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ABSTRACT

NEUROFILAMENT LIGHT CHAIN AS CLINICAL PLASMA BIOMARKER OF CHARCOT-MARIE-TOOTH DISEASE TYPE 2A

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Charcot-Marie-Tooth disease type 2A (CMT2A) is an inherited sensory-motor peripheral neuropathy caused by mutations in the Mitofusin2 (MFN2) gene. Unfortunately, no curative treatment is available, but several innovative strategies are under investigation. Blood biomarkers are accessible and low-cost tools that may guide diagnosis and monitor progression, especially within clinical trials. Neurofilament light chain (NfL) is a neuronal cytoplasmic protein abundant in neuronal axons and released into the blood proportionally to the degree of axonal damage in a variety of neurological disorders, including some CMT subtypes. We thus decided to investigate whether NfL could be a suitable biomarker for CMT2A.

We collected serum from CMT2A (n=9), amyotrophic lateral sclerosis (ALS; n=10) and spinal muscular atrophy (SMA) type 3 (n=6) patients and from non-neurological controls (n=10) during routine evaluations at our Clinic. Additionally, we collected serum from wild-type (C57BL/6J) and transgenic mice expressing the R94Q mutation in the *MFN2* gene under the Thy1.2 promoter (C57BL/6J Tg(Thy1-MFN2*R94Q)44Balo/J), already present in our Lab, at 5 months of age. We quantified the serum concentrations of NfL using Ella™ Biotechne immunoassay. The study was supported by *Associazione Progetto Mitofusina 2*, *Associazione Amici del Centro Dino Ferrari* and *ACMT-Rete*.

We observed significantly higher NfL values in CMT2A patients compared to controls (39.3 vs. 1.9 pg/ml, median; $P< 0.001$, Mann-Whitney U-test). NfL levels were also significantly higher compared to untreated SMA type 3 patients (39.3 vs. 12.9 pg/ml, median; $P< 0.05$, Mann-Whitney U-test) but not compared to ALS patients (39.3 vs. 92.0 pg/ml, median; *ns*, Mann-Whitney U-test). Nfl values in CMT2A correlated negatively with age (rho -0.83, $P<0.01$) and disease duration (rho -0.73, $P<0.05$; Spearman correlation test). Analyses performed in mice showed similar results, with higher values in diseased mice than controls.

We observed higher NfL levels in CMT2A patients compared to controls and patients with SMA type 3, a mimicker of CMT2A, representing a potentially useful diagnostic biomarker. NfL levels seem to be higher in younger CMT2A patients and in those with a shorter disease duration, reflecting a more aggressive disease subtype. Similar results were observed in mouse models.

ATYPICAL PHENOTYPE OF AMYOTROPHIC LATERAL SCLEROSIS WITH DOUBLE MUTATION IN FUS AND TARDBP GENES: AN INSIDIOUS CASE OF LOWER LIMBS MOTOR NEURONOPATHY

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Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease characterized by concurrent damage to both upper and lower motor neurons. Only 5-10% of cases are classified as familial (fALS), while 90% are considered sporadic (sALS). In Europe, the most involved genes are C9ORF72 (40% of familial cases), SOD1 (10-20%), FUS (5%), and TARDBP (2-5%) [1]. We describe a rare case of fALS with a double mutation in FUS and TARDBP genes.

A 40-year-old Italian man came to our attention for a severe weakness in lower limbs. His mother received ALS diagnosis and died at the age of 34 for complication of the disease. His symptoms began two years prior with difficulty in walking, progressively leading to wheelchair need. Neurological evaluation showed: lower limb palsy, severe hypotonia and absent deep tendon reflexes. Upper limb strength and reflexes were normal, with no bulbar or pyramidal involvement. Sensibility and sphincter function were normal. Routine blood tests, including inflammatory markers, systemic autoimmune testing and anti-gangliosides antibodies were negative. Cerebrospinal fluid examination and spinal MRI were normal. Nerve conduction studies documented severe motor axonal neuropathy exclusively in the lower limbs. Needle electromyography showed clear signs of active and chronic denervation in the lumbosacral region. Motor evoked potentials were normal. Considering family history, slowly progressive motor symptoms and exclusive involvement of lower motor neuron (LMN), the patient underwent genetic testing. He carried heterozygous mutations of *TARDBP* gene (c.800A>G, p.Asn267Ser) and *FUS* gene (c.1540A>G, p.Arg514Gly), both pathogenic for ALS.

