action potential (SAP) was recorded in multiple sites, covering the whole length of the tail going from proximal to distal, translating the electrodes from the base of the tail towards the tip of 2 cm each time: the reference and active recording electrodes (interelectrode distance: 1 cm) were placed 3 cm apart from the cathode and anode (interelectrode distance: 1 cm), and ground electrode was placed midway between the 2 dipoles. The whole caudal nerve was harvested at the end of treatment and, after fixation, the same segments we studied with NCS were included and then processed for histopathological examination.

At the end of treatment, NCS showed a moderate-severe PN ensued in PTX group with a clear length-dependent phenomenon. Notably, as soon as 4 cm from the base of the tail SAP was not recordable in all PTX animals with an increasing damage going distally, with SAP completely unrecordable in all animals as soon as 8 from the base of the tail. A similar pattern in axonal damage was clearly demonstrated by histopathological examination.

We obtained a refinement of our experimental procedures to detect PN in rat models. A more careful study design would be possible in subsequent studies; the site in which the caudal nerve is to be studied is crucial. Therefore, careful planning should be implemented to select

the appropriate sites to be tested, adapting for multiple recordings to detect the complexity of observed phenomena.

ANXIETY AND DEPRESSION IN CHARCOT-MARIE-TOOTH DISEASE: DATA FROM THE ITALYN CMT NATIONAL REGISTRY

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Aim of the study was to assess frequency of anxiety and depression in Charcot-Marie-Tooth (CMT) patients and to compare them to a control population.

We administered the Hospital Anxiety-Depression Scale (HADS) through an online questionnaire filled by CMT patients adhering to the Italyn CMT registry and a control population recruited among friends and relatives. HADS-A and HADS-D scores >10 define moderate-to-severe anxiety/depression and HADS total score >21 indicates moderate-to-severe general distress. We used the t-test/Mann-Whitney U-test, and Chi Square/Fisher's exact test to analyse associations between HADS scores and type of participants (CMT patients vs controls), gender, age, disease duration, disease severity (CMT examination score, CMTES), walking ability and/or use of orthotics, hand disability, sensory symptoms, and medication use (antidepressant and anxiolytic drug; analgesics).

We collected data from 252 CMT patients, with mean age 47.1 ±13.1 years; 137 patients were females. Mean scores for anxiety (6.7 ±4.8), depression (4.5±4), and total score (11.5±8.1) did not differ from healthy controls and the normal Italyn population. However, compared to controls, the percentage of subjects with moderate-to-severe depression (10% vs 2%), and general distress (14% vs 4%) were significantly higher among CMT patients ($p=0.04$ and $p=0.03$, respectively). We did not find any association between HADS scores and age, disease duration, CMT type (CMT1A versus other CMTs). However, compared to the others, patients with moderate-to-severe depression and general distress (total HADS scores) had more severe disease as assessed by the CMTES (median CMTES of 10 vs 7, $p=0.03$), a higher rate of walking difficulties (81% vs 73%, $p=0.04$), and positive sensory symptoms (66% vs 40%, $p<0.01$). Nineteen percent of CMT patients assumed anti-depressant and/or anxiolytics drugs (12% every day) and 73% analgesic drugs (17% >twice/week). Patients with moderate-to-severe anxiety, depression and general distress reported significantly higher consumptions of anti-depressant and/or anxiolytics drugs (34% vs 14% $p<0.01$, 52% vs 16% $p<0.01$, 44% vs 15% $p<0.01$, respectively). About one half of patients with moderate-to-severe anxiety, depression, and/or general distress did not receive any treatment.

There is a high proportion of CMT patients showing general distress (14%), which is more frequent than in controls and is associated with disease severity, positive sensory symptoms and consumption of anti-depressant and/or anxiolytics, suggesting that the disease itself is contributing to general distress. A high proportion of depressed/distressed patients is not appropriately treated.

FATIGUE IN CMT: A WEB BASED SURVEY FROM THE ITALYN CMT NATIONAL REGISTRY

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Fatigue is a disabling symptom in many neuromuscular disorders. We investigated the presence of fatigue in Charcot-Marie-Tooth disease (CMT) and its relationship with disease features and anxiety/depression.

We administered the Modified Fatigue Impact Scale (MFIS) through an online questionnaire filled by CMT patients adhering to the Italyn registry and a control group. The MFIS consists of 21 items aggregated into three subscales (physical, cognitive, and psychosocial) with three partial and one total score; higher scores indicate greater impact of fatigue, with >38 as cut-off for abnormal fatigue (*Flachenecker P et al., 2002*). We used the t-test/Mann-Whitney U-test and Chi Square/Fisher's exact test to analyse associations between MFIS score and type of participants (CMT patients vs controls), gender, age, disease duration and severity (CMT examination score, CMTES), walking ability and/or use of orthotics, hand disability, sensory symptoms, Hospital Anxiety and Depression (HADS) scale's scores, and medication use (antidepressants/anxiolytics).

We collected data from 251 CMT patients, whose mean age was 47 ±13 years, 136 females. Mean MFIS total score (32±18.3), physical (18.9±9.7) and psychosocial (2.9±2.4) subscores were significantly higher in CMT patients than in healthy controls ($p<0.0001$ for all comparisons). We could not find any association with CMT type (CMT1A vs other CMTs). When compared to patients with normal scores (<=38), CMT subjects with abnormal total MFIS score (>38) had more severe disease as assessed by the median CMTES (9.8 vs 7.2, $p<0.0001$), more frequent use of orthotic aids (41% vs 35%, $p=0.01$), support for walking (21% vs 8%, $p<0.005$), positive sensory symptoms (56% vs 36%, $p=0.002$), hand disability (70% vs 52%, $p<0.01$). We found also a strong association between fatigue and anxiety (rho 0.7, $p<0.0001$), depression (rho 0.69, $p<0.0001$), general distress (rho 0.76, $p<0.0001$) based on HADS scores. Nineteen percent of patients assumed anti-depressant and/or anxiolytic drugs, and 70% used analgesics; in both cases drug consumers had higher mean MFIS total, physical, psychosocial and cognitive scores as compared to non-consumers.

Fatigue is a relevant symptom in CMT as 36% of our patients had scores indicating abnormal fatigue and all mean scores were higher than controls. Fatigue was significantly associated with disease severity as assessed by the CMTES and several disease severity indicators, but also with anxiety and depression, indicating different components in the generation of fatigue. Patients' management must include treatment of fatigue and its different generators, disease severity and general distress.

POST-COVID-19 VACCINE RELAPSE OF GUILLAIN-BARRÉ SYNDROME (GBS) FOLLOWING AN ANTECEDENT PARA-INFECTIOUS COVID-19-RELATED GBS: A CASE REPORT

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We report on a patient who presented with para-infectious COVID-19-related, GD1b IgM-seropositive Guillain-Barré syndrome (GBS), and, subsequently, post-COVID-19 vaccine GBS, with antibody polyreactivity of ganglioside IgM.

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.

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.

COVID-19 vaccination in patients with previous para-/post-COVID-19 GBS, especially whether they result seropositive for ganglioside antibodies, deserves reappraisal. Molecular mimicry and anti-idiotype antibodies might have contributed to the vaccine-related GBS. 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 expectedly yielded several cases of post-COVID-19 vaccine GBS, which prompted the search for a possible causal link. This is difficult to demonstrate without mechanistic evidence, 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. Besides, among the rare neurological complications of COVID-19 vaccines, the mRNA vaccine ChAdOx1 nCov-19 was found to increase the risk of GBS, a finding confirmed in a second cohort. The main limitations of these studies include the passive reporting systems and presumptive case definition biases. Unusual adverse events, such as vaccine-induced immune thrombotic

thrombocytopenia, myocarditis, and IgA vasculitis also suggest potential links with COVID-19 vaccines. However, the demonstration of such links is still lacking. We report on a patient with post-COVID-19 vaccine GBS, who had previously had a COVID-19-related GBS, thus suggesting that SARS-CoV-2 infection could have triggered, in a genetically predisposed subject, peripheral nerve-specific autoimmunity. The study obtained ethical approval and patient's signed informed consent.

EARLY MOLECULAR DIAGNOSIS OF MUTATIONS ON THE TRANSTHYRETIN GENE AS A STRATEGY TO IMPROVE THE PROGNOSIS OF HEREDITARY TRANSTHYRETIN-MEDIATED AMYLOIDOSIS - AN UPDATE OF THE GENILAM PROJECT

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Hereditary transthyretin-mediated amyloidosis-hATTR is an autosomal dominant disease caused by mutations in the transthyretin (TTR) gene. hATTR is a potentially life-threatening condition characterized by extracellular deposition of amyloid fibrils composed of transthyretin (TTR) with an altered structure. Due to the great variability in clinical presentation and non-specific nature of the symptoms, hATTR represent a diagnostic challenge for neurologist and cardiologist. The hATTR diagnosis in patients with subclinical and non-specific pictures is therefore likely to be delayed for a long time, with obvious prognostic and therapeutic consequences. As part of the Italyn project named Genilam, started in 2019, clinical centers were offered a genetic test service at no charge with the aim of shortening the time of molecular diagnosis and early identify the disease in order to slow its progression and identify eligible patients for targeting treatments.

The hATTR test was performed by gene amplification (PCR) of exons 2, 3 and 4 of the TTR gene and subsequent automated sequencing for the investigation of the main mutations.

In the first 36 months, about 300 specialized medical centers were involved, and 2241 patients were tested for hATTR. A total of 155 patients (155/2241; 6.91%) tested positive, among whom two had a double mutation in the TTR gene (Val142Ile/Phe84Leu and Val50Met/His110Asn) and one had a Phe84Leu homozygous mutation. Among the mutations found in TTR gene, the most common were Phe84Leu (47/157; 29.94%), Val50Met (25/157; 15.92%), Ile88Leu (19/157; 12.10%), Val142Ile (17/157; 10.83%), His110Asn (12/157; 7.64%), Glu109Gln (10/157; 6.37%) and Phe84Leu (10/157; 6.37%). The majority of patients identified as positive were male (92/155; 59.35%); three Italyn regions have shown a higher incidence of positive individuals, Sicilia (60/155; 38.71%), Lazio (21/155; 13.55%) and Puglia (17/155; 10.97%). Of the patients who tested positive, more than half had a known family history of the condition (54.84%), while 15.48% indicated that they were unaware of a family history of the disorder and 29.68% had no family history of hATTR. The project data showed that the most frequently occurring symptoms are sensitive dysfunction (57.24 %), motor dysfunction (30,26 %) and heart disease (30,26 %) of which sensitive dysfunction and motor dysfunction are very often encountered together.

Molecular diagnosis offered by Genilam project has helped to rapidly identify patients improving management of potentially at risk family members and promoting the personalized surveillance, thanks also to the great consensus received by the specialized healthcare professionals.

THR124MET MYELIN PROTEIN ZERO MUTATION MIMICKING MOTOR NEURON DISEASE

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Mutations in myelin protein zero (*MPZ*) are found in 5% of CMT patients and are associated with heterogeneous phenotypes.

In our study we report clinical, electrophysiological, pathological, and muscle MRI findings from two relatives harboring the same *MPZ* variant, disclosing different phenotypes. The proband was a 73-year-old female with a 12-year-history of atrophy, weakness and fasciculations in her proximal and distal lower limbs. Neurophysiological examination showed neurogenic signs with active denervation together with reduced sensory action potentials, in the absence of sensory symptoms. The initial diagnosis was of a slowly progressive lower motor neuron disease (MND) with subclinical sensory axonal neuropathy. Two years later, the observation of her 60-year-old nephew, who had a distal sensory-motor neuropathy, prompted the analysis of inherited neuropathies-related genes and revealed the *MPZ* Thr124Met mutation in both cases. The most confounding feature in the proband was the absence of the classic length dependent pattern of muscular weakness. Furthermore, fasciculations were present in the lower limbs and needle EMG examination showed abundant fibrillation potentials.

Among *MPZ*-related neuropathies with adult-onset, the form associated with the Thr124Met variant shows a peculiar phenotype characterized by relevant positive sensory symptoms, frequent pupillary abnormalities and hearing loss. The onset occurs in the fourth to fifth decade and some patients show severe course, leading to loss of independent walking. A minority of patients show severe swallowing difficulties and an involvement of respiratory muscles. These findings

indicate that clinical manifestations of the *MPZ* Thr124Met variant may mimic a motor neuron disease.

The detection of sensory abnormalities in the diagnostic workup of ALS suspicion represents a challenging diagnostic problem. Several ALS mimicking conditions characterized by sensory involvement have been described. On the other hand, subjective sensory symptoms, or a reduction of sensory action potentials, are reported in a proportion of patients with otherwise typical ALS. In these cases, one possibility is that a peripheral neuropathy of different etiology may co-occur with ALS. Finally, there is a possibility that sensory involvement might be part of multisystem extra-motor manifestations of ALS. Recent genetic discoveries established that cell type impairment in ALS may extend beyond upper and lower motor neurons, thus linking ALS to different conditions over a continuum.

Our findings expand the clinical spectrum of MPZ-related neuropathy and highlight that Thr124Met mutation may cause a syndrome mimicking MND. The challenging issue to detect sensory features in the diagnostic MND work up is discussed.

TORSIONAL NEUROPATHY IN PARSONAGE TURNER SYNDROME FOLLOWING ANTI-COVID19 VACCINATION. HOW TO DETECT AND MANAGE WITH IT?

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Introduction: Torsional lesions of peripheral nerves have rarely been described. The most frequent nerves involved in torsional lesions are the main trunk of the radial nerve and most of all its distal branch, while rarer is the involvement of the musculocutaneous and axillary nerves. The aetiology is still unknown although both traumatic and spontaneous forms have been described. In particular, in this second case, an autoimmune inflammatory genesis is hypothesised and rare cases of Parsonage-Turner Syndrome (PTS) characterised by torsional neuropathy, have been reported.

We describe the case of a 45-year-old patient, who a few days after receiving the anti-COVID19 vaccine, presented with a pain localised to the left shoulder, site of the vaccine inoculation and initially thought to be connected to it, with subsequent irradiation to the entire left upper limb.

Materials and methods: The patient carried out several investigations including neurological examination, shoulder ultrasound and magnetic resonance (MR), electrodiagnostic testing (EDX) and finally plexus ultrasound and MR.

Results: The neurological examination evidenced hypotrophy of the left shoulder and arm muscles with associated weakness, hyporeflexia, and mild hypoesthesia and dysesthesia in the shoulder region and in the lateral face of the arm.

The EDX showed denervation signs in the dorsal interosseous muscle, brachial bicep, brachial triceps and left deltoid.

Ultrasound and MR examination demonstrated an enlargement of the brachial posterior cord with a swollen axillary and musculocutaneous nerves in which an hourglass morphology and typical features of multifocal torsion neuropathy was detected. In the follow-up ultrasound and MR examinations, performed after a clinical worsening, the extension of these findings to the brachial plexus divisions proximally and to the radial nerve and its posterior interosseous branch distally, was observed.

Conclusions: Cases of torsional neuropathy associated with PTS have rarely been described. The pathophysiological mechanism leading from hourglass-like constrictions to nerve entwinement is not clear although it could be the natural consequence of such constrictions. At the basis of this process it is not possible to exclude a physical component linked to mechanical torsion by rolling of the fascicles during movements. For this reason, in all cases of PTS, we want to focus on the importance of neuroimaging investigations to early detect nerve alterations potentially favouring dramatic clinical worsening if associated with particular movements during rehabilitation programs and to open the discussion on the better therapeutic approach in a setting of multi neural torsional neuropathy: immunomodulation or surgical approach?

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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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 were seen in male adolescents and young adults, typically within several days from COVID-19 vaccination (Pfizer-BioNTech or Moderna), and more commonly after the second dose.

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.

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 systems, 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, but 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.

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.

ISOLATED MUSCULOCUTANEOUS INVOLVEMENT IN PARSONAGE-TURNER SYNDROME ASSOCIATED WITH SARS-COV2 VACCINATION

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Neuralgic amyotrophy (NA) or Parsonage Turner syndrome is a clinical syndrome typically characterized by sudden pain attacks in the shoulder and upper arm, followed by patchy muscle paresis in the upper limb. The isolated musculocutaneous nerve involvement is extremely rare. We describe a case of NA with isolated musculocutaneous nerve involvement which developed a few days after administration of this vaccination.

A 50-year-old healthy female on 1ST June 2021 received her first dose of the SARS-CoV-2 BNT162b2 vaccination. Two days later she developed sudden onset severe pain in the left shoulder. The day after, the pain moved to the right shoulder then disappeared. On 11th June 2021 she complained again of severe pain on her left arm, more pronounced on the shoulder and elbow. Neurological examination was unremarkable with the exception of weakness in the right biceps brachii. Sensation was diminished to light touch throughout the right C5 dermatome. Left biceps brachii tendon reflex was decreased. Blood tests were unremarkable. MRI of the cervical spine was normal. On 23rd June 2021 a first electromyography and nerve conduction studies were performed: there was a decrease in the recruitment pattern in the left biceps brachii at the needle examinations. On 24th July 2021 a second neurophysiological evaluation was executed: NCS showed the absence of the sensory nerve action potential for the left lateral antebrachial cutaneous sensory nerve and the compound motor action potential at the biceps brachii was absent. Furthermore, 3+ fibrillations and 3+ positive sharp waves were present at the right biceps brachii as well as the absence of the voluntary recruitment pattern. Treatment with oral prednisone was immediately started.

We describe a case of NA with isolated musculocutaneous nerve involvement following administration of the SARS-CoV-2 BNT162b2 vaccine. Although other brachial plexopathies have been reported, to the best of our knowledge this represents the first description of isolated musculocutaneous nerve involvement. Neuralgic amyotrophy represents a rare disorder; its overall incidence is estimated to be about 1 in 1000, but isolated musculocutaneous involvement is anecdotal. Post vaccination NA is also very rare. Up to now more than 5 billion SARS-CoV-2 vaccine doses have been administered globally thus it remains to be seen whether the incidence of vaccination triggered NA or other rare neurological side effects more than was expected as some authors point out.

Further studies are needed to determine whether a causal relationship exists between these vaccines and neurological sequelae.

NEONATAL FC RECEPTOR EXPRESSION IN PATIENTS WITH CHRONIC DYSIMMUNE NEUROPATHY. A FEASIBILITY STUDY

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The neonatal Fc receptor (FcRn) has an important role in regulating the immunoglobulin G (IgG) plasma level. Over 40% of IgG plasma levels are determined by their recovery through binding to FcRn, therefore FcRn has a protective role by reducing the catabolism of both autologous and therapy-infused IgG.

In this study we aim to evaluate through flow cytometry, the expression of FcRn in peripheral blood leukocytes of healthy subjects and patients with chronic dysimmune neuropathy in relation to treatment.

We will evaluate different groups of patients: a) non-treated (naive patients or non-treated for at least 6 months); b) treated with intravenous (IVIg) or subcutaneous (SCIg) immunoglobulin, responders or non-responders to therapy. For patients treated with IVIg, correlation between FcRn expression and the time elapsed between two successive administrations of the drug will also be evaluated.

The results will allow us to verify:

- Whether the expression of FcRn changes according to treatment
- Whether the clinical response correlates with the expression of FcRn

To date, we have only collected data of 12 patients: 5 non-treated and 7 treated (6 responders and 1 non responder) Preliminary data show:

- There is very low or no expression of FcRn on the surface of peripheral blood cells.
- All neutrophils stain positive for intracytoplasmic FcRn with variable amount among patients
- Intensity of intracytoplasmic expression seems to be repeatable when evaluated in the same patient in different days.

With these premises, we reasonably believe that the study can be continued.

GAIT ANALYSIS IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)

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Despite an extensive set of clinical, neurophysiological, laboratory and imaging criteria defined by the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) in 2021, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) frequently undergoes misdiagnosis. Therefore, the identification of additional tools (i.e nerve ultrasound) and reliable biomarkers is crucial to avoid possible delays in the diagnosis. Moreover, sensitive outcome measures able to evaluate the response to immunomodulatory therapy are still lacking, slowing down access to treatment and leading to an increase of disability.

Twenty-one patients (8 female, mean age 57 ± 13 years, range 27-79) diagnosed with definite CIDP (according to the EFNS/PNS criteria) were considered. All patients underwent neurological evaluation [Inflammatory Neuropathy Cause and Treatment (INCAT) disability score, MRC Sum Score, INCAT Sensory Sum Score ISS], neurophysiology and nerve ultrasound study. Computed gait analysis was also performed to evaluate the spatio-temporal parameters, kinematics and kinetics of the walking. Twelve patients were being treated for CIDP (8/21 intravenous immunoglobulins, 3/21 subcutaneous immunoglobulins, 1/21 steroid therapy). Whenever possible, baseline assessment was performed before starting the treatment. We included a control group with sex and age-matched healthy subjects. Moreover, 13/21 patients (5 female, mean age 54±13 years, range 27-69) underwent a 6-month follow-up evaluation.

Median INCAT score was 1, with range 0-3 and range 0-1 at upper and lower limbs respectively. Median INCAT total score was 2 (range 0-4). Median MRC Sum Score was 30, with range 27-30 and range 23-30 at upper and lower limbs respectively. Median MRC Total Sum Score was 60 (range 50-60). Median ISS total score was 2 with a wide variability in the range (0-13) and predominant impairment in tactile and pain sensory items. Preliminary results for gait analysis showed a Center of Pressure standard deviation (stdCOP) significantly higher in patients ($p < 0.033$), and an index of reduced stability during the static analysis. Regarding the spatial-temporal variables of the gait analysis, a significant difference between patients and controls was found in step width ($p = 0.017$).

In conclusion, the definition of specific and sensitive outcome measures is crucial to allow the modulation of treatment based on both objective and subjective responses, and to monitor patients in the long term.

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PERIPHERAL NEUROPATHIES AFTER COMMON ORGAN TRANSPLANTATIONS. LITERATURE REVIEW AND THE USE OF ELECTROPHYSIOLOGICAL TESTS AND ULTRASOUND

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Transplantation represents important management in organ failure and is often the lonely possibility to save patients' life. Besides the risks directly related to the surgical intervention and, in general, the side effects of medications, other clinical effects can be seen after the transplantation. Regarding the possible peripheral nerve disorders, infections, immune-related and drug-related neuropathies may be revealed. The surgery and the following prolonged bed rest are commonly associated with the occurrence of peripheral neuropathies. Furthermore, sarcopenia and skeletal muscle damage can be seen. The listed conditions can be very severe and are associated with poor recovery after the transplantation and its rehabilitation. Considering its importance, the knowledge of this topic may be fundamental for patients' health.

We have performed a search on PubMed, in order to define the literature about the most common transplantations (liver, kidney, heart, lung, pancreas) and peripheral neuropathies. We assessed the diagnostic tools used to determine the nerve diseases and the way to manage them. We have considered the last 20 years and the papers published in the English language. Additionally, we present a 71-year-old woman, with primary cirrhosis, treated with liver transplantation 2 months before our evaluation. She showed, after the intervention, cachexia and focal strength deficit of foot dorsiflexion. The patient was examined with clinical, electrophysiological and ultrasound evaluations. The exams showed the ability to overcome their respective limits and to define the type and severity of the damage.

The literature showed 106 papers with a predominance of liver transplantation. In the abstracts, sensory, motor and autonomic neuropathies were mentioned. Electrophysiological tests were present, but no specific studies displayed nerve or muscle ultrasound. In our case, the electrophysiological test revealed severe axonal damage of the fibular nerve, with a major impairment at the right side, and nerve ultrasound just presented a slight enlargement of the nerve at the fibular head. Muscle ultrasound showed a general fibrotic substitution of the right tibialis anterior muscle and a partial change of echogenicity at the left muscle, with more areas of preserved pattern. A rehabilitation protocol aimed at the amelioration of joint and muscle functions was administered. Ankle orthotic was indicated to help the ambulation.

The literature is currently scarce and, probably, large studies with long follow-up are needed to understand the manage neuropathies after

transplantation. Our case shows the potentialities of the association of electrophysiology and ultrasound to define the patient's condition and decide the treatment.

ULNAR NEUROPATHY AT THE ELBOW IN ACQUIRED BRAIN INJURY PATIENTS: UTILITY OF NERVE ULTRASOUND

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Patients hospitalized for long periods are at risk of peripheral nerve injury due to compression or entrapment as a result of bed rest, frequently prolonging the period of hospitalization with negative consequences on motor and functional recovery. Coexisting common conditions in hospitalized patients, such as malnutrition, diabetes mellitus and chronic vasculopathy, increase the likelihood of peripheral nerve damage. In bedridden patients, the ulnar nerve in particular has a high risk of compression at the cubital tunnel due to its superficial course at this level. Therefore, effective and relatively simple diagnostic methods are needed in order to rapidly recognize and manage these complications. Nerve ultrasound (US) is a very useful imaging tool, in relation to its high degree of spatial resolution and versatility of execution, even at the patient's bedside. In addition a recent meta-analysis [1] confirmed the high diagnostic power of US for ulnar neuropathy at the elbow (UNE). We studied 50 patients admitted to our Neurorehabilitation Unit, suffering from acquired brain injury (ABI), in order to investigate through US the prevalence of UNE in this type of patients. We also investigated the possible relationship between UNE and motor deficit due to brain injury and the possible influence of body mass index (BMI). We found an increase of Cross Sectional Area (CSA) in at least one of each patient's ulnar nerves at the cubital tunnel in 72% of cases. There was also a statistically significant association between paretic/plegic side and UNE on the same side. In contrast, no correlation between BMI and CSA was found. US has been shown to be a safe, simple and rapid method for evaluation of peripheral nerves at the patient's bedside. In addition, the prevalence of signs of ulnar nerve damage at the cubital tunnel is high in patients with ABI and more frequent in the paretic/plegic side, likely related to prolonged reduced mobility. The prevention of these complications is crucial for motor and functional recovery in this type of patients.

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ALLELE-SPECIFIC SILENCING AS THERAPY FOR FAMILIAL AMYOTROPHIC LATERAL SCLEROSIS CAUSED BY THE P.G376D TAR DNA-BINDING PROTEIN 43 MUTATION

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Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disease characterized by a progressive loss of motor neurons. About 90% of ALS cases are related to the sporadic form of ALS, while others are caused by mutations in several different genes (familial ALS). In an Italyn family, a heterozygous mutation in the TARDBP gene (c.1127G>A; p.G376D) is related to the onset of ALS. TARDBP encodes TAR DNA-binding protein (TDP-43), a ribonucleoprotein involved in mRNA processing and stability. Under pathological conditions TDP-43 migrates from the nucleus to the cytosol where it forms aggregates. In this study we aimed to develop a small interfering RNA (siRNA) approach that could induce an allele-specific silencing of the expression of mutant TDP-43G376D.

To this aim we designed different siRNAs and we used them to silence HEK293T and dermal fibroblasts from patients carrying TDP-43G376D. We evaluated the ability of these siRNAs to silence specifically the mutated allele using qPCR analysis and western blotting. We also investigated with confocal immunofluorescence the presence of pathological TDP-43 aggregates induced by the presence of the mutated allele in Neuro2A cells and in patients' cells before and after the treatment with the siRNAs.

Among the different siRNAs tested, the siRNA called M10 reduced the protein and the mRNA levels of TDP-43G376D in transfected HEK293T cells, while TDP-43wt levels remained unchanged. We silenced control and patients' cells using M10 and TDP-43i, a siRNA that recognizes TDP-43 wild type. TDP-43i reduced the amount of TDP-43 both in control and in patients' cells, while M10 strongly reduced TDP-43 levels in ALS but not in control cells. These data were confirmed by RT-PCR and Western blot. We also investigated the presence of TDP-43 aggregates and we noticed that in control cells there were no aggregates, while in patients' cells we found a progressive accumulation of TDP-43 in advanced stages of the disease compared to the earlier ones. Importantly, treatment with M10 reduced the formation of cytosolic TDP-43 aggregates in patients' cells. We confirmed these data also in Neuro2A cells transfected with GFP-TDP-43G376D.

In conclusion, we identified a siRNA able to specifically silence the mutated allele of TDP-43G376D and to strongly reduce the presence

of TDP-43 aggregates in the cytoplasm of patients' cells, reverting the pathological phenotype. Thus, importantly, RNA interfering could be used to selectively target allele mutations in patients' cells and it could be a potential therapeutic tool for ALS in the future.

THE ROLE OF THE LONGITUDINAL EXTENT OF ULTRASONOGRAPHIC ABNORMALITIES IN ULNAR AND PERONEAL ENTRAPMENT NEUROPATHIES AS PREDICTIVE OUTCOME

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Objective: In order to improve the availability of reliable ultrasonography (US) outcome measures in entrapment neuropathies and to define the eligibility for surgery, we aimed to evaluate the length of abnormal nerve segments (LANS) in ulnar and peroneal entrapment neuropathies, before and after surgery.

Material and methods: We enrolled consecutive patients with common peroneal nerve entrapment (CPNE) at fibular head and ulnar nerve entrapment (UNE) at elbow, and using electrodiagnostic (EDX) and US classified in subgroups with reduced motor nerve conduction velocity only, nerve conduction blocks and prevalent axonal impairment. In all ulnar and peroneal nerves studied, the following US-parameters were collected: maximal CSA, maximal/minimal CSA ratio, LANS, and a new parameter of LANS/Maximal CSA ratio (LMC ratio). For CPNE, to evaluate the distal extension of nerve enlargement, the superficial and deep peroneal nerve were studied bilaterally and an additional parameter of CSA side-to-side difference was collected for both nerves. All patients performed clinical, EDX and US evaluation at 3 and 6 months. Only patients underwent surgery and with a mean follow-up of at least 6 months were enrolled.

Results: We included 32 patients (35 arms) with UNE and 52 patients with CPNE. In UNE group, the site of entrapment was at the Osborn's arcade in 24, at the medial epicondyle (ME) in 6 and at 2 cm proximal to the ME in 5. In 14 the nerve lesion was mainly axonal, in 15 was mixed and in 6 was demyelinating. In axonal lesions the LANS was longer than in demyelinating entrapments (mean Δ 3.8cm), and maximal/minimal CSA ratio was lower (mean Δ 0.4). In the CPNE group, in 12 the lesion was mainly axonal, in 34 was mixed and in 8 only demyelinating. The LANS was longer in mixed lesion. In all groups shorter LANSs were related to a better clinical and EDX outcome, and considering the group of axonal and mixed lesions, the LMC ratio > 0.45 is related to the worse outcome. Moreover, there was high concordance of pre-operative US studies with surgical view, and the pre-operative study allowed a tailored surgical plan.

Discussion: These preliminary results suggest the possible role of LANS and LCM ratio as predictive outcome for UNE and CPNE after surgery.

CUTANEOUS SILENT PERIOD IN THE ASSESSMENT OF PRE-SYMPTOMATIC H-ATTR PATIENTS: PRELIMINARY RESULTS

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Introduction: Hereditary Transthyretin Amyloidosis (hATTR) is a genetic condition due to mutation of the *TTR* gene. Once the instable protein is produced, it deposits in different tissues, especially peripheral nerves and heart. A progressive and disabling axonal polyneuropathy is the most common neurological manifestation. The recent approval of new drug treatments able to significantly improve the clinical outcomes when started early raises a major question about the possibility of the recognition of the first symptoms in carriers. Cutaneous silent period (CSP) is a physiological response of nervous system to pain: when a noxious stimulus is applied to a muscle in activity, a brief interruption of contraction is observed. This response is altered in case of A-delta small fibres damage. This function could be determined by an electrophysiologic test that measures the latency and the duration of CSP; we suppose that CSP could be a useful tool in monitoring the disease onset in carriers.

Materials and methods: We analysed the CSP latency and duration obtained with a painful stimulation of the III digit registering from abductor brevis pollicis in 10 pre-symptomatic carriers (6 females and 4 males) harbouring an amyloidogenic mutation of *TTR*. Data where compared with those obtained from 11 controls (6 females and 5 males) without polyneuropathy and controls obtained from literature.

Results: Mean pre-symptomatic age was 46,4 ± 9,9 years. In pre-symptomatic hATTR the mean CSP latency was 77,1 ± 11,3 msec and mean duration was 49,5 ± 18,7 msec. In our controls the mean age at test was 45,6 ± 8,9 years, the mean CSP latency 72,3 ± 8,9 msec and the mean CSP duration 52,6 ± 8,8 msec. Considering controls obtained from literature the mean age was 33,8 ± 10,3 years, the mean CSP latency was 70,7 ± 11,7 msec, and the mean CSP duration 52,3 ± 9,1 msec. No significant differences were found respect to controls at Mann-Withney U-test (respectively p=0,94 and p=0,46 compared with our controls and p=0,14 and p=0,52 with the literature controls).

Conclusions: In a small cohort of pre-symptomatic carriers fo hATTR we didn't found any differences in the CSP latency and duration compared with controls. Larger studies are necessary to confirm our result.

PUPILLOMETRIC FINDINGS IN ATTRV PATIENTS AND CARRIERS: RESULTS FROM A SINGLE-CENTER EXPERIENCE

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Introduction: Hereditary transthyretin amyloidosis (ATTRv) is a treatable multisystemic disease with a great phenotypic heterogeneity. Among extra-neurological features, pupillary abnormalities have been reported, either related to amyloid deposition in the eye or to a progressive autonomic neuropathy. Besides neurophysiological and cardiac outcome measures, there are few markers aimed at monitoring disease progression and response to treatment. Automated pupillometry is a non-invasive and rapid test able to provide objective and reproducible data on pupil size and reactivity. In our study, we aimed to evaluate the role of automated pupillometry as a marker of disease progression in late-onset ATTRv and, eventually, as a marker of disease onset in pre-symptomatic TTR mutation carriers.