TARDBP and *FUS* are implicated in the regulation of transcription, RNA splicing, and transport. This suggests a common mechanism underlying the degeneration of motor neurons. fALS cases with *TARDBP* mutations commonly present with a spinal onset phenotype, and only in 30% of cases involve LMN. Otherwise, fALS with *FUS* mutations typically had a cervical onset and predominant involvement of the LMN [2]. The p.Asn267Ser mutation in TARDBP was detected in a limited number of cases of neurodegenerative diseases, including a young man with ALS who displayed a clinical phenotype closely resembling that of our patient. [3]. It will be very interesting to evaluate how the concomitant mutation of *FUS* will influence the progression of the disease. Furthermore, in both forms of fALS the average onset of symptoms is around 55 years [4]. We speculate that the double pathogenic mutation may lead to an earlier onset. This case broadens knowledge about the possible clinical presentations of genetic ALS.

OXALIPLATIN-INDUCED PERIPHERAL NEUROTOXICITY: MOLECULAR INSIGHTS

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Among neurotoxic anticancer drugs, Oxaliplatin (OHP) has a specific neurotoxicity profile (oxaliplatin-induced peripheral neurotoxicity [OIPN]): OHP doesn't only cause a chronic sensory polyneuropathy, but it also causes an acute neurotoxicity syndrome (transient cold-induced paresthesia/cramps), as soon as the first administration, usually lasting 24-72 hours after each administration. In the last decade it emerged that acute OIPN could be linked to ion channel dysfunctions and these, despite being transient, have been related to chronic axonal damage development: the more pronounced the acute OIPN is, a more severe chronic OIPN ensues (Lucchetta et al, 2010; Argyriou et al, 2013). We aimed at better characterizing the painful acute and chronic OIPN profile relying on neurophysiology and morphological analyses.

We compared an OHP-treated (3 mg/Kg, 2qw4ws, iv) and a control group (n=12/group, female rats). Acute OIPN spectrum was assessed via nerve excitability testing (NET), whereas chronic OIPN via behavioral test, nerve conduction studies (NCS), and neuropathology. Morphological analyses were performed on specimens collected at the end of treatment and after 6 weeks of follow-up: morphological and morphometric analysis of caudal nerves and dorsal root ganglia (DRG); intraepidermal nerve fiber density (IENFD) assessment; immunohistochemistry for the transient receptor potential vanilloid type-1 (TRPV1) receptor on lumbar spinal cord specimens.

NET demonstrated that acute OIPN ensued as soon as the first OHP administration, and it completely resolved 1 week after the end of treatment. Our multimodal approach allowed us to also demonstrate the full onset of chronic OIPN at the end of treatment; however, over the 6 weeks of follow-up chronic neuropathy encountered signs of recovery, specifically for large fibers involvement. Densitometric analysis of TRPV1 immunolabeling in the dorsal horn of the spinal cord at the end of treatment showed an increased density of TRPV1 staining in OHP animals (in lamina I and inner lamina II); this difference was maintained at follow-up.

Our data showed that acute OIPN (i.e., alterations of ion channels) is a different phenomenon respect to neuropathic pain, despite some "painful manifestations" as part of the acute OIPN presentation: we, in fact, observed a mismatch between NET alterations (completely resolved 1 week after treatment) and persistence of neuropathological alterations (spinal cord and IENFD) up to 6 weeks after end of treatment. Therefore, in future studies, both clinical and preclinical, acute and chronic OIPN should be explored as separate sides of the same coin and confounding factors should be ruled out when assessing painful manifestations.

SUDOSCAN IN THE EVALUATION OF ATTR POLYNEUROPATHY: A SINGLE-CENTRE EXPERIENCE

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Transthyretin Amyloidosis variant (ATTRv) is a hereditary disease characterised by a deposit of amyloid in several tissues, particularly in peripheral nerves. In many patients, the axonal loss of small (autonomic and somatic) nerve fibres causes a small-fibers neuropathy whose symptoms may pass unrecognised. In the era of disease-modifying therapies, starting a treatment as soon as the disease becomes symptomatic is crucial to prevent disability in patients. Unfortunately, the study of small fibres requires sophisticated tests, which may lead to unnecessary diagnostic delay of such forms. On the other hand, Sudoscan® proved a reliable, non-invasive and fast test to detect early signs of small-fibers neuropathy by measuring electrochemical skin conductance (ESC). In this study, we describe the relation between ESC, traditional nerve conduction studies and functional scores in a population of 18 aTTR patients.