Patients and methods: We performed automated pupillometry on a cohort of ATTRv patients (64 eyes) and pre-symptomatic TTR mutation carriers (22 eyes) and compared the results to 50 eyes from healthy controls. An exhaustive clinical and instrumental evaluation was performed in all enrolled subjects.

Results: A statistically significant difference in all pupillometry parameters (except for Neuropupillary index, or NPi) was found in ATTRv patients as compared to both carriers and healthy controls, but no difference was evident between carriers and healthy controls. Moreover, in ATTRv patients, we found a significant correlation between pupillometry findings and disease duration, as well as widely accepted clinical scales and investigations, such NIS, Sudoscan values from feet and Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire.

Conclusions: We suggest pupillometry may play a role as a reliable and non-invasive biomarker to evaluate ATTRv disease severity and monitor its progression. Unfortunately, it does not seem to have a role as a disease onset biomarker.

PATISIRAN IN HATTR AMYLOIDOSIS AFTER 9-MONTHS OF FOLLOW-UP: A SINGLE CENTER REAL-LIFE EXPERIENCE

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Introduction: Hereditary amyloid transthyretin amyloidosis is a multisystemic rare, inherited, progressive adult-onset disease, affecting the sensorimotor nerves, heart, autonomic function and other organs. It is caused by mutations in the TTR gene, leading to misfolded monomers which aggregate generating amyloid fibrils. Patisiran is a small, double-stranded interfering RNA encapsulated in a lipid nanoparticle, able to penetrate into hepatocytes, where it selectively targets TTR mRNA, reducing TTR production. We report and discuss a single-center experience from real-life of Patisiran treatment in hATTR.

Methods and materials: We enrolled patients with genetically-confirmed diagnosis of ATTRv, followed since 2020 to 2022 in Neuromuscular clinic of Policlinico "Paolo Giaccone" - University of Palermo. All subjects underwent neurologic evaluation, each obtaining a Polyneuropathy Disability (PND) score (with higher scores indicating more impaired walking ability), Neuropathy Impairment Score (NIS) (with higher scores indicating more impairment), and quality of life assessment with the Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QOL-DN) questionnaire (with higher scores indicating worse quality of life), Karnofsky performance status, evaluation of autonomic involvement through COMPASS-31 scale (with higher scores indicating more impairment) and 6-minutes walking test (6MWT) at baseline and after 9 months of treatment.

Results: Twelve patients with a diagnosis of ATTRv amyloidosis, of which 6 men with a mean age of 65.0±8.0 years have been recruited. F64L (p.F84L) mutation in the TTR gene was encountered in 13 patients, E89Q (p.E109Q) in 1, V122I (p.V142I) in 1 and H90A (p.H110A) in 1 patient. PND score was stable in 13 and improved in 3 patients. In particular, 5 (42%) patients gained body weight, 8 (67%) patients improved on 6MWT, 6 (50%) patients reported reduced NIS scores, COMPASS-31 score was reduced in 4 (33%) patients and 8 (67%) reported a better quality of life with lower Norfolk scores and Karnofsky performance status was improved in 5 patients (42%). All patients were satisfied of the treatment and only one patient showed mild clinical progression. The drug was safe in 11 patients without side effects; only one patient reported hypertension following premedication with steroids.

Conclusions: Our data show that patisiran is effective and safe improving neurological symptoms of ATTRv amyloidosis, and QoL, especially in patients with low burden of the disease. We think that patisiran should be considered a valid therapeutic option for the management of patients with ATTRv amyloidosis with polyneuropathy since the clinical onset.

MACHINE-LEARNING FOR THE EARLY DIAGNOSIS OF HATTR AMYLOIDOSIS: A PILOT STUDY

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Introduction: Hereditary transthyretin amyloidosis with polyneuropathy (hATTR) is an adult-onset multisystemic disease, affecting the sensorimotor and autonomic functions along with other organs, especially heart, gastrointestinal tract, eyes and kidney. The clinical phenotype is heterogeneous and often unpredictable; hence, the

diagnosis may be quite difficult. Nowadays, avoiding misdiagnosis is crucial because it implies high costs for the community and, moreover, several treatment options are available particularly effective in early disease stages. We hypothesize that the use of Machine learning (ML) in the genetic screening for hATTR might lead to a higher sensitive and specific diagnostic approach, contributing to significantly reduce the diagnostic delay in non-endemic areas, as well as ensuring the early treatment for this rare inherited disease.

Methods and materials: After a screening program of two years, 215 patients underwent genetic testing for hATTR in Neuromuscular Clinic of Palermo. Each patient was examined with a detailed questionnaire exploring the presence of specific red flags (CIDP, diabetes, gender, unexplained weight loss, bilateral CTS, symptoms of neuropathy, ataxia, renal pathology, positive biopsy for amyloid, lumbar canal stenosis, gastrointestinal symptoms, autonomic dysfunction, renal or ocular involvement, cardiac amyloidosis and family history of neuropathy, cardiopathy or hATTR). Hence, a cohort of 82 patients, 38 with positive and 44 with negative genetic results, was considered for the classification task. The Sequential Forward Selector was used to select the most discriminating features before the algorithm training task. The K-Nearest Neighbors (KNN) was used as a Machine Learning algorithm and the related performance was calculated using the Stratified 10-Fold Cross Validation, repeating the cross-validation procedure 10 times and reporting the mean result across all folds from all runs.

Results: The selected features were diabetes, gender, unexplained weight loss, bilateral CTS, symptoms of neuropathy, ataxia, renal pathology, positive biopsy for amyloid, and family history of hATTR. The trained KNN algorithm showed an accuracy of 0.771 +/- 0.141, a specificity of 0.770 +/- 0.194, a sensitivity of 0.771 +/- 0.196, and an AUC-ROC of 0.762 +/- 0.159.

Conclusions: Our data show that ML might potentially be a useful diagnostic tool, will make easier to identify patients affected by ATTR-PN that should undergo genetic testing. Also, it might lead to an earlier diagnosis of hATTR allowing for timely treatment at the clinical onset, thus reducing costs for the community in terms of hospitalization and mortality.

MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODIES AND PERIPHERAL NEUROPATHIES: A CLINICAL AND NEUROPATHOLOGICAL RETROSPECTIVE STUDY

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The involvement of both peripheral and central nervous systems (PNS and CNS) has been rarely reported in patients with myelin oligodendrocyte glycoprotein antibodies (MOG-Abs). The aim of the present study is to test MOG-Abs in patients with undetermined peripheral neuropathy (PN).

Consecutive patients with available paired serum sample and sural nerve biopsy performed in a single center between January, 1st 2016 and November, 1st 2021 were retrospectively identified. Sera were tested for MOG-Abs with in-house live cell-based assay (CBA) using H+L secondary antibody. Patients with MOG antibody titre ≥1:160 were also tested with live CBA using IgG-FC secondary antibody to confirm the presence of immunoglobulins G (MOG-IgG). Patients with H+L titer ≥1:160 and IgG were defined as MOG-IgG positive. Positive samples were also tested with CBAs for Neurofascin-155 and Contactin-1 and analysed with immunohistochemistry to rule out the presence of other concomitant antibodies.

Clinical and neuropathological data of MOG-IgG positive patients were collected through available clinical reports.We analysed 163 patients and 5 of them (3%) were tested positive for MOG-IgG (median titer 1:320, range 1:160-1:5120) and were further characterized. None of these patients harbored other autoantibodies. Median age of included patients was 74 years (range 55-81), and 60% of them were female. Disease duration was 60 months (range 1-167). Clinical features were suggestive of acute (n=1) or chronic (n=3) inflammatory demyelinating neuropathy, whilst one patient had a chronic progressive neuropathy. Notably, 3/5 patients had isolated PNS involvement, whilst 2/5 fulfilled the diagnostic criteria for combined CNS and PNS demyelination (CCPD).

Neuropathological findings demonstrated predominant demyelination (3/5) or mixed axonopathy and demyelination (2/5). Cluster of regenerations were found in 4/5 patients, myelin outfolding in 4/5, paranodal demyelination in 3/5, and onion bulbs in 3/5. Intriguingly, 3/5 patient presented slight inflammatory infiltrates.

Our study demonstrates that: a) MOG-IgG may be found in patients with PNS involvement and b) MOG-IgG may be present even in patients with PN in absence of concomitant CNS involvement. Patients with MOG-IgG and PN usually present with clinical findings suggestive of inflammatory neuropathy and neuropathological features of demyelination with slight inflammatory infiltrates.

Further studies are required to elucidate the relevance of MOG-IgG in PN and to evaluate whether testing MOG-IgG is cost-effective in these conditions.

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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To assess whether vaccination for SARS-CoV-2 increases the risk of relapse in chronic inflammatory neuropathies. In this multicenter prospective cohort study we evaluated the risk of relapse in c inflammatory demyelinating polyradiculoneuropathy (CIDP) and multifocal motor neuropathy (MMN) after vaccination for SARS-CoV-2 and the safety of the SARS-CoV-2 vaccines. We compared the frequency of relapse in the three months after the first dose of vaccine in patients who underwent vaccination with the frequency of relapse in the three months after enrollment in patients who did not undergo vaccination. We also compared the frequency of relapse in CIDP and MMN patients undergoing vaccination for SARS-CoV-2 in the three months prior and after vaccination. All included patients were in stable condition and treatment regimen. Clinical relapse was defined using objctive outcome measures while safety of vaccination was evaluated using a specific questionnaire. Relapse occurred in 11 (4.5%) (9 CIDP, 2 MMN) of 246 patients (209 CIDP, 35 MMN) who underwent vaccination, and in 1 (4%) (MMN) of 25 patients (15 CIDP, 10 MMN) who did not undergo vaccination. The relative risk of relapse associated with exposure to vaccination was 1.1 (95 percent confidence interval, 0.15-8.30). Relapse occurred at a mean 48 days (22-90 days) after the first dose and 25 days (1-60 days) after the second dose of vaccine. Six patients who relapsed after vaccination received treatment adjustment. There was no increase in the specific risk of relapse associated with each specific brand of vaccine. There was no significant difference in the frequency of relapse in the three months prior and after vaccination (2% vs 4.5%). The safety profile of SARS-CoV-2 vaccines was characterized by mild-to-moderate pain at the injection site, fatigue, fever, and headache. There was no serious adverse events.Vaccination for SARS-CoV-2 does not appear to increase the short-term risk of relapse in CIDP and MMN.

COMPARISON OF THE DIAGNOSTIC ACCURACY OF THE EAN/PNS AND EFNS/PNS DIAGNOSTIC CRITERIA FOR CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

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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. Sensitivity and specificity of the two above-mentioned criteria were evaluated in 492 CIDP patients and 156 controls with axonal or immune-mediated neuropathy. Comparison of the utility of nerve conduction studies of varying extensiveness and of the sensitivity of the two sets of criteria in typical CIDP and variants were also assessed. EFNS/PNS criteria had a sensitivity of 91% for possible CIDP and 78% for probable/definite CIDP, while the EAN/PNS criteria had a sensitivity of 81% for possible CIDP and 67% for CIDP. Using supportive criteria, the sensitivity of the EAN/PNS criteria for possible CIDP increased slightly to 83%, thus remaining lower than that of the EFNS/PNS criteria. The EAN/PNS criteria were less sensitive for the diagnosis of distal CIDP

than for the diagnosis of typical CIDP, whereas no difference in the sensitivity of the EFNS/PNS criteria among the different CIDP variants was observed. Specificity of the EFNS/PNS criteria was 55% for possible CIDP and 74% for probable/definite CIDP, while the EAN/PNS criteria had a specificity of 70% for possible CIDP and 83% for CIDP. More extensive studies increased the diagnostic sensitivity of both the sets of criteria but reduced the specificity. In our patient populations, the EAN/PNS criteria were more specific but less sensitive than the EFNS/PNS criteria. More extensive nerve-conduction studies improved diagnostic yield but resulted in loss of specificity.

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.
We aimed to verify whether patients with fibromyalgia and small-fibre neuropathy share similar sensory phenotypes and to detect the existence of a common pathological background between patients with FMG associated with small fibre pathology and patients with small fibre neuropathy, by comparing their QST sensory profiles.
We enrolled 64 consecutively-diagnosed patients with fibromyalgia, according to the American College of Reumatology criteria 2016, and 30 patients with a diagnosis of small-fibre neuropathy relied on BESTA criteria and associated with a definite aetiology (11 patients with amyloidosis, 8 with diabetes and 11 with systemic lupus).
We compared the different clinical and quantitative sensory testing measures in three groups of patients
(patients with fibromyalgia with and without small-fibre pathology, and patients with small-fibre neuropathy). We performed a profile allocation of the three groups of patients by defining four distinct sensory profiles clusters based on quantitative sensory testing .
We found that patients with small-fibre neuropathy were slightly older and with a longer disease duration than fibromyalgia patients with and without small-fibre pathology. The mean variables of quantitative sensory testing of patients with fibromyalgia fell within normative ranges, with the exception of mechanical pain sensitivity. Patients with fibromyalgia and small-fibre neuropathy have distinct sensory phenotypes. We observed a predominantly gain of function phenotype in FMG patients with or without SFP, while SFN subgroup had a component of sensory loss.
Our sensory profile results are in line with the hypothesis that small fibre pathology doesn't lead to functional sensory deficits in FMG and indicate that the small-fibre damage is probably associated with different pathophysiological mechanisms in patients with fibromyalgia and small-fibre neuropathy.

MARCHE REGISTRY OF NEUROMUSCOLAR DISEASES

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Despite COVID-19 pandemic, all Neurology Units of the Marche Region managed to carry out follow-up visits and to guarantee adequate assistance to patients suffering from neuromuscular diseases, sometimes using telehealth, and to continue the activity of the Marche registry of chronic neuromuscolar diseases.
To obtain a reliable estimate of the prevalence and characteristics of patients affected by the main chronic neuromuscular diseases in adults in the Marche Region (inhabitants as of 01/01/21 according to ISTAT: 1.498.236), from 1 January 2020 all Neurology Units (Pesaro-Fano AO Ospedali Riuniti Marche Nord, Jesi, Senigallia, Ancona AOU Ospedali Riuniti, Ancona INRCA, Macerata, Fermo, San Benedetto del Tronto) have elaborated and continuously updated a shared regional register.
The regional registry is aligned with the international standard diagnostic criteria of neuromuscolar diseases and includes the following chronic neuromuscular diseases: Chronic Inflammatory Demyelinating Polineuropathy (CIDP), Demyelinating Polyneuropathies associated with monoclonal gammopathy, Charcot-Marie-Tooth disease, Myasthenia Gravis, Myotonic Dystrophies, non-myotonic genetic myopathies, Amyotrophic Lateral Sclerosis (ALS), Transthyretin Amyloid Neuropathies and all types of SMA.
Here we present the updated data up to 28 February 2022. For example, the prevalence of patients with ALS was 11.41/100.000 (171 cases), Myasthenia Gravis 25.63/100.000 (386 cases) and CIDP 8.87/100.000 (133 cases).
The constant updating of the register is extremely useful to know the approximate prevalence of the main chronic neuromuscolar diseases in the Regional Healthcare System (avoiding the count of deceased

patients and of patiens who are followed up simultaneously in different centers of the region), to obtain epidemiological considerations, to study the extra-regional flows of patients from the Marche region, to develop and implement a clinical quality improvement program, to plan the health care, and to organize treatment paths.

RARE AMONG RARE: PHENOTYPES OF UNCOMMON CMT GENOTYPES

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(1) Background: Charcot–Marie–Tooth disease (CMT) is the most frequent form of inherited chronic motor and sensory polyneuropathy. Over 100 CMT causative genes have been identified.
Previous reports found PMP22, GJB1, MPZ, and MFN2 as the most frequently involved genes.
Other genes, such as BSCL2, MORC2, HINT1, LITAF, GARS, and autosomal dominant GDAP1 are responsible for only a minority of CMT cases.
(2) Methods: we present here our records of CMT patients harboring a mutation in one of these rare genes (BSCL2, MORC2, HINT1, LITAF, GARS, autosomal dominant GDAP1). We studied 17 patients from 8 unrelated families. All subjects underwent neurologic evaluation and genetic testing by next-generation sequencing on an Ion Torrent PGM (Thermo Fischer) with a 44-gene custom panel.
(3) Results: the following variants were found: BSCL2 c.263A > G p.Asn88Ser (eight subjects), MORC2 c.1503A > T p.Gln501His (one subject), HINT1 c.110G > C p.Arg37Pro (one subject), LITAF c.404C > G p.Pro135Arg (two subjects), GARS c.1660G > A p.Asp554Asn (three subjects), GDAP1 c.374G > A p.Arg125Gln (two subjects).
(4) Expanding the spectrum of CMT phenotypes is of high relevance, especially for less common variants that have a higher risk of remaining undiagnosed. The necessity of reaching a genetic definition for most patients is great, potentially making them eligible for future experimentations.

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

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Background and purpose: Guillain-Barré-Syndrome (GBS) is a rare immune-mediated neurological disorder that can be associated with COVID-19 vaccination, with features still to be precisely assessed. Herein we report on a cohort of patients who developed GBS after vaccination with different COVID-19 vaccines.
Methods: Patients with post-COVID-19 vaccination GBS, admitted to the six hospitals of the Liguria region, Northwestern Italy, from February 1st 2021, to October 30th 2021, were included. Clinico-demographic and paraclinic data were retrospectively collected.
Results: Among the 13 patients with post-COVID-19 vaccination GBS (9 males; mean age at onset, 64.1 years), 5 had been vaccinated with Oxford-AstraZeneca, 7 with Pfizer-BioNTech, and one with Moderna. The mean time between vaccination and GBS onset was 11.5 days. Ten patients (77%) developed GBS after the first vaccination dose, 3 after the second dose. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) was the predominant variant. Bilateral seventh cranial nerve involvement followed AstraZeneca vaccination. Three patients presented treatment-related fluctuations, and 4 mild symptoms that delayed treatments and negatively affected prognosis. Poor prognosis occurred in 38.4% of the patients (disability rate, 23.1%).
Conclusions: Our findings confirm that most post-COVID-19 vaccination GBS belong to the AIDP subtype, and occur after the first vaccine dose. Some clinical features, such as the presence of treatment-related fluctuations or diagnostic delay , very mild symptoms at onset, affect prognosis and deserve recognition. Temporal correlation and the absence of infectious episodes during the month preceding disease onset, suggest a generic relationship between the vaccines and GBS.

AN OVERVIEW OF CHILDHOOD NEUROPATHIES: A 24 YEARS' EXPERIENCE

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Charcot-Marie-Tooth disease (CMT) is a heterogeneous group of inherited peripheral neuropathies. Disease onset is usually in the second decade of life, but early onset patient is frequently described, ranging from congenital cases to prepuberty. Childhood forms of CMT are often associated with mutations in genes with autosomal recessive inheritance, but *de-novo* dominant mutations are also described. To date several genes are known to be involved in childhood neuropathies, some of them more outstanding than others, but a single major actor cannot be identified.

During the last 24 years, we recruited 223 cases of early onset (0-10 years) hereditary peripheral neuropathies (EOHPN), in which *PMP22* duplication/deletion were excluded. Seventy-two patients came from IRCCS Istituto Giannina Gaslini while the rest from all over Italy. Thus, we could draw an exhaustive picture of the EOHPN in Italy and compare the diagnostic rate between a heterogeneous cohort and one from a specialistic pediatric hospital. Due to the retrospective type of this study, a different number of genes was analyzed for each patient and different molecular techniques were applied, according to the historical period.

Re-evaluating the whole cohort, we reach a mean diagnostic rate of 51%, which falls to 43% excluding cases from Istituto Gaslini. Conversely, focusing only on these cohort, diagnostic yield increases to 67%, underlying the importance of a child neuropsychiatry guidance to address the correct diagnostic pathway. This is particularly relevant in gene-by-gene approach used until few years ago. Excluding *PMP22* duplication/deletion, difference in diagnostic rate between demyelinating and axonal forms almost disappear (49% vs 48%). *De-novo* mutations amount to the 38% of all diagnosed sporadic cases with similar percentage in both groups. By a methodological point of view, we found a 52% diagnostic yield in the cases analyzed with a gene-by-gene approach, a 43% in the cases analyzed with NGS panel and a 57% in seven cases in which exome analysis was performed. Differences in effectiveness between the three methodologies are not so high, but NGS analyses was performed on a smaller sample for which major genes were already excluded.

Excluding *PMP22*, genes as *MPZ*, *MFN2*, *GDAP1* and *SH3TC2* represent the most frequent actors in EOPN, but the new advances in DNA sequencing technologies will allow the identification of new genetic defects or already known genes but associated to wider phenotypes in which peripheral neuropathy is the clinical sign at onset.

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

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The amyloidoses constitute a large group of diseases in which misfolding of extracellular protein has a prominent role. This dynamic process, which occurs in parallel with or as an alternative to physiologic folding,generates insoluble, toxic protein aggregates that are deposited in tissues. The most frequent hereditary Amiloidosys is hATTR, there are about 130 point mutations known that favour tetramer dissociation. His110Asn mutation is reported in two case reports but the authors concluded that his90asn (old nomenclature) is a nonpathogenic polymorphism for FAP in the Italyn family investigated.

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 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. An EMG study revealed a sensory axonal polyneuropathy in the four 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. She was promptly started on RNA interference therapy with patisiran with a brilliant response at six and nine months of follow-up. 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%), 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%).

In conclusion, His110Asn genotype was associated to severe polyneuropathy with significant gastrointestinal involvement and confirmed biopsy. This mutation should be considered pathogenetic for FAP. Patients with His110Asn genotype can benefit from therapies with RNA interference.

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 an unsupervised clustering analysis to investigate whether there was evidence of different subtypes of neurological long COVID-19.

Results: One hundred and nine patients referred to the neurological post-COVID outpatient clinic. Clustering analysis on the most common neurological symptoms returned two well-separated and well-balanced clusters: long-COVID type 1 contains the subjects with memory disturbances, psychological 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.

Conclusion: Peripheral neuropathy in patients with COVID-19 is frequent and predominantly due to immune mechanisms and to the compression of peripheral nerves resulting from prolonged bedding in ICU. Therefore, unlike what we have observed for the long-COVID type 1 in which even contact with the virus is enough to determine the neurological complication, in most of the disorders of the long-COVID type 2 the damage is caused by prolonged hospitalization or by inflammatory immune- mediated process. These observations could explain why long-COVID type 2 correlates with a worse clinical course in the acute phase of infection. We analyzed the characteristics of neurological long-COVID and presented a method to identify well-defined patient groups with distinct symptoms and risk factors. The proposed method could potentially enable treatment deployment by identifying the optimal interventions and services for well-defined patient groups, so alleviating long-COVID and easing recovery.

PATISIRAN TREATMENT IN A PATIENT WITH ACQUIRED AMYLOID POLYNEUROPATHY AFTER DOMINO LIVER TRANSPLANT

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We report a case of acquired transthyretin amyloidosis in a patient who received at the age of 63 (2008) a liver from a donor with a rare Ser23Asn mutation for hepatocellular carcinoma associated with HCV infection. Nine years after domino liver transplant (LT, 2017), he began to note gait instability, distal paresthesias and hypesthesia in the four limbs. EMG demonstrated a significant sensory-motor polyneuropathy. In the following years the disease worsened rapidly. He developed alternating diarrhea and constipation and progressive weight loss (-15Kg). In year 2020 he was admitted to hospital due to congestive heart failure. EKG documented sinus rhythm with left bundle branch block not present in a previously performed EKG. Echocardiogram revealed signs of amyloid cardiomiopaty (IVS 18 mm, PP 15mm, LVEF 48%). The 99mTc-PYP planar myocardial imaging confirmed dense myocardial tracer uptake: Bologna score 2. After diuretic treatment symptoms improved but few months later patient had a syncopal episode. An advanced atrioventricular block was detected and PM implanted. On neurological examination he had mildly bilateral reduced strength on finger spread and thumb adduction and proximal leg weakness; absent triceps and lower limb reflexes; reduced vibration sensation on both fingers and absent on both toes. Neuropathy Impairment Score (NIS)=45; Karnofsky=80%; Compass=46,1; Norfolk QoLDN=63. Assessment of cardiovascular reflexes documented: no orthostatic hypotension; pathological response to the Valsalva maneuver and reduced pressure and cardiovagal responses Due to this progressive worsening of clinical conditions patient was started on Patisiran infusion 300 mcg/Kg every 3 weeks. Patient reported no side effects. After few months of treatment, he reported no further weight loss and amelioration of gut function and muscle strength and sensation. He had no falls or syncope. On last follow-up after 18 Patisiran infusions neurological examination documented improvement of muscle strength and sensory defcicits; . NIS=27; Karnofsky=90%; Compass= 62,6; Norfolk QoLDN=24. Cardiological evaluation documented clinical and instrumental stability (NYHA II, IVS 18 mm, PP 15mm, LVEF 48%). Assessment of cardiovascular reflexes resulted unchanged. LT from hATTR-positive donors has been considered when prospective recipients with other liver diseases would otherwise have a long wait or are seeking palliation. Recipients of a domino hATTR liver can develop analogous manifestations to hATTR donors after the transplantation. The advent of new disease-modifying therapies

represents a unique opportunity to prevent cardiac and neurological deteriorations. This case report shows promising results in a patient with acquired amyloid polyneuropathy after domino LT following one year therapy with Patisiran.

DORSAL SURAL NERVE: NORMATIVE DATA FROM A SINGLE-CENTRE AND ITS POTENTIAL APPLICATION IN MONITORING ATTRV PRE-SYMPTOMATIC SUBJECTS

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Hereditary transthyretin amyloidosis is an autosomal dominant and late onset disease resulting from progressive extracellular deposition of transthyretin amyloid fibrils, leading to progressive organ damage and death.

Safe and feasible protocols for pre-symptomatic genetic testing are available and they are particularly important in the current era of new emerging treatments. Indeed, the recent approval of new drug treatment able to significantly improve the clinical outcomes, especially when early started, highlights the relevance to define the symptoms at their onset.

Usually, the tests and investigations used in the follow-up of *TTR* mutation carriers include neurophysiological assessments with nerve conduction studies. The sural nerve is the lower limb sensory nerve routinely examined, but it is well known that this site is often proximal to the sites affected by the earliest signs of a distal polyneuropathy. In this context, the investigation of dorsal sural nerves (DSN) could overcome this limitation, exploring one of the most distal sensory nerve branches. DSN sensory conduction study is suitable for daily practice and comfortable for subjects, so it can be accurately and easily tested in all EMG laboratories. We produced normative data of SNAP amplitude and nerve conduction velocity (NCV) for DSN, corrected for age and height, obtained from our single-centre experience achieved in 231 normal controls.

On this background, clinical examination and nerve conduction studies were performed in eleven pre-symptomatic subjects (eight with Val30Met mutation and three with Phe64Leu mutation) and no symptoms or signs of peripheral nerve damage were found with neurophysiological evaluation limited to the sural nerve. Nevertheless, including DSN in the neurophysiological examination we found abnormalities, characterized by significant reduction in the amplitude of the sensory nerve action potential (SNAP) of five out of eleven subjects (45.5%).

In conclusion, diagnosis in the early stages of hereditary transthyretin (ATTR) amyloidosis is mandatory to support timely treatment to prevent disease progression and the examinations of DSN in clinical trials, as well as in routine practice, could help to early detection of peripheral nerve damage.

EVALUATION OF ADHERENCE AND REACTOGENICITY TO COVID-19 VACCINES IN 115 PATIENTS WITH POLYNEUROPATHY

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Background: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) usually lead to respiratory tract infection, although several neurological complications are described. The safety and the efficacy of the new vaccines against coronavirus disease 2019 (COVID-19) have already been showed, although this data on patients with polyneuropathy are still lacking. The aims of this study are to evaluate the adherence and the reactogenicity to COVID-19 vaccination in a cohort of patients with polyneuropathy.

Methods: A web-based interview using a web-questionnaire was conducted among the patients affected by polyneuropathy (PN) followed-up at the Neuromuscular Unit of University Hospital "Policlinico Paolo Giaccone", Palermo, Italy. The questionnaire included: demographic data (age, gender), diagnosis (type of polyneuropathy), vaccination (yes or not), adverse events (AEs) related to vaccination. AEs refers to a local and systemic reactogenicity following the first or the second dose of COVID-19 vaccines. Qualitative and quantitative data were analyzed through non-parametric tests.

Results: A total of 115 patients affected with PN (dysimmune [n=44], hereditary [n=39], diabetic [n=20], toxic [n=5], deficiency [n=7]) answered the questionnaire and the 94% of these (N=108; 39% females; median age 60 year [IQR:51-80]) were fully vaccinated. The median time between vaccine's last dose and web-based interview was 107 days (IQR: 80-139). The adherence to vaccination was 100% in the group of hereditary polyneuropathies whereas it reached the 91% (n=40), 95% (n=19), 80% (n=4) and 86% (n=6) in the groups of dysimmune, diabetic, toxic and deficiency polyneuropathies, respectively. Fear of getting vaccinated was higher in toxic polyneuropathy compared to dysimmune (20% vs 9%; p=0,4). Fourty-nine patients (53% females; median age 61 years [IQR: 49-70]) experienced at least one AEs after vaccination: local pain (69%), fatigue (25%), myalgia (10%), fever (14%), gastrointestinal symptoms (10%), cephalalgia (8%) and erythema (4%). AEs were more common in younger, especially cephalalgia (p=0.02) and myalgia (p=0.03), and in females (62% vs 35%; p=0,006). Patients with dysimmune polyneuropathies reported lower AEs compared to other ones (30% vs 50%; p=0,01).

Conclusion: The adherence to COVID-19 vaccines reached the 94% of adherence in patients with polyneuropathy. COVID-19 vaccines showed a good short-term safety in these patients, although fear of getting vaccinated was not completely disrupted.

LATE-ONSET HEREDITARY TRANSTHYRETIN AMYLOID NEUROPATHY: THINK ABOUT IT TO DIAGNOSE IT

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Transthyretin amyloidosis is a life-threatening disease characterized by extracellular deposition of amyloid fibrils composed of transthyretin (TTR). Aggregate deposition may involve several tissues leading to polyneuropathy, cardiomyopathy, renal and leptomeningeal amyloidosis. Early-age onset range from the late 20s to early 40s, but clinical manifestations of disease may occur also over 50 years old, thus making it difficult the differential diagnosis with age-related acquired neuropathies. In this report, we describe the case of a severe late-onset amyloid polyneuropathy with a confirmed genetic mutation in *TTR* gene.

A 77-year-old woman underwent several neurological examinations for progressive gait disorder in the past three years. Spinal magnetic resonance imaging revealed stenosis of the lumbar canal but no benefit was observed after decompression surgery. Following an episode of loss of consciousness, transthoracic cardiac ultrasound showed signs of mild hypertensive heart disease with septum-basal thickening.

No familial history for neurological disease emerged. Past medical history was negative for systemic significant pathologies. Neurological examination disclosed severe distal lower limb weakness associated with sensory ataxia, as well as milder upper limb distal weakness. Laboratory tests ruled out possible acquired causes of peripheral neuropathy such as diabetes, B12 vitamin deficiency, endocrinological and immunological disorders. Electroneurography showed lower limb sensory-motor axonal neuropathy and reduced motor conduction of the left median and ulnar nerve. *TTR* gene analysis was performed and the already known c.250T>C (p.Phe84Leu) heterozygous variant was found. Patisiran treatment was administrated with stabilization of neurological symptoms.

ATTR-related neuropathy is a rare and disabling neurological disease. Since age of onset may be extremely wide, the risk of misdiagnosis increases over the years due to comorbidities of elder age. Even if the known red flags (tunnel carpal syndrome, lumbar canal stenosis, dysautonomic symptoms) are not well defined or are present only partially, neurologist consider TTR amyloidosis as a possible cause of neuropathy in elderly people to give these subjects the opportunity to be treated with the appropriate therapy.

PURE MOTOR LUMBOSACRAL RADICULOPATHY AFTER INTRATHECAL METHOTREXATE ADMINISTRATION

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Intrathecal (IT) administration of methotrexate (MTX) is one of the cornerstones for the treatment and prophylaxis of central nervous system (CNS) involvement in Acute Lymphoblastic Leukemia (ALL). We present the case of a 23-year-old man who received diagnosis of ALL and started chemotherapy according to the LAL1913 protocol (involving Peg-Asparaginase administration). He underwent CNS prophylaxis with intrathecal administration of 12.5 mg methotrexate and 4 mg dexamethasone. About one month after he developed significant lower limb weakness, preventing autonomous walking. Neurological exam showed flaccid paraparesis, absence of deep tendon reflexes, lower limb bilateral muscular hypotrophy. Neither sensory, sphincter, autonomic disturbances nor pyramidal signs were detected. Upper limbs and cranial nerves were unremarkable. He underwent cerebrospinal fluid analysis, showing albumin/cytologic dissociation (170 mg/dL proteins - n.v. 15-50; 4 cells). Cytological examination showed no leukemic cells; infectious screening was negative. Serum antiganglioside antibodies were absent. Spinal MRI showed thickening of the ventral roots of the *cauda equina* with contrast enhancement. Nerve conduction study showed severe lower limb motor axonal neuropathy (marked CMAP amplitude reduction and relatively spared conduction velocities in all nerves). F waves were absent from tibial nerve, bilaterally. Lower limb sensory findings and upper limb examination were in the normal range. On needle examination, marked acute denervation involving L3-S1 roots was found, bilaterally. Motor evoked potentials were normal. IT-MTX was stopped and the patient was treated with intravenous immunoglobulins (0.4g/Kg/day for 5 days), followed by high-dose intravenous methylprednisolone (1 g/day for 5 days). The patient gradually improved, although he still had some mild paraparesis. Three months later the spine MRI was normal.