Eighteen aTTR patients referring to our clinic underwent nerve conduction studies at sural, tibial, peroneal, median and ulnar nerves, Sudoscan®, 6-minutes walking test (6MWT) and Neuropathy Impairment Score (NIS). Correlation analyses were run using Pearson's r test between Sensory Nerve Action Potential (SNAP) amplitude, distal latency and conduction velocity, compound Motor Action Potential (cMAP) amplitude, distal latency and conduction velocity, lower limb average ESC, upper limb average ESP, 6MWT and NIS upper limb and lower limb items.

Lower limbs ESC showed a positive correlation with sural nerve SNAP amplitude ($r = 0.842$, $p = 0.004$) and peroneal nerve cMAP amplitude ($r = 0{,}657$, $p = 0.015$) and a negative correlation with sural nerve conduction velocity ($r = -0743$, $p = 0.022$). No significant correlation was found with clinical measures or between upper limb ESC and nerve conduction studies.

Sudoscan® may constitute an alternative hallmark of neuropathy in aTTR patients; however, further studies are needed to prove its role as a marker of clinical severity and progression of disease.

BRENTUXIMAB-VEDOTIN DOSE ADJUSTMENT TO PREVENT DISABLING POLYNEUROPATHY

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Brentuximab Vedotin (BV) is a monoclonal antibody, indicated for treatment of stage III-IV or relapsed/refractory Hodgkin's lymphoma (HL, R/RHL) systemic anaplastic large cell lymphoma (sALCL) and cutaneous T-cell lymphoma (CTCL). Major BV side-effect is the axonal sensory-motor length-dependent polyneuropathy, often severely disabling[2]. We longitudinally followed a cohort of patients treated with BV, monitoring for early signs of polyneuropathy and adapting the drug dosage to reduce the risk of long-term disability. Patients were enrolled at the Hematology and Transplant Center of the University Hospital "San Giovanni di Dio e Ruggi d'Aragona" in Salerno. The inclusion criterion was current treatment with BV. Neurological evaluation (performed at baseline and every 4-6 weeks for 6 months) included: neurological exam, clinical scales (MRC sum score, modified INCAT Sensory Sum Score, DN4 questionnaire) and motor and sensory conduction studies. Reduction of the BV dosage from the planned schedule was performed when a worsening from the previous clinical/electrophysiological picture was detected (20% in two clinical scales score and/or 50% in 2 CMAPs/SAPs values), with cumulative BV dosage unchanged. We consecutively enrolled 9 HL and 1 sALCL patients (age: 41.2±19.3years). 7 patients were treated with poly-immune-chemotherapy and 3 only with BV. Three patients received 1.8 mg/Kg of BV every three weeks and seven 1.2mg/kg every two weeks (time window: 5,6±2.4 months). Distal paresthesia was the most common symptom (80%), whereas neuropathic pain was rarer (20%). Distal hyposthenia was found in 50% of cases, reduced/loss of DTRs in 70%, reduced vibration sense in 50%, pin-prick hypoesthesia in 30%. Nerve conduction study demonstrated a non-significant (<50%) reduction in 60% of CMAPs (especially of peroneal nerve) and in 30% of SAPs. Three patients reduced by 25% of scheduled BV dosage because of a worsening in clinical scales and neurophysiological findings. All patients completed chemotherapy cycles. No patient developed disabling neuropathy. A BV dose adjustment of 25% may be sufficient to reduce the risk of developing moderate-to-severe neuropathy while maintaining the drug's effectiveness on hematological diseases.

EARLY ONSET SENSORIMOTOR AXONAL NEUROPATHY AS SOLE MANIFESTATION OF MITOCHONDRIAL TRIFUNCTIONAL PROTEIN DEFECT

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Pathogenic variant of HADHA and HADHB genes are associated with impairment of mitochondrial trifunctional protein (MTP). MTP deficiency is a disorder of long-chain fatty acid oxidation with different clinical presentations: the neonatal-onset form expressing with severe cardiac phenotype, the infantile-onset form with intermediate hepatic phenotype with metabolic crises and the late-onset form with mild neuromyopathic phenotype. Long-term complications in patients with the intermediate and late-onset phenotypes include peripheral neuropathy and retinopathy.