Several neurotoxic effects of IT MTX have been reported, including acute and subacute polyradiculopathies. In our patient, electrophysiological findings and gadolinium enhancement of the *cauda equina* anterior roots were consistent with a pure motor L3-S1 polyradiculopathy. The negativity for malignant cells CSF examinations, the absence of upper limb and cranial nerve involvement and of spinal

cord alterations on MRI ruled out myelopathy, neoplastic polyradiculopathy or acute motor axonal neuropathy (AMAN).

Pathophysiologic mechanism of IT-MTX related polyradiculopathy remains to be clarified. Although a direct MTX toxicity and a localized folate deficiency were postulated, the CSF albumin-cytological dissociation and the response to immunomodulatory treatments could suggest an immune-mediated mechanism. Finally, pure motor polyradiculopathy of the lower limbs is a rare but predictable complication of IT-MTX administration, which must be promptly recognized because it can benefit from early withdrawal and immunomodulatory treatment.

ASSESSMENT OF THE STRENGTH DURATION CURVE OF SMALL FIBRES IN HEALTHY SUBJECTS

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Direct recording of responses at the peripheral or central level of the nervous system is the current technique used in clinical neurophysiology to assess the underlying function. The old method to search for the threshold value of excitability of motor fibres has been abandoned because of limited use. However, function of the small diameter fibres remains not investigated in most clinical setting. A newly designed micropatterned electrode that was introduced for selective stimulation of the intraepidermal small fibre endings is being used for recording nociceptive evoked potentials from the scalp. We now report a different use of the electrode, as a tool to assess the pain perception threshold as a function of stimulus intensity and duration, a method requiring simpler equipment than evoked responses and potentially feasible in any outpatient clinic.

Fourteen healthy subjects aged 21-26 years have been studied. The micropatterned electrode with 150 um gap has been used to assess the perception threshold of nociceptive fibres. The evoked perception was a pinprick evocative of selective Adelta fibre recruitment. Stimuli had duration between 0.2 ms and 100 ms in ten steps and were delivered in form of a high frequency train to cross the electrode-stratum corneum interface. Per each duration step (independent variable) the intensity was varied (dependent variable) to assess the perception threshold. The chronaxie and rheobase were also determined.

Reliable data could be obtained in all subjects. The resulting strength duration graph had the shape of a hyperbolic function, fitting the Lapique formula. The mean rheobase was 0.86 mA and chronaxie 8.25 ms.

Summing up, the obsolete method of searching chronaxie and rheobase of mixed nerves, is brought to new life by the possibility of selective activation of a definite fibre group, the nociceptive small fibres. Selectivity is a crucial factor to obtain reliability and sensitivity. The techinque is simpler and faster than the recording of evoked potentials in diagnosing functional impairment. It is proposed that it may be used as as screening tool in most peripheral neuropathies and in neuropathic pain.

SKIN AMYLOID DEPOSITS AND NERVE FIBER LOSS AS MARKERS OF NEUROPATHY ONSET AND PROGRESSION IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS: DATA FROM A LARGE FRENCH COHORT

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Objective: To assess skin biopsy as marker of disease onset and severity in hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN).

Methods: In this single center retrospective study, skin Congo red staining and intraepidermal nerve fiber density (IENFD) were evaluated in ATTRv-PN patients and asymptomatic carriers. Non-ATTRv subjects with small fiber neuropathy suspicion who underwent skin biopsy in the same timespan were used as controls.

Results: One-hundred-eighty-three symptomatic ATTRv-PN, 36 asymptomatic carriers, and 537 non-ATTRv patients were included. Skin biopsy demonstrated amyloid depositions in 80% of the 183 symptomatic cases. Skin amyloid deposits were found in 75% of early-stage ATTRv-PN patients, and in 14% of asymptomatic carriers. All 183 symptomatic and 34/36 asymptomatic patients displayed decreased ankle IENFD with a proximal-distal gradient distribution, and reduced IEFND correlated with disease severity and duration.

Conclusions: Our study demonstrates that skin amyloid deposits are a marker of ATTRv-PN disease onset, and decreased IENFD a marker of disease progression. These results are of major importance for the early identification of ATTRv-PN patients in need of disease-modifying treatments.

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COMPARISON OF DIFFERENT DIAGNOSTIC CRITERIA FOR ATYPICAL CIDP

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Objectives: There are different definitions of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) variants in the literature; this may explain the conflicting results observed across studies regarding their frequency, clinical presentation, outcome, and treatment response.

Methods: We compared the clinical features and response to therapy in relation to the different criteria used for the diagnosis of atypical CIDP in 473 Italyn patients included in the Italyn CIDP database.

Results: Patients with multineuropathic Lewis-Sumner syndrome (LSS) and those with length-dependent sensory demyelinating acquired distal symmetric (sensory DADS) neuropathy had distinct demographic and clinical features, 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. Patients with a length-dependent sensory CIDP (sensory DADS) but not those with a non-length-dependent sensory CIDP (sensory CIDP) had a lower response to treatment and to IVIg compared to 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.

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 different pathogenic mechanisms.

HOME THERAPY FOR PATIENTS AFFECTED BY ATTRV AMYLOIDOSIS: REAL-WORLD EVIDENCE FROM THE AMYCARE PROGRAM

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Background: AMYCARE is a real-world (RW), nation-wide patient support program (PSP) for ATTRv amyloidosis, a highly disabling disease that demands continuous efforts to effective treatment. The PSP provides pre-medications and intravenous injections of the RNA interference agent patisiran at patients' homes, in agreement with protocols shared with specialists, thus guaranteeing high ethical and safety standards. AMYCARE aims at adapting to patients' and caregivers' needs while maximizing therapeutic adherence, with the ultimate goal of improving quality of life (QoL) and outcomes. Patients and specialists' experiences were investigated to monitor the efficacy and safety of the ongoing PSP.

Methods: A trained Contact Centre conducted telephone surveys to 59 Italyn patients aged 46-83 (μ=69; μo=67; σ=9) from 10 Italyn regions. The survey (closed-ended, 4 points verbal scale) explored patients' satisfaction towards the PSP, its (perceived) quality and efficacy, its impact on therapeutic adherence, therapy management,

patients' QoL and unmet needs. Similarly, web-based questionnaires were collected from 14 specialists prescribing the PSP.

Results: Overall, 78% of patients were *very satisfied* with the PSP and they found it in line with their expectations (97%): the PSP substantially improved their treatment management with respect to going to the hospital (96%) and it improved their living conditions (99%); indeed, 87% of patients found it *very complex* or *considerably complex* to reach the hospital and specialists confirmed their opinions. Patients reported to be less dependent on caregivers (50%), they had more time to invest in activities of daily living (ADLs) (86%) and leisure (83%), they felt more confident with the disease (12%). Positive opinions towards the program nurses in terms of courtesy, attention, precision were collected. Specialists believed that the PSP improved adherence, it had a moderate impact on disease monitoring, it significantly and positively affected the emotional wellbeing of patients. In terms of organisational impact, the PSP cut transfer costs that burden to patients and reduced waiting lists therefore expanding the capacity of the hospital unit. Patients claimed more engagement by understanding their treatment and injection-related symptoms. No safety issues were reported.

Conclusions: this RW study supports the feasibility and benefits of a PSP in a rare and complex condition such as ATTRv amyloidosis, which is characterized by unmet needs and paucity of services. Findings are valuable to further prioritize interventions targeting patients affected by rare and chronic diseases.

FOODBORNE BOTULISM AS A POTENTIAL STROKE MIMIC: A CHALLENGING NEUROPHISIOLOGICAL DIAGNOSIS IN AN EMERGENCY SETTING. THE ROLE OF THE SINGLE FIBER EMG (SFEMG)

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Botulism is an acute neuromuscular disorder caused by the binding of a neurotoxin from the anaerobic bacterium, Clostridium botulinum, to the presynaptic nerve terminal, preventing release of synaptic vesicles containing acetylcholine. The illness begins with gastrointestinal manifestation followed by autonomic symptoms and descending paralysis that spreads from extraocular and bulbar muscles to the limbs. Foodborne botulism neurological symptoms may develop acutely and may therefore be confused as ischemic stroke. This may delay antitoxin treatment worsening the prognostic outcome of the patient.

Electrophysiological tests generally show reduced compound muscle action potentials (CMAPs), low amplitudes and short durations of motor unit potentials (MUPs) and increment greater than 100% in repetitive high-frequency stimulations (RNS). Single-fiber EMG (SFEMG) studies typically reveal increased jitter and blocking, which become less marked following activation.

However, stroke diagnosis can be challenging in time restrains. A number of nonvascular medical conditions can be confused with stroke, leading to misdiagnosis and delayed recognition. These conditions are commonly referred to as "stroke mimics". When involving posterior circulation syndromes, the spectrum of possible differential diagnosis becomes even broader. Posterior circulation ischemia, in fact, is usually blurred in clinical presentation and could manifest in non-focal neurological deficits. 2; Herein we present a case of a patient with foodborne botulism, acutely begun with dizziness, diplopia, dysarthria and dysphagia, who was identified in neurological emergency room as a suspected ischemic stroke. Neurological examination revealed divergent strabismus in the right eye, right facial nerve impairment, dilated fixed pupils and dysarthria. CT and CT angiography scan showed no abnormalities. When clinical conditions rapidly deteriorated and amnestic data revealed that the patient had eaten a poorly preserved food, clinical suspicion of foodborne botulism was made. Electrophysiological study was performed promptly in emergency room and showed reduced CMAPs, low amplitudes and short durations of MUPs, and non-incremental response in RNS. The SFEMG on the right "orbicularis oculis" showed instable MUPs with prolonged abnormal jitter. Botulin toxin was found in stool sample, but not in the serum. Antitoxin was administered and a progressive improvement in neurological picture was observed.

In this case, the role of SFEMG was central to leave the correct diagnosis and to allow the early administration of the antitoxin. SFEMG is a very sensitive method for studying the neuromuscular transmission defect in botulism and in obtaining further information on the course of the syndrome.

A NOVEL NONSENSE MUTATION CAUSING INFANTILE-ONSET MULTISYSTEM NEUROLOGIC, ENDOCRINE AND PANCREATIC DISEASE: A FIRST ITALYN FAMILY

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Here we report two Italian brothers with consanguineous parents. The proband, 48 years old, has psychomotor delay, diagnosed at 18 months, demyelinating sensorimotor polyneuropathy and bilateral sensorineural hearing loss since he was 13. At 32 years, drug-resistant epileptic seizures occurred. The younger brother, 47 years old, exhibits an overlapping clinical presentation without epilepsy.

DNA extracted from leukocytes was first analyzed with a CMT-associated-panel by Next Generation Sequencing on PGMTM Ion Torrent.

The panel includes the exons and flanking regions of 56 genes associated with hereditary neuropathies. Data were analyzed using Ion Reporter v.5.4 (ThermoFisher Scientific) and ANNOVAR software. As this analysis resulted negative, we consequently performed, on collaborative research basis, whole-exome sequencing (Illumina, PE 2x150) followed by bioinformatic analysis (GATK software) on both brothers and their mother. The father sample was not available.

The analysis revealed a novel substitution at position 256 of the coding sequence of the *PTRH2* gene (c.256C>T, NM_001015509) located on chromosome 17q23 (17: 59697726G>A; GRCh38) in homozygous state in both patients and in heterozygous state in the mother. The variant resulted in a premature stop codon at position 56 of the protein (p.Gln56Ter). According to ACMG guidelines, this variant has been classified as pathogenic. Biallelic mutations in *PTRH2* gene have been associated with an infantile multisystem neurologic, endocrine, and pancreatic disease (IMNEPD), a rare autosomal recessive disorder with clinical variable expression, reported for the first time in 2014 and so far described only in Middle East and Asiatic populations.

The classic features of this disorder include global developmental delay or isolated speech delay, intellectual disability, sensorineural hearing loss, ataxia and pancreatic insufficiency (both exocrine and endocrine). Additional features may include peripheral neuropathy, facial dysmorphisms, liver fibrosis and epilepsy. The identification of p.Gln56Ter pathogenic variant in our patients, which do not present the whole clinical features associated with IMNEPD, suggest that *PTRH2* testing should be performed in patients with developmental delay, sensorineural hearing loss and peripheral neuropathy regardless of the disease severity or the presence of whole phenotypic spectrum, allowing the diagnosis of this novel disease entity.

PAIN EXPERIENCE IN SYMPTOMATIC AND ASYMPTOMATIC SUBJECTS CARRYING A TRANSTHYRETIN GENE MUTATION: PRELIMINARY RESULTS FROM AN ITALYN MULTICENTRE STUDY

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Introduction: Pain may be a relevant symptom of hereditary transthyretin amyloidosis (ATTRv) even though it has never been thoroughly investigated especially in the late-onset form.

Our aim was to describe the pain experience and its impact on quality of life (QoL) in symptomatic (patients) and asymptomatic (carriers) subjects harbouring a TTR gene mutation.

Patients and Methods: From four Italyn centres, we enrolled 95 TTR-mutated subjects, 68 symptomatic (F/M=13/55; mean age 69.4±9.5 years) and 27 asymptomatic (F/M=14/13; mean age 51.3±11.8 years). Forty-two subjects had Val30Met and 36 Phe64Leu mutation, the remaining 17 had rarer mutations (Ala109Ser, Ala120Ser, Glu89Gln, Ile88Leu, Thr59Lys, Val32Arg).

Clinical disability was assessed using FAP stage and NIS score, QoL was evaluated using the Norfolk questionnaire, the presence of neuropathic pain was computed by the DN4, the intensity of pain and its impact on daily life were assessed using the Brief Pain Inventory (BPI) severity and the BPI Interference subscores. We collected data of type of TTR mutation, presence of dysautonomia and treatment.

Results: Thirty-five patients were in FAP 1 stage, 31 in FAP 2 and 2 in FAP 3, with a mean NIS 67.9±49.2 (2-173) and mean Norfolk 55.1±32.4 (-1-120). Dysautonomia was reported in 39 patients with a mean CADT 14.5±3.2 (6-19). Nineteen patients were treated with Tafamidis, 14 with Inotersen and 24 with Patisiran.

Neuropathic pain (DN4≥4) was recorded in 48/68 (70.6%) patients and in 4/27 (14.8%) carriers.

In patients, BPI severity score was 3.9±2.5 (0-10) and BPI interference score was 3.8+2.8 (0-9.7). In carriers, BPI severity score was 1.2±2 (0-7) and BPI interference score was 1.2±2.1 (0-6.4).

Subjects with neuropathic pain respect to those without neuropathic pain (DN4: ≥4 vs <4) was older (68.3±10 vs 59.4±14.2), had worse FAP stage and had higher scores of NIS (74.2±48.9 vs 23.1±37.9), Norfolk (63.3±29.2 vs 16.3±21.8), BPI severity (4.7±2.1 vs 1.3±2) and BPI interference (4.4±2.6 vs 1.5±2.3). Neuropathic pain was associated to the presence of dysautonomia and cardiomyopathy. No difference for gender, type of mutation and treatment was found.

Conclusions: Our study showed that 70% of late-onset ATTRv patients complain of neuropathic pain that worsens as neuropathy progresses and increasingly interferes with daily activities and quality of life.

Clinicians should not neglect this aspect in patient management. Moreover, clinicians should pay attention on pain complained by carriers as a potential early manifestation of disease.

NEUROGRAPHIC RECORDINGS AFTER SELECTIVE STIMULATION OF INTRAEPIDERMAL FIBRES

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The small afferents of the peripheral nervous system 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 fibre group is involved. A new micropatterned electrode has recently been designed for selective stimulation of the intraepidermal endings of the small fibres, 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 into the study, a preliminary check of normal conduction of the fast fibres of their radial nerve was performed with traditional methods. The commercially available micropatterned electrode with a 150 um interrail gap was used to stimulate the radial nerve innervated area of 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 Teflon™ coated, inserted near 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 um micropatterned electrode yielded two small amplitude responses at approximate latencies between 3 and 4 ms, suggesting the evoked activity of two fibre groups conducting at 25 and 18 m/s. Separate group averaging confirmed their reliability. The faster fibres 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 fibre 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.

HATTR-RELATED POLYNEUROPATHY: A SINGLE-CENTER EXPERIENCE

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Hereditary transthyretin-mediated (hATTR) amyloidosis 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 intend to describe the characteristics of the cohort of patients followed at Neurological Clinic of San Martino Polyclinic Hospital in Genoa.

We retrospectively analyzed the demographic features and clinical evolution of 12 patients treated in our center and we described how presymptomatic carriers are monitored.

The patients followed at our clinic over the years were 12 (2 of whom died), 10 males and 2 females, with an average age of 76 years. The mean age at diagnosis was 69 years. The number of different TTR gene mutations is the following: 5 (36%) Phe64Leu, 4 (29%) Val30Met, 1 (7%) Ile68Leu, 1 (7%) Tyr98Phe, 1 (7%) Arg125Cys, 1 (7%) Val122Ile and 1 (7%) Ala140Thr. According to the Polyneuropathy disability (PND) scoring system, 2 patients have score of 0, 4 have score of I, 3 have score of II, 1 has score of IIIa, 2 have score of IIIb and none have score of IV. The routine biannual work-up includes BMI (Body Mass Index), neurological examination, NIS (Neuropathy Impairment Score-244) and NIS-LL (Neuropathy Impairment Score Lower Limbs-88), Karnofsky Performance Status (0-100), Compound Autonomic Dysfunction Test (CADT, 0-20), Norfolk QOL (Quality Of Life) and Sudoscan. Patients also periodically undergo blood tests, cardiological examination and electroneurography (ENG). 5 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, one from diflunisal to patisiran and another one from tafamidis to inotersen due to clinical and neurophysiological worsening. A patient switched from inotersen to patisiran because of persistent thrombocytopenia during inotersen therapy. We start monitoring presymptomatic patients ten 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, BMI and ENG. In our center, several presymptomatic tests were performed and we found a mutation of the TTR gene in two relatives of patients with hATTR.

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 patients over time to assess the need for therapy. Drug choice should be oriented according to severity of disease, comorbidities and features of individual patients.

SCREEN AND CARE IN HEREDITARY TTR-MEDIATED AMYLOIDOSIS: AN ITALYN MULTICENTRE PROJECT

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Purpose: The goal of the project is to spread awareness of the importance of screening for hATTR. 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.
Methods: 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.

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; 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.

ACUTE ONSET OF PARANODOPATHY ASSOCIATED WITH ANTI-CASPR1 ANTIBODIES AND PROMINENT CRANIAL NERVES INVOLVEMENT

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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 Italyn Chronic Inflammatory Demyelinating Polyneuropathies (CIDP) cohort.

A 38-year-old man was admitted to our Hospital for acute onset of distal numbness and proximal weakness (MRC sum score 54, Guillain-Barré Syndrome (GBS) Disability Score 2). Cerebrospinal fluid (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 "very 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, 37 days from clinical onset, showed only a mild increase in the F-wave and distal motor latencies. A cervical MRI showed mild hyperintensity in cervical spinal roots. Onco-neural antibodies were negative, autoimmune screening test and PET-TC were normal. Patient had only a modest clinical response to plasma exchange treatment (MRC sum score from 36 to 38), so that immunosuppressive treatment with Rituximab was started. NCS performed at 2 months from symptoms onset showed demyelinating features consistent with a diagnosis of CIDP according to the EFNS/PNS criteria. Ultrasonography disclosed cervical roots and nerves enlargements with increased CSA. Additional investigations, including serum analysis for paranode antibodies, were negative for CNTN1 and positive for Caspr1/CNTN1 complex. After Rituximab 2 g, the patient showed a clear and constant clinical motor and sensory improvement (MRC sum score 48, GBS Disability Score 3).

Very few cases of paranodopathy associated to Caspr1 antibodies are reported in the literature. Ongoing sensory-motor demyelinating neuropathy associated with severe cranial nerves involvement, pain, and gait ataxia, with scarce response to IVIg, should suggest a diagnosis of paranodopathy associated with anti-Caspr1 antibodies.

THE ROLE OF SORBITOL DEHYDROGENASE GENE IN THE DIAGNOSTIC ALGORITHM OF CHARCOT-MARIE-TOOTH DISEASE 2 AND DISTAL HEREDITARY MOTOR NEUROPATHY PATIENTS

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Biallelic mutations in sorbitol dehydrogenase (*SORD*) gene have been recently identified as a genetic cause of both autosomal recessive axonal Charcot-Marie-Tooth disease 2 (CMT2) and distal hereditary motor neuropathy (dHMN). To date, as less than 30% of CMT2 and dHMN patients receive a genetic diagnosis, the identification of *SORD* mutations can increase the diagnostic rate. To investigate the frequency of *SORD* mutations in our population and the genotype-phenotype correlation, we screened an Italyn cohort of 89 unrelated CMT2/dHMN patients, selected on the basis of clinical phenotype, mode of inheritance and electrophysiological features. Among these, 64 had diagnosis of CMT2 and 25 of dHMN

We first evaluated the presence of the hotspot c.757delG (p. A253Qfs*27) by Sanger sequencing also to detect mis amplification with *SORD2P* pseudogene. Then the entire *SORD* coding region, including intron-exons boundaries, was analyzed by Next Generation Sequencing (NGS) on a CMT-associated panel.

This analysis revealed *SORD* biallelic mutations in 6 patients, four of them were homozygous for the c.757delG (p. A253Qfs*27) and two were compound heterozygous for the c.757delG and c.458 C>A (p. Ala153Asp) mutations. In addition, the hotspot mutation has been also identified in a heterozygous state in 2 patients.

The molecular analysis of *SORD* in our cohort achieved a genetic diagnosis in 6.7 % (6/89) of patients. In particular, the frequency of *SORD* biallelic pathogenic variants in CMT2 and dHMN resulted respectively 6.2% (4/64) and 8% (2/25). Our results confirm that molecular testing for *SORD* must be included in the diagnostic algorithm for CMT2/dHMN patients. Indeed, *SORD* characterization could help close the genetic diagnostic gap in hereditary neuropathies, as one of the most common recessive cause of neuropathy. In addition, considering that *SORD* biallelic mutations lead to a deficiency of sorbitol dehydrogenase, treatable with aldose reductase inhibitors, the identification of this defect could open to future therapeutic strategy.

INCIDENCE OF GUILLAIN BARRÉ SYNDROME IN LAZIO DURING SARS-COV2 PANDEMIC PERIOD

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The relationship between the SARS-COV2 infection and the Guillain Barré Syndrome ((GBS) 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. 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. 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 and 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, 1160 patients were diagnosed with GBS in the Lazio Region. The data available to us has shown a downward trend in number of new diagnosis of GBS 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 vaccinations. A lower diffusion of SARS-COV2 in Lazio region and the reduction of the other respiratory 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.

A THREE-YEAR FOLLOW-UP STUDY OF A POPULATION OF PATIENTS WITH DIAGNOSIS OF CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP): AN UPDATE

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Introduction: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) represents a chronic and disabling immune-mediated polyradiculoneuropathy involving peripheral nerves and characterized by sensory alterations and weakness with gradual progression over years. Neurophysiological criteria proposed by the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS) are applied for the diagnosis of CIDP, considering the typical and atypical forms: distal acquired demyelinating symmetric neuropathy (DADS), purely motor or sensory CIDP, Lewis-Sumner syndrome (LSS) and focal CIDP, multifocal, pure sensory, and other variants, however several conditions can mimic CIDP.

Methods and materials: We enrolled 57 patients with a diagnosis of CIDP according to EFNS/PNS criteria, followed since 2019 to 2022. At enrolment, all patients underwent a detailed clinical history; more specifically we reported onset of motor and sensory symptoms, clinical disease course and response grade to previously therapies. At the end a revision of EFNS/PNS criteria was performed again through a neurological evaluation and neurophysiologic assessment.

Results: 57 patients have been enrolled, satisfying EFNS/PNS criteria at the study start. At the end of follow-up, the diagnosis of CIDP was confirmed in 42 patients: 71,4% with a defined diagnosis of CIDP, 28,6,1% possible diagnosis. All of them have a clinical response to immunoglobulin intravenous therapies and 15 of them are on subcutaneous immunoglobulin therapy. Clinically 36 (85,7%) patients with typical CIDP while 6 (14,3%) with atypical CIDP, including 2 with DADS, 1 with purely motor and 3 with LSS. However, after three-years of follow-up in 15 patients EFNS/PNS criteria were any more satisfied leading to a different diagnosis: 2 (13,33%) diabetes mellitus, 2 (13,33%) monoclonal gammopathy of undetermined significance (MGUS), 1 (6,66%) hereditary amyloidosis ATTR, 2 (13,33%) anti-myelin-associated glycoprotein (anti-MAG), 2 (13,33%) deficit of vitamin B12, 1 (6,66%) paraneoplastic neuropathy, 1 (6,66%) multifocal motor neuropathy (MMN), 1 (6,66%) Charcot Marie Tooth (CMT) and 3 (20%) with other diagnosis.

Conclusions: We concluded that a careful revision of criteria to confirm diagnosis results essential for CIDP. There are other diseases that can mimic CIDP, and result important the correct diagnosis to permit the access to the correct therapies.

A CASE OF CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY RELAPSE AFTER VACCINATION FOR COVID-19

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Vaccines are effective measures against the COVID-19 pandemic and evidence suggests that vaccination in people with inflammatory neuropathies or autoimmune disorders is safe and effective in most cases. Indeed, until now a single case of chronic inflammatory demyelinating polyneuropathy (CIDP) post COVID-19 infection and subsequent

ChAdOx1 nCoV-19 vaccination has been described, as well an exacerbation of pre-existing CIDP remains to be established.

Herein, we reported the case of a patient with CIDP, who experienced a relapse after COVID-19 vaccination. The patient was a 78 years-old man affected by sensory variant of CIDP diagnosed in June 2007. He was on treatment two times per year with intravenous methylprednisolone (IVMP) and had a stable clinical condition.

In July 2021, he received IVMP and in October 2021, he underwent first dose of COVID-19 Pfizer-BioNtech vaccine. About ten days after, he developed severe ataxic gait with inability to walk and standing without bilateral support. Moreover, neurological examination showed positive Romberg's sign, distal hypoesthesia and marked reduction of vibration sense at lower limbs, and absence of deep tendon reflexes. The patient underwent again IVMP without clinical improvement. Thus, he was admitted to our hospital and was started on five sessions of plasma exchange (PE). Two weeks after PE therapy, his clinical status significantly improved especially for the ataxic gait that became possible without support.

To our knowledge, this is the first report of a relapse following Pfizer-BioNtech COVID-19 vaccine in a patient with a long-lasting history of CIDP. The temporal association between the first dose of COVID-19 vaccine and the relapse of CIDP might suggest a causal association, even though this link needs to be confirmed.

IS THERE A LINK BETWEEN SARS-COV-2 INFECTION AND CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY?

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Introduction: The potential association between immune-mediated neuropathies and SARS-CoV-2 is largely debated. Guillain-Barré syndrome is a commonly identified neurological complication of COVID-19 while only two cases of exacerbation of pre-existing chronic inflammatory demyelinating polyneuropathy (CIDP) and a single case of CIDP after COVID-19 infection and vaccination have been reported.

The aim of our study was to demonstrate whether, during the two years of the pandemic, there was an increase in the frequency of CIDP supporting an association between CIDP and SARS-CoV-2 infection or vaccination.

Patients and methods: We revised the new CIDP patients referred to our neuromuscular centre of Federico II Hospital in Naples from January 2020 to February 2022 and compared the frequency of new diagnosis during the pandemic with that from 2000 to 2019.

Results: From January 2020 to February 2022, we have seen 20 new CIDP patients. Eleven patients (10 males and 1 female) received a diagnosis of new onset CIDP and in detail, 9 of them in our centre and 2 in another hospital before being addressed to us.

Instead, the remaining nine patients had received a diagnosis of CIDP before 2020 and during the pandemic were shifted to our referral centre for neuromuscular disorder.

Six out of 11 patients had a typical CIDP, two had a multifocal variant and three a sensory variant.

None of them had disease onset following SARS-COV-2 infection. Nine patients had been vaccinated after having already received the diagnosis while two patients developed CIDP after ChAdOx1 nCoV-19 vaccination. Notably, vaccination preceded CIDP by 5 months in one patient, and by 10 days, in another who had acute-onset CIDP.

The median frequency of new onset CIDP cases during the pandemic was overall 4 cases by year and 3.5 cases considering only the patients diagnosed at our centre. From 2000 to 2019, we recorded 70 CIDP diagnosis resulting in a median frequency of 3.5 cases by year.

Conclusions: Our findings do not support a link between SARS-COV-2 infection and CIDP, as well the association with vaccine remains to be determined.

INVESTIGATING THE SATELLITE GLIAL CELLS INVOLVEMENT IN CHEMOTHERAPY-INDUCED PERIPHERAL NEUROTOXICITY

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Chemotherapy-induced peripheral neurotoxicity (CIPN) is a severe and disabling side effect in cancer treatment. Paclitaxel (PTX) and cisplatin (CDDP) are commonly used chemotherapeutic agents that carry a significant risk of neuropathic symptoms including numbness, paraesthesia and burning pain. It is known that satellite glial cells (SGC) are in intimate contact with the soma of sensory neurons in dorsal root ganglia (DRG) and essential for their metabolic needs. Previous evidence suggested that SGCs can be activated, increased in number and morphologically modified after painful injuries of different origins, including chemotherapy. In these conditions, SGCs showed an increased expression of glial fibrillary acidic protein (GFAP) as well as increased coupling. The maintenance of SGC coupling is supposed to be due to gap junctions communication mediated by connexins (Cx). Among them, connexins 36 (Cx36) and 43 (Cx43) has been identified in the perineuronal SGCs in DRG. In this work, we investigated whether SGCs are altered in animal models of CIPN induced by chronic administration of PTX and CDDP.

Forty-eight rats were used: 12 were injected i.v. with PTX 10 mg/Kg once a week for 4 weeks, 12 with CDDP 2 mg/Kg, i.p., twice a week for 4 weeks whereas 24 animals were administered with the

respective vehicles. Neurophysiological analysis and behavioural tests were performed at baseline and at the end of the treatments. DRG, peripheral nerves and skin biopsies were harvested for morphological and morphometric analyses. Moreover, DRG were collected for electron microscopy, GFAP and Cxs protein expression and localization, and finally for *ex vivo* electrophysiological and coupling studies with fluorescent dye Lucifer yellow.

Neurophysiological and behavioural tests, conducted at the end of the treatments, confirmed the onset of a painful sensory axonopathy and a milder sensory neurotoxicity in PTX and CDDP-treated rats, respectively. A remarkable reduction of interstitial space between neuron–SGC units were observed in DRG of PTX-treated animals. Quantitative and qualitative immunohistochemical analyses revealed an increased GFAP-positivity following PTX treatment, supporting SGCs activation. In addition, perineuronal spot-like staining of Cxs was evident at immunofluorescence analysis in PTX-treated rats with a higher Cx43 signal, and this data was supported by western blot analysis. Otherwise, preliminary experiments showed no Cx43 overexpression in DRG of CDDP-treated animals.

In conclusion, the investigation of SGC-SGC and SGCs-neurons interactions and their cross-talk could be important in the identification of new molecular mechanisms underlying CIPN pathogenesis, helping in the identification of new therapeutic strategy against CIPN.

VCMTES: A VALIDATED VIRTUAL EVALUATION FOR PEOPLE WITH CHARCOT MARIE TOOTH DISEASE

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The CMT Exam Score (CMTES) has been used since 2005 in clinics to measure impairment in patients with CMT and has provided natural history data for patients with CMT1A, CMT1B, CMTX1, CMT2A and many other subtypes. However, CMTES requires an in person visit and many individuals are unable to travel to CMT centers because of distance from the clinic, physical disability, or more recently because of COVID-19 restrictions. We therefore developed the virtual CMTES (vCMTES) as outlined below.

We modified the CMTESv2 replacing the pinprick and vibration items with light touch and position sense, which can be performed remotely by the patient or the patient with an assistant while being observed by the clinic evaluator. Motor evaluations were performed similar to CMTESv2 by the assistant or patient, while being observed remotely. We developed a standardized protocol to be used with a Zoom or similar format, a training and certification program and enabled the vCMTES data to be housed in the Inherited Neuropathy Consortium databases. Patients were evaluated in person and remotely for inter and intra-examiner validation studies.

Sixty-four patients with genetically confirmed CMT were evaluated by vCMTES and CMTESv2; fifty-three were evaluated virtually three weeks after their initial exam. Ten patients were evaluated with vCMTES by different examiners five days apart. CMTESv2 correlates strongly with the vCMTES in person and virtually ($p<0,0001$). There was a strong correlation between the vCMTES made in person and virtually ($p<0,0001$). Similar results were obtained comparing symptoms score items, sensory items and the motor items. Test-retest reliability, interclass correlation coefficients (ICCs) were ≥0,92.

Statistical analyses demonstrated that vCMTES is valid and reliable as a clinical outcome assessment for CMT. Further studies are needed to test responsiveness to change and progression in different subtypes. vCMTES may also offer the potential to reach diverse populations that do not have access to CMT centers.