We report a childhood case of early onset, progressive sensorimotor axonal polyneuropathy, Charcot Marie Tooth 2 (CMT2) phenotype like, associated with two variants of the HADHA gene (maternal p.Tyr724*; and paternal p.Gly319Ser), without metabolic alterations or any other systemic manifestations typical of MTP deficiency.

The patient is a now 13-year-old female girl, presenting with slight delay in postural-motor development and a history of exercise intolerance, clumsiness in fine manipulation and weakness of distal lower limbs. No history of rhabdomyolyses, myoglobinuria, hypoglycemia, cardiomyopathy or other metabolic signs were reported.

Neurological assessment at age 8 years documented distal hypotrophy and weakness, with complete defect of foot dorsiflexion and claw-hands posture. Deep tendon reflexes were diffusely absent. At ambulation she presented stepping gait with equinus-varus-foot and retraction of the achilles tendon. No alterations of creatine kinase, lactate, glycaemia, very low chain fatty acid (VLCFA) and acylcarnitine profile, were described.

Nerve conduction studies at age of 9 years old, showed decreased amplitudes and decreased conduction velocity of both sensory action

potentials and compound muscle potentials with greater impairment in the lower limbs.

A diagnosis of sensorimotor axonal length dependent polyneuropathy was assumed. Next generation sequencing investigation for the most common genetic causes of CMT resulted negative.

To provide further insight into the frequency and characteristics of HADHA related neuropathy, we also performed a literature review of HADHA mutated patients presenting with neuromuscular phenotype in childhood. Less than 30 such patients are described. It is well known that other genes involved in mitochondrial metabolism, such as MFN2 and GDAP1, are responsible of inherited neuropathies.

We suggest considering HADHA in the plethora of genes causing inherited peripheral neuropathy of children since a MTP diagnosis should not be missed, given its potential therapeutic approach.

ANTI-NEUROFASCIN186-RELATED NEUROPATHY MIMICS MILLER-FISHER SYNDROME: A CASE REPORT

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Anti-neurofascin186 (NF186)-antibodies are typically associated to a sensory-motor demyelinating neuropathy with subacute onset, cranial nerve involvement and good clinical response to steroids and intravenous immunoglobulins (IVIg); however, clinical severity may require intensive care. We report an atypical case of anti-NF186-antibodies positivity.

Fixed cell-based assay (CBA) was used to detect anti-NF186 antibodies.

In 2014, a 55-year-old woman presented with acute-onset ataxia. Neurological examination disclosed ophthalmoparesis in every gaze direction, evident gait ataxia and global areflexia. Electroneurography, cerebrospinal fluid (CSF) analysis and blood tests resulted uninformative. Suspecting Miller-Fisher syndrome, the patient was treated with IVIg (2g/kg over 5 days), prompting ataxia resolution but only mild ophtalmoparesis improvement. In 2015, ocular motility deteriorated further, slightly improving after initiation of steroid therapy. Ten years later, the patient experienced bilateral ptosis and diplopia in all gaze directions. Electroneurography revealed mild upper limb sensitive axonal neuropathy, while brain MRI demonstrated hypertrophic oculomotor nerves. Fixed CBA for nodal and paranodal antibodies identified anti-NF186 antibodies positivity. Treatment with IVIg prompted a rapid, but transient, clinical improvement.

We report an atypical case of anti-NF186 antibody positivity with acute onset of predominantly ocular involvement and ataxia, the latter observable at onset only, and subsequent axonal sensory involvement in the upper extremities, in the absence of motor or respiratory symptoms. This case highlights the variety of clinical presentations related to node-paranodopathies and emphasizes the importance of identifying potentially misleading forms early on.

CEREBRAL VENOUS SINUS THROMBOSIS AS THE ONSET MANIFESTATION OF POEMS: A CASE REPORT

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POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell disorder and Skin changes) syndrome is a rare paraneoplastic disease associated with monoclonal plasma cell disorders. Clinical manifestations of POEMS are protean; by definition, all patients have peripheral neuropathy and monoclonal gammopathy (lambda light chain isotype). Additionally, most patients disclose osteosclerotic lesions, Castleman disease, increased serum levels of vascular endothelial growth factor (VEGF) and thrombocytosis. Central nervous system involvement is rare and can include both papilledema and thrombotic cerebrovascular events. We describe a case presenting with cerebral venous thrombosis (CVT) at disease onset.

In 2016 a 35-year-old man presented with an extensive CVT, resulting in the initiation of long-term anticoagulation with Warfarin. In 2020, while still on Warfarin, he experienced a thrombosis of the right iliac femoral artery. In 2018, due to the onset of neuropathic pain in the lower limbs, an electrodiagnostic study demonstrated a demyelinating sensorimotor polyneuropathy, blood tests revealed an IgG lambda monoclonal gammopathy, while CSF examination disclosed hyperproteinorrachia with mirror pattern oligoclonal bands. The patient was diagnosed with CIDP and treated with IV methylprednisolone followed by intravenous immunoglobulin (IVIg) every 2 months.

After the appearance of multiple rapidly growing angiomas on chest and scalp, he underwent a chest CT scan, revealing an osteolytic lesion in the right V rib and vertebral soma of D5. In 2021 he became non-responder to IVIg and was admitted to our department. Neurological examination showed predominant distal weakness, severe hypotrophy at thenar eminence bilaterally and claw hands. POEMS syndrome was suspected. VEGF assay demonstrated a significative increase in VEGF serum levels (1175 pg/ml, ref values 0-200). A diagnosis of POEMS was then made, based on current diagnostic criteria, and the patient underwent heterologous stem cell transplantation (HSCT). Following HSCT, the patient presented both an important improvement in distal muscle strength in all four limbs, and normalization of serum VEGF and monoclonal immunoglobulin levels.

Thrombotic diathesis—particularly deep vein thrombosis and ischemic stroke— is an observed manifestation in the advanced stages of POEMS, despite not being included in the current diagnostic criteria. Our patient, however, presented with CVT at disease onset and was misdiagnosed as CIDP, while the presence of osteosclerotic lesions and monoclonal gammopathy in a young subject should have raised early diagnostic suspicion for this syndrome.

This case highlights the importance of promptly detecting potentially deceptive forms, as early treatment is crucial for long-term prognosis.

WHAT MAINTENANCE THERAPY TO PERFORM IN PATIENTS WITH ANTI-MAG NEUROPATHY AFTER THE FIRST CYCLE OF RITUXIMAB? A COMPARISON BETWEEN TWO REGIMENS

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Rituximab is an effective treatment in myelin-associated glycoprotein antibody polyneuropathy (MAG), nonetheless the definition of a standardized maintenance regime is lacking.

Twenty-nine patients with anti-MAG polyneuropathy who were responsive to a first course of rituximab (375 mg/m2/wk for 4 weeks) were followed for a mean of 8.5 years (range 2-20 years). Two distinct retreatment schedules were adopted: single full course (375 mg/m2/wk for 4 weeks) at the time of clinical relapse (n=20), or single infusion of rituximab (375 mg/m2) whenever the frequency of reemerging CD27+ memory B cells in peripheral blood, as measured with flow cytometry, exceeded 0.05% in the first 2 years and 0.1% thereafter (n=9), as proposed by Kim et al in treatment of Neuromyelitis Optica Spectrum Disorder.

Serum levels of anti-MAG antibodies and IgM class immunoglobulin, and scores obtained in the validated INCAT, MRC, and ISS clinical scales were assessed prior to the first course of rituximab, after nine months, and at the last follow-up.

We compared the assessment scores between baseline and the last follow-up. In the 9 patients treated upon CD27+ reappearance, MRC score remained unchanged in 67%, and improved in 33% (3.8 points mean reduction); ISS score improved in 100% with a mean reduction of 3 points; INCAT score remained unchanged in 22% and improved in 78% (1.6 points mean reduction). Tremor was present at baseline in 6 patients: 83% showed an improvement, while in 17% it remained unchanged. In the 20 patients treated at clinical relapse, MRC score remained unchanged in 45%, worsened in 10% (6.5 points average increase), improved in 45% (1.9 points average reduction); ISS score remained unchanged in 25%, worsened in 35% (1.5 average increase), and improved in 45% (3.3 points mean reduction); INCAT score remained unchanged in 25%, improved in 65% (1.2 points mean reduction), and worsened in 10% (2 points mean increase). Tremor was present at baseline in 70% of patients: 57% improved, and 43% remained unchanged. Overall, patients retreated upon clinical worsening, disclosed an accumulation of disability over tie when compared to the other treatment regimen.