ILE68LEU-RELATED TTR AMYLOIDOSIS WITH MIXED PHENOTYPE: THE NEED FOR DIALOGUE BETWEEN SPECIALISTS

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Introduction: TTR amyloidosis is an autosomal dominant rare, progressive and fatal disorder characterized by extracellular deposition of misfolded transthyretin protein. It can affect many organs and even if some mutations are associated with predominant polyneuropathy or cardiomyopathy, most patients have mixed clinical phenotypes.

Ile68Leu *TTR* mutation is usually associated with a cardiological presentation. Neuropathic involvement is often subclinical, associated with worse prognosis and should be always investigated.

Patient and Methods: A 75-years-old Caucasic man was admitted to the Emergency Department of our Hospital because of sudden dyspnea and chest tightness. His past medical history was significant for hypertension, benign prostatic hyperplasia, MGUS (IgG and IgM with *k* light chain) and a previous bilateral carpal tunnel surgery. He was an active smoker, and his familial medical history was positive for unspecified cardiopathy (paternal grandfather).

Results: Cardiac ultrasound (CU) showed only moderate tricuspid valve insufficiency. Due to a second-degree atrioventricular block, he was treated with a dual chamber pace-maker implantation. Five months later, worsening of dyspnea occurred despite diuretic therapy. CU demonstrated marked hypertrophy, 45% ejection fraction and

severe reduction of the longitudinal deformation indices with an "apical sparing", a pattern suggestive of cardiac amyloidosis.

He underwent an abdominal subcutaneous fatty tissue biopsy which revealed the presence of amyloid. A bone scintigraphy showed intense cardiac radiotracer fixation and high heart/whole body uptake ratio, thus suggesting a form of transthyretin-related amyloidosis. In this perspective, *TTR* molecular analysis was carried out which detected the c.262A>T (p.Ile88Leu) variant.

Neurological examination showed impaired walking on toes and heels, mild tactile and vibratory sensory impairment and hyporeflexia at the lower limbs. No autonomic symptoms were detected. ENG study confirmed the presence of an axonal sensory-motor polyneuropathy. The diagnosis of Transthyretin Familial Amyloid Polyneuropathy allowed us to initiate specific therapy with Patisiran.

Conclusion: As already described, the neurologic impairment, though often subclinical, is not infrequent in the mainly cardiogenic Ile68Leu-related TTR amyloidosis. In recent years, the therapeutic landscape of this disease has greatly expanded with several molecules acting as gene silencers and specifically indicated only for patients with neurologic involvement. Due to the natural history of the disease, it is mandatory not to miss diagnosis to address patients to the best available treatment.

MOTOR NERVE BIOPSY STUDIES IDENTIFY A PTDP-43 ENDOPHENOTYPE IN A SUBGROUP PATIENTS PRESENTING WITH PERIPHERAL AXONAL NEUROPATHY

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Background: We have previously shown that motor nerve biopsy may be used for an early diagnosis in lower motor neuron syndromes (LMNS). Most importantly, we have more recently demonstrated that the detection of phosphorylated TAR DNA-binding protein-43 (TDP-43) deposits within motor axons nerve axons as well as within the cytoplasm of Schwann Cells may represent an useful pathologic biomarker for the distinction of ALS patients from neuropathy patients.

Specifically, pTDP-43 axonal accumulation was detected in 56 ALS cases (98.2%) versus seven in non-ALS samples (30.4%) ($P < 0.0001$), while concomitant positive Schwann cell cytoplasmic staining was found in 40 ALS patients (70.2%) versus four non-ALS cases (17.4%) ($P < 0.001$)

Therefore, although our study demonstrates a high specificity of pTDP-43 aggregates for the diagnosis of ALS, our results also imply that a pTDP-43 pathology can be detected in a non-neglectable percentage of non-ALS cases.

Aims and Results

Herein we aim to describe the clinical and pathological features of patients presenting with clinical and histological features of a peripheral neuropathy and displaying a pTDP- 43 pathology within motor nerves. Our study identifies a subgroup of patients displaying a peripheral chronic, predominantly motor axonal neuropathy with distinguishing clinical features. Next Generation Sequencing genetic analysis are undergoing in order to identify the molecular basis of these cases.

Conclusions: Our findings highlight that a pTDP- 43 pathology may be detected in patients presenting with a a non-inflammatory motor neuropathy and support the existence of a continuum between motor neuron diseases and a specific subgroup of peripheral neuropathies that need further characterization.

CHARACTERIZATION OF A NOVEL RAB7A MUTATION ASSOCIATED WITH A NEW PHENOTYPE OF CHARCOT-MARIE-TOOTH TYPE 2B

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RAB7A is a ubiquitous small GTPase that regulates late endocytic traffic, autophagy, mitophagy and lipophagy. RAB7A carries out also specific functions in neurons such as neurotrophin receptor trafficking and signaling, and regulation of neurite outgrowth, as well as assembly of the two intermediate filament proteins vimentin and peripherin. Five missense mutations (L129F, K157N, N161T/I, V162M) in the RAB7A gene determine the onset of Charcot-Marie-Tooth type 2B (CMT2B) disease, a rare neurodegenerative disorder affecting the peripheral nervous system. These mutations are associated with predominant sensory loss, ulcero-mutilating features, with lesser or absent motor deficits. We previously demonstrated that RAB7A

mutants display altered nucleotide Koff affecting RAB7A-regulated processes. Indeed, they inhibit the autophagic flux, lipophagy and neurite outgrowth, they interact more strongly with and affect the assembly of vimentin and peripherin, and increase lysosomal degradative activity. Recently, a new RAB7A mutation was discovered (p. K126R) in associatio with a different early-onset phenotype characterized by walking difficulties, progressive distal muscle wasting, weakness in lower limbs and only mild sensory signs.

In order to clarify the molecular mechanisms underlying the different phenotypes identified, we tried to characterize the novel missense variant p. K126R using western blot analysis, confocal microscopy and biochemical assays.

The RAB7AK126R mutant displays higher nucleotide Koff (higher for GDP than for GTP), impaired GTP hydrolysis per binding event, inhibits neurite outgrowth and interacts more strongly with peripherin compared to RAB7A wild-type, similarly to the other CMT2B-causing RAB7 mutants. Although for most of the studied phenotypes we detected no significant differences between the K126R mutation and other CMT2B-causing RAB7 mutations, we found a strong accumulation of Epidermal Growth Factor Receptor (EGFR) caused by inhibition of EGFR degradation in patient's skin fibroblasts carrying the K126R; this contrasts with findings observed in fibroblasts carrying the V162M classical CMT2B mutation. Indeed, in fibroblasts from patients with the K126R mutation, EGFR remains in the early endosomes; the impairment of EGFR trafficking to late endosomes and lysosomes determines inhibition of EGFR degradation with consequent accumulation. Moreover, we found that cells expressing the RAB7K126R mutant protein were characterized by an impairment of autophagy and lipophagy and by a moderate increase in lysosomal activity compared to the previously studied cells carrying the RAB7V162M mutation.

Thus, we concluded that the specific predominantly motor phenotype observed in K126R patients could be induced by EGFR trafficking alterations and a moderate increase in lysosomal activity with concomitant impairment of autophagy.

NONSENSE MUTATIONS IN RFC1 CAUSE CEREBELLAR ATAXIA, NEUROPATHY VESTIBULAR AREFLEXIA SYNDROME (CANVAS)

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Cerebellar Ataxia, Neuropathy and Vestibular Areflexia Syndrome (CANVAS) is an autosomal recessive neurodegenerative disease characterized by adult onset and slowly progressive sensory neuropathy, cerebellar dysfunction, and vestibular impairment. In most cases, the disease is caused by biallelic $(AAGGG)_n$ repeat expansions in the second intron of the Replication Factor Complex subunit 1 (RFC1). However, a small number of cases with typical CANVAS do not carry the common biallelic repeat expansion.

Eight individuals diagnosed with CANVAS and carrying only one heterozygous $(AAGGG)_n$ expansion in RFC1 underwent WGS or WES to test for the presence of a second mutation in RFC1 or other unrelated genes. To assess the impact of nonsense mutations on RFC1 expression we tested the level of RFC1 transcript and protein on patients' derived cell lines.

We identified 3 patients from 2 unrelated families with clinically defined CANVAS carrying a heterozygous $(AAGGG)_n$ expansion together with a second c.1267C>T;(p.Arg423Ter) or c.2876del;(p.-Pro959GlnfsTer24) nonsense mutation in RFC1. The presence of a c.1267C>T;(p.Arg423Ter) mutations was associated in patients' fibroblasts with nonsensemedicated mRNA decay and reduced RFC1 transcript and protein.

Our report expands the genotype spectrum of RFC1 disease. Full RFC1 sequencing is recommended in cases affected by typical CANVAS and carrying monoallelic $(AAGGG)_n$ expansions. Also, it sheds further light on the pathogenesis of RFC1 CANVAS as it supports the existence of a loss of function mechanisms underlying the complex neurodegenerative condition.

PURE MOTOR AXONAL NEUROPATHY FOLLOWED BY THE SYRINGOMYELIA-LYKE PHENOTYPE: A NOVEL PRESENTATION OF TANGIER DISEASE

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Tangier disease (TD) is an autosomal recessive genetic disorder characterized by high-density lipoprotein deficiency and accumulation of cholesterol esters in various tissue resulting from reverse cholesterol transport deficiency. The disease is caused by mutations in the ATP binding cassette transporter (ABCA1).

Peripheral neuropathy is observed in approximately 50% of patients with TD and is characterized by heterogeneous manifestations. TD neuropathy may present with two different phenotypes: a) an early onset form, usually beginning in the first two decades, characterized by a spontaneously remitting course with multifocal sensory and motor distribution b) an adult-onset syringomyelia-like neuropathy (SMLN) characterized by slowly progressive, bilateral hand muscle wasting and weakness associated with selective pain and temperature anaesthesia.

We describe a patient with a two-stage clinical course in which both phenotypes were observed. At the age of 20 years he had a subacute, remitting polyneuropathy and after 20 years he showed the typical chronic progressive syringomyelia-like manifestations. Furthermore, in our patient clinical and electrophysiological and pathologic features of the early onset manifestation were consistent with a pure motor axonal neuropathy with distal symmetric distribution, a feature which has never been described so far in TD. His brother at the age of 43 y developed a typical syringomyelia-like neuropathy, and homozygous pTyr573Ter in the ABCA1 gene was detected in both siblings .

These are the first cases reported in the literature in which the 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.

AGGRESSSIVE TETRAPARETIC AUTOIMMUNE NODOPATHY WITH ANTIBODIES TO CNTN1/CASPR1 COMPLEX

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Nodo- and paranodopathies are autoimmune neuropathies associated with antibodies to nodal-paranodal antigens (neurofascin, contactin-1, caspr1) characterized by poor response to intravenous immunoglobulins (IVIg) and benefit from anti-CD20 monoclonal antibody (rituximab) therapy.

The forms with antibodies to caspr1/contactin-1 complex are rare, rapidly progressive, sometimes associated with pain and cranial nerves involvement.

We report on a 26-year-old woman, affected by cystic fibrosis, who developed a disabling anti-CNTN1/CASPR-mediated polyneuropathy.

She presented with subacute onset of sensory symptoms at 4 limbs, followed two weeks later by motor weakness. For neurophysiological evidence of demyelinating neuropathy, she was diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy and treated with IVIg without benefit. The symptoms rapidly worsened, the patient was forced to discontinue her job and lost autonomy in daily activities. Three months after symptoms onset she was admitted to our Hospital. She had ataxic-stepping gait, severe (distal>proximal) motor weakness at four limbs, upper limbs low frequency postural tremor, sensory loss up to the trunk, loss of vibration sense at four limbs, areflexia. Electrodiagnostic evaluation confirmed a severe demyelinating polyradiculoneuropathy with sensory and motor conduction blocks. MRI with 3D Neurographic sequences showed diffuse, symmetrical, homogenous hypertrophy and marked T2-STIR signal hyperintensity of roots and main divisions of brachial and lumbosacral plexi. Brain MRI was unremarkable.

Cerebrospinal fluid analysis showed high protein levels (710 mg%), 13 WBC/μL, severe blood–spinal nerve root barrier damage.

Despite intravenous methylprednisolone and physical therapy, she progressively worsened, sensory loss spread to chin and tongue, distal strength was further reduced and she became unable to stand independently being restricted to wheelchair.

Antibodies to nodal-paranodal antigens were searched for by ELISA and cell-based assay. Anti CNTN1/CASPR1 IgG4 antibodies resulted positive, and diagnosis of CNTN1/CASPR1-mediated neuropathy was made.

The patient underwent rituximab therapy (375 mg/m^2 every week for four weeks). One month later she presented mild improvement in the fine movements at upper limbs and more stability when standing, always assisted. Neurophysiology revealed signs of demyelinating neuropathy, with severe secondary axonal degeneration, both proximally and distally at the four arms. Signs of complete denervation were present at distal muscles at lower limbs.

Nerve ultrasound showed increased cross sectional area of the brachial plexus (CSA of 134 mm^2 on the left side, 132 mm^2 on the right side) and of all nerves at the four arms. The patient is currently undergoing intensive rehabilitation. Possible maintenance therapy will be considered based on clinical response and antibody titer monitoring.

MAGNETIC RESONANCE NEUROGRAPHY AND DIFFUSION TENSOR IMAGING IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS:A STUDY OF THE SCIATIC NERVE IN PATIENTS AND PRE-SYMPTOMATIC CARRIERS

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Objective: To quantitatively assess Magnetic Resonance Neurography (MRN) and Diffusion Tensor Imaging (DTI) properties of the sciatic nerve in subjects with hereditary transthyretin amyloidosis (ATTR).

Methods: 19 subjects with a TTR gene mutation (mean age 62,32), including 13 patients affected by axonal or predominantly axonal polyneuropathy (ATTR-FAP) and 6 pre-symptomatic carriers (ATTR-carriers) were prospectively evaluated with Magnetic Resonance imaging at 3 Tesla and compared with 19 healthy controls (mean age 61.42). 2D MRN and DTI sequences were conducted at the right thigh from the ischiatic foramen to the popliteal fossa. Cross-section area (CSA), normalized signal intensity (NSI), DTI metrics, including

fractional anisotropy (FA), mean (MD), axial (AD) and radial diffusivity (RD) were measured at proximal, mid and distal thigh. Neurologic and electrophysiologic examinations were conducted in ATTR-FAP and ATTR-carriers and correlated with MR parameters.

Results: increased CSA, NSI, MD, RA and reduced FA reliably differentiated ATTR-FAP from ATTR-carriers and controls at all levels ($p<0.01$). NSI was able to differentiate ATTR-carriers from controls at proximal (1.50±0.28 vs 1.11± 0.14 $p=0.001$) and midthigh (1.56 ± 0.29 vs 1.19± 0.17 $p<0.05$), FA at midthigh (0.52±0.02 vs 0,58 ±0.04 $p<0.05$) and RD at proximal (1.02±0.10 vs 0.86±0,12 p) and midthigh (1.08±0.11 0 vs.93±0.15 p <0.05). CSA and AD were unable to differentiate ATTR-FAP from ATTR-carriers. CSA, MD and RD positively correlated with NIS-LL (average 20.56 ±17.65 in ATTR-FAP) and negatively with cMAPs and NCVs. FA positively correlated with cMAPs and NCVs and negatively with NIS-LL.

Conclusion: The combination of MRN and DTI can be reliably used to differentiate between ATTR-FAP, ATTR-carriers and healthy controls, based on quantitative structural and functional parameters information obtained from the sciatic nerves which are significantly correlated with neurophysiology. More importantly MRN-DTI is able to non-invasively identify early microstructural changes in pre-symptomatic carriers, thus representing a potential tool for monitoring disease progression.

LONG-TERM OUTCOME IN COVID-19 RELATED CRITICAL ILLNESS POLYNEUROPATHY

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Introduction: 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 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 (T2/3: 6 and 9 months).

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 patients presented recurrent infectious episodes or septicemia during hospitalization. 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 (T0UL 2.93 ± 1.16, T0 LL 4.4 ± 0.73; T1UL 1.29 ± 0.83, T1LL 2.29 ± 1.14, p<0,00001, n.14), with the exception of one patient that did not undergo an intensive rehabilitation treatment. On average, a further significant improvement was found at the T2 (n.6) and T3 (n.9) visits: T2UL 0.5 ± 0.55, T2 LL 0.67 ± 0.82, p<0,05); T3 UL 0.33 ± 0.5, T3 LL 0.33± 0.5; p < 0.05).

Conclusions: CIP/CIM in patients SARS-COV-2 infection has clinical and neurophysiological features similar to non-covid cases. Unexpectedly, the longterm clinical course is more benign, with a recovery in a shorter time than previously described in non-covid patients (*Lancet Neurol, 2011*). We also demonstrate the central role of early rehabilitation, to optimize clinical-functional recovery and prevent functional disability.

A CASE OF SEVERE INCREASE OF LIVER ENZYMES IN A ATTRv PATIENT TREATED WITH INOTERSEN

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Hereditary transthyretin amyloidosis (ATTRv) is a progressive and life-threatening disease, due to deposition of amyloid fibrils of TTR. Inotersen, an antisense oligonucleotide inhibitor of the hepatic production of transthyretin protein, can be administrated in the early stages of disease. The most common drug-related adverse effects (AE) of Inotersen include thrombocytopenia and glomerulonephritis, which require monitoring platelet count every two weeks and renal function every three months. Moreover, liver enzymes monitoring was mandatory every year. We report a case of severe increase of liver enzymes in a ATTRv patient treated with Inotersen.

A 70-years-old man with ATTRv (Val30Met) started therapy with Inotersen in November 2020. His basal evaluation showed Familial Amyloid Polyneuropathy (FAP) stage I, Polyneuropathy Disability (PND) score II, total Neuropathy Impairment Score (NIS) = 50.75 and Norfolk quality of life questionnaire = 70 points. Basal platelet count ($201x10^3/\mu L$), renal function tests and liver enzymes (AST= 12 U/L; ^{3}ALT= 58 U/L; GGT= 27 U/L) were normal. The serum transthyretin concentration at baseline was 0.39 g/L. During the treatment a non-significant reduction of platelet count was recorded (mean

value= 151x10/μL; [3]min value= 111x10/μL). Renal function and liver enzymes remained stable and serum transthyretin concentration was suppressed (0.08 g/L) during the treatment.

At 1-year follow-up, neurological evaluation showed a stable disability (FAP stage I, PND score II, NIS Total = 50.7) and an improvement of quality of life (Norfolk= 51). However, at blood analysis a severe increase of ALT (833 U/L), AST (665 U/L) and GGT (135 U/L) was documented. Bilirubin level and cholinesterase were normal. Patients suspended Inotersen and other causes of acquired hepatitis were excluded: liver echography showed mild steatosis with normal biliary tracts, and screening for acute hepatic infections (HAV, HBV, HCV, HIV, CMV, EBV, HSV, VZV, toxoplasma) and auto-immune hepatitis (ANA, ENA, AMA, LKM1) was negative. Therefore, the hypothesis of an Inotersen-related hepatic toxicity was proposed and supported by the normalization of liver enzymes after 40 days from drug withdrawal. Transthyretin concentration at that time still remained suppressed (0.14 g/L).

Our case shows that 1-year Inotersen treatment can stabilize neurological impairment and even improve quality of life. Although platelet count and renal function were normal, our patient developed after a 1-year treatment severe increase of liver enzymes that has forced Inotersen interruption, thus highlighting the need for careful liver enzyme monitoring to avoid Inotersen-related hepatic damage.

MME-RELATED CHARCOT-MARIE-TOOTH NEUROPATHY MASQUERADING AS CHRONIC IDIOPATHIC AXONAL POLYNEUROPATHY IN A PATHOLOGY COHORT

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Bi-allelic loss-of-function (LoF) variants of the Membrane metalloendopeptidase (MME) gene, encoding neprilysin, cause autosomal recessive (AR) axonal Charcot-Marie-Tooth disease (CMT2T) with onset in adulthood; recent studies pointed at heterozygous LoF or missense variants of MME as a dominantly inherited susceptibility factor for axonal neuropathies of the elderly. We aimed at investigating the contribution of MME variants in a pathologically selected series of probands with chronic idiopathic axonal polyneuropathies.

234 probands with chronic axonal neuropathy which had remained "idiopathic" after a sural nerve biopsy were analysed by Next Generation Sequencing using a custom-designed panel covering all coding exons of 24 CMT-associated genes. Relevant characteristics were abstracted from clinical and pathological reports prior to genetic analysis.

Focusing on MME, 3 sporadic patients (one born from consanguineous parents) were homozygous for the common p.Pro156LeufsX14 mutation. Those patients had a sensorimotor polyneuropathy with onset between the fifth and sixth decade. Large myelinated nerve fibers were predominantly affected on biopsy and associated to regeneration changes to a variable degree. Nine sporadic probands carried 3 heterozygous rare missense variants previously associated with dominant, incompletely penetrant, CMT and/or AR-CMT2T: p.-Asn689Lys (n=4), p.Tyr347Cys (n=3), p.Ile649Ser (n=1), p. p.-Pro156LeufsX14 (n=1); those patients had a relatively mild sensorimotor polyneuropathy with onset between the sixth and eighth decade (range: 50-75 years), in most cases limited to large myelinated nerve fibers and often associated to regeneration clusters. Three further probands carried four missense rare variants of uncertain significance and 10 harbored 2 likely benign variants.

The report highlights the pathogenic relevance of MME in apparently sporadic, chronic axonal neuropathies in adult and elderly patients.

SMALL NERVE FIBERS INVOLVEMENT IN RFC1-RELATED NEUROPATHY: A CLINICAL AND PATHOLOGY STUDY

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Peripheral nervous system involvement with early and prominent sensory ataxia and loss of touch and vibration sensation is a common feature on presentation in Cerebellar Ataxia with Neuropathy and Vestibular Areflexia Syndrome (CANVAS) associated to Replication Factor C subunit 1 biallelic intronic AAGGG expansion mutation ($RFC1_{exp}$). The clinical picture is often completed by signs and symptoms of small fiber neuropathy, albeit frequently overshadowed by sensory complaints. Available pathology studies are limited but suggest a ganglionopathy as the process underlying the peripheral disorder, however the degree and distribution of small nerve fiber involvement has yet to be elucidated. Here, we report the results of clinical and pathology investigations on small nerve fibers involvement in $RFC1_{exp}$ patients.

We enrolled $RFC1_{exp}$ subjects with different clinical presentation from isolated neuropathy to full-fledged CANVAS. All patients were staged for severity using SPATAX scale and examined for signs of sensory, cerebellar or vestibular impairment. Nerve conduction studies, laser evoked potentials (LEP), sympathetic skin response (SSR) and/or electrochemical skin conductance (ESC) were obtained to assess both large and small nerve fiber function. Microneurography was obtained in a subset of patients. Distal and proximal lower limb skin punch biopsy samples were evaluated for somatic intraepidermal and autonomic subepidermal structures innervation.

On an interim analysis, median age at visit of the available sample was 65 years (IQR 54-75) after a median disease duration of 13.5 years (IQR 8-19). Patients had a mild-to-moderate overall impairment with a median SPATAX score of 3 (IQR 2-4). A full CANVAS phenotype was

observed in 3 patients, an incomplete phenotype in 6 and isolated neuropathy in 2. Decreased nociception was observed in most patients in the absence of a clear length-dependent pattern, LEP being abnormal and often not evocable at the four limbs. SSR/ESC were commonly altered. Microneurographic recording did not detect muscle and skin sympathetic activities in the two patients tested. Skin biopsy revealed an almost complete depletion of intraepidermal and subepidermal plexus nerve fibers in all examined patients with a similar degree at both distal and proximal sites together with a marked autonomic denervation involving both cholinergic innervation of sweat glands and adrenergic innervation of arterioles and muscle arrector pilorum.

In addition to the characteristic large nerve fibers involvement, RFC1-related neuropathy is associated to an extensive and diffuse loss of somatic and autonomic small nerve fibers. Small fiber involvement did not differ between proximal and distal skin sites supporting an underlying ganglionopathy.

GENETIC TESTING IN CHARCOT-MARIE-TOOTH DISEASE AND RELATED INHERITED NEUROPATHIES: FOUR-YEAR EXPERIENCE OF A SINGLE CENTRE

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Charcot-Marie-Tooth disease (CMT) and related inherited peripheral neuropathies (IPN) are clinically and genetically heterogeneous. More than 100 genes have been associated with IPN; currently, Next-Generation Sequencing (NGS) has become the preferred method in genetic testing. We report the 4-year experience of our diagnostic activity as a referral centre.

From January 2018 through January 2022 we performed more than 1200 analyses in patients referred for suspected IPN. Thirty-three percent of the tests were Multiplex ligation-dependent probe amplification (MLPA) to investigate copy number variations of *PMP22*, *MPZ*, *GJB1*; 21% were Sanger sequencing of *TTR* to rule out hereditary *TTR*-related amyloidosis (hATTR); almost 7% were Repeat-primed-PCR (RP-PCR) investigating the biallelic pentanucleotide expansion in the *RFC1* gene associated with Cerebellar Ataxia with Neuropathy and Vestibular Areflexia Syndrome (CANVAS); 40% of tests were targeted-NGS performed on an Ion Torrent PGM DX System using two custom panels comprising 40 presumably common disease genes (including *TTR*) and 62 presumably rarer genes associated with CMT1, CMT4, CMT2, AR-CMT2, CMT-I as well as with hereditary motor neuro(no)pathy (HMN) and hereditary sensory autonomic neuro(no) pathy (HSAN).

Diagnostic yield was 40% for *PMP22* MLPA tests (CMT1A, n=94, HNPP, n=74); 25% for *RFC1* RP-PCR protocol (CANVAS, n=19); 15% for *TTR* Sanger-sequencing analysis in hATTR probands (n=41). Focusing on variants belonging to ACMG classes 4 and 5, the 40-gene panel revealed 71 allelic mutations leading to a definite diagnosis in 12% of probands (n=55/452); the most frequent genetic subtypes included: CMT1B/CMT2I/J (n=13), CMT4C (n=9), CMTX1 (n=6), CMT2K (n=6), CMT1E (n=4); the remaining 17 probands were associated to 11 different CMT genes. The 62 gene-panel revealed 14 allelic mutations leading to a definite diagnosis in 20% of probands (n=12/60); the most frequent genetic subtype was CMT2T (n=3); the remaining 9 probands were associated to 7 different genes.

Our results confirm the heterogeneity of CMT-related neuropathies partially diverging from mutational frequencies observed in larger multicentre studies. Taking into account the wide and flat distribution of the mutational landscape and the frequent unavailability of phenotypical details, a comprehensive and systematic approach in genetic testing protocol design is needed to guarantee an adequate diagnostic coverage in the suspicion of an inherited peripheral neuropathy.

VEPS AND BAEPS IN ATTRV PATIENTS: IS THERE A ROLE?

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Hereditary transthyretin amyloidosis (ATTRv), is a progressive autosomal dominant disease characterized by deposits of amyloid in peripheral nerves and several organs, including the eye. Moreover, some studies describe a correlation between ATTRv and hearing loss. The objective of our study is to evaluate whether ATTRv patients show alterations of visual evoked potentials (VEPs) or brainstem auditory evoked potentials (BAEPs), that may suggest an amyloid deposition even in cranial nerves.

We recruited ATTRv patients followed at the Center for Rare Neuromuscular Diseases of Palermo University hospital. As controls we selected a group of healthy subjects (HS) with same demographic characteristics. Regarding VEPs, we recorded two potentials for each eye, calculating P100 wave mean latency (ms) and amplitude (μV), using full field pattern reversal stimulation (30' checks). About BAEPs, we recorded two potentials for each ear and included I, III and V waves latencies and I-III, III-V and I-V interpeak ones (ms), I and V amplitudes (μV) and V/I amplitude ratio. Montages and stimulation parameters were performed using American Clinical Neurophysiology Society guidelines. Statistical analysis was conducted using Mann-Whitney U test.

We included 11 patients (mean age 68.1±6.86 years old, 6F) and 11 age- and gender-matched HS. There was no significant difference in P100 latencies between patients and HS (right 106.91±1.92 vs 105.43±7.41ms, p=0.973; left 108.59±4.11 vs 106.06±6.82ms, p=0.654); differently, we found a significant difference in P100 amplitude (right 1.92±1.50 vs 3.58±1.37μV, p=0.020; left 1.95±1.01 vs 3.17±0.76μV, p=0.043). Lastly, we did not find differences in any of BAEPs parameters studied.

Both ocular involvement and retinal abnormalities (ERG) are described in ATTRv patients, but no study evaluated VEPs. We can suppose that the smaller P100 amplitude in ATTRv patients might suggest a retinal damage or an axonal optic neuropathy; however, we should have collected ERG data to partially solve this issue. Moreover, such finding may have even scarce clinical relevance and it should be confirmed with a wider population. On the other hand, even if hearing loss is described in ATTRv patients, we did not find any BAEPs alteration; we can explain this result since the stimulation used is above the hearing level; however, we did not explore the presence of any sensory-neural hearing loss. Lastly, BAEPs normal findings suggest that the auditory pathway is spared in such disease.

REPORT OF SUBACUTE INFLAMMATORY POLINEUROPATHY AFTER SARS-COV2 VACCINATION: MYTH OR REALITY?

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Introduction: Few cases of Guillain Barrè syndrome (GBS) and acute onset CIDP (AIDP) and one case of sub-acute onset CIDP after recent COVID-19 vaccination have been reported in liteature, but a clear cause-effect relationship is not yet confirmed.

Mehods: A 61-year-old woman came to our attention presenting a gradual onset of dysesthesia/paresthesia especially at lower limbs, postural instability and deambulation impairment. Medical history was positive for diabetes mellitus hypertension, dysdlipidemia; about a month earlier, the patient received the first dose of BNT162b2 vaccination. None previous infection was reported. Neurological examination showed ataxic gait possible with monolateral support, weakness in feet dorsiflexion, hypoesthesia and reduction of pin-prick sensation distally at four limbs, absence of Achilles' tendon reflexes. Neurophysiological study showed, both motor and sensitive demyelinating damage on nerve conductions especially at lower limbs, whereas a previous study was normal. Cervical and lumbosacral spine MRI was unremarkable. Cerebrospinal fluid analysis revealed albumin-cytologic dissociation. Searching for onconeural and antigangliosides antibodies was negative.

Results: A diagnosis of subacute inflammatory demyelinating polyneuropathy (SIDP) was done, and the patient received three courses of intravenous immunoglobulins (2g/die for 5 days) with improvement of the clinical picture.

Conclusion: Based on reports available, both COVID-19 infection and COVID-19 vaccination are mostly associated to the classic form of GBS and AIDP within 2 weeks by the event. In our case, a subacute course occurred, increasing the spectrum of clinical presentations of inflammatory neuropathies related with vaccination, nevertheless a clear causal link is not clear. Clinicians should be aware of these possible side effects to prompt recognize and treat them adequately.

EXTENSOR DIGITORUM BREVIS ATROPHY AS ISOLATED ULTRASOUND FINDING IN AXONAL POLYNEUROPATHY WITH PREVALENT SENSITIVE SYMPTOMS

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Introduction: Distinctive US findings have been reported in patients with hereditary, immune- mediated, infectious and metabolic peripheral neuropathies (PN). However, in some cases peripheral nerve findings may be inconsistent, mainly in axonal neuropathies, and the ultrasound diagnosis relies on the indirect signs as muscle atrophy. The extensor digitorum brevis muscle (EDB) is a small muscle located on the dorsum of the foot in the front of the lateral malleolus innerved by a branch of the deep peroneal nerve. EDB atrophy (EDBA) has been reported to be a sign of anterior tarsal tunnel syndrome, L5 radiculopathy, lumbar canal stenosis and diabetic symmetric polyneuropathy. In our experience, isolated EDBA could be found in other conditions involving the peripheral nervous system. Our aim is to describe the clinical and electrophysiological features of peripheral nerve affections in which EDBA is the only ultrasound indirect sign.

Materials and methods: Patients suffering from monolateral or bilateral sensory and/or motor lower limbs disturbances were consecutively enrolled for US study. US examination was performed using a 18-5 Mhz linear array probe and a 22-5 Mhz J-stick probe. In all the patients, the sciatic nerve, femoral nerve and respective terminal branches have been systematically evaluated. In case of muscle atrophy, it was classified as mild, moderate and severe. Patients with lumbosacral disk herniation, radiculopathy and lumbar canal stenosis were excluded. After ultrasound examination, patients with evidence of anterior tarsal tunnel syndrome were excluded. All the patients completed their diagnostic workup with clinical, laboratory and electrophysiological studies.

Results: Over a period of 6 months, n=60 consecutively patients were enrolled for the US examination. In n=8 patients (13%) the only ultrasound finding was monolateral (n=3) or bilateral (n=5) EDBA. N=2 patients with mono-lateral EDBA presented thickening of the nervous branch for EDB resulting affected by anterior tarsal tunnel syndrome. In the remaining patients with EDBA (n=6) undetermined sensitive

axonal polyneuropathy was found in n=2 cases, sensitive mixed axonal and demyelinating polyneuropathy with likely immuno-mediated etiology in n=2 cases, motor and sensitive axonal metabolic neuropathy in n=2 cases.

Conclusion: Although the number of patients was too low to drive meaningful conclusions, EDBA could represent the only ultrasound finding associated with axonal neuropathies presenting with prevalent sensory symptoms. The altered touch and vibratory sensitivity in the distal lower extremities may cause an altered mechanics at the level of the ankle joint leading to stretching of the nerve branch for EDB determining or accelerating EDBA.