Rituximab represents an established therapy in anti-MAG polyneuropathy. The choice of retreatment method and timing, however, seems unclear. Our results disclose an accumulation of disability in patients treated upon clinical relapse compared to those treated upon memory B cells reappearance, thus favoring the retreatment scheme proposed by Kim in the long-term management of patients with anti-MAG polyneuropathy.

MYELIN PROTEIN ZERO MUTATIONS: CLUSTERS ACROSS ITALY

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To investigate the clinical features of a large cohort of Charcot-Marie-Tooth patients with *MPZ* (myelin protein zero) mutations, focusing on five main clusters across Italy.

We retrospectively gathered a minimal dataset of clinical and neurophysiological information in a series of patients recruited among Italian CMT Registry centers, including type of mutation, disease onset/severity (CMTES-CMT Examination Score), motor/sensory symptoms, and use of orthotics/aids.

We collected data from 185 patients: 60 had the p.Ser78Leu variant ("classical" CMT1B; from Eastern Sicily), 41 the p.Pro70Ser (CMT2I; mainly from Lombardy), 38 the p.Thr124Met (CMT2J; mainly from Veneto), 25 the p.Ser44Phe (CMT2I; from Sardinia), and 21 the

p.Asp104ThrfsX13 (mild CMT1B; from Apulia) mutation. Disease severity (CMTES) was highest in p.Thr124Met patients (9.4±6.6), followed by p.Ser44Phe (7.8±5.7), Pro70Ser (7.6±4.8), p.Ser78Leu (6.1 ±3.5), and p.Asp104ThrfsX13 (1.2±1.5). Disease onset occurred later in the p.Pro70Ser cohort (56.4±5.8) as compared to p.Thr124Met (45.2±9.4) and p.Ser44Phe (41.4±10.9) patients. However, disease progression, both calculated through cross-sectional (rs, Spearman's rank correlation) and longitudinal analysis, was faster in the p.-Pro70Ser cohort (rs=0.81, p<0.001; ΔCMTES/year=0.8±1.0) followed by p.Ser44Phe (rs=0.72, p=0.003; ΔCMTES/year=0.7±0.4), p.Thr124Met (rs=0.43, p=0.024; ΔCMTES/year=0.4±0.5), and p.-Ser78Leu (rs=0.57, p < 0.001; ΔCMTES/year=0.2±0.4) patients. Disease progression was negligible in the p.Asp104ThrfsX13 (rs=0.21, p=0.438; ΔCMTES/year=0.1±0.4) patients, who, however, frequently (78%, p<0.001) complained of neuropathic pain. In the other four clusters, walking difficulties were reported by 69-84% of patients, orthotic aid use ranged between 40-62% (24-52% for AFOs), while walking support devices were used by 16-28% of subjects, with higher frequency in those carrying the p.Ser44Phe (26%) and p.-Pro70Ser (28%) mutations. Hearing loss and pupillary abnormalities were almost exclusive to the p.Thr124Met mutation (47% and 74%, respectively).

Values of motor conduction velocity (MCV) of ulnar nerve were in the demyelinating range in patients with the p.Ser78Leu (23.4±6.7 m/s) amino acid change, intermediate range in those with the p.-Asp104ThrfsX13 (39.8±5.6) variant and axonal range in the p.-Thr124Met (48.3±7.6), p.Pro70Ser (54.8±5.2), and p.Ser44Phe (50.1 ±4.8) cohorts (p<0.001).

This is the largest *MPZ*-related CMT cohort ever collected, reporting the clinical features and disease progression of the five clusters across Italy. Such geographical distribution underlines the importance of always asking patients about the origin of their ancestry to properly address genetic testing. Furthermore, our findings confirm the broad phenotypic heterogeneity of *MPZ* mutations reflecting different pathomechanisms, to date yet largely unknown, and suggest the importance of differentiating between "classical" childhood-onset demyelinating, late-onset axonal, and mild *MPZ*-related neuropathies in clinical prospective studies.

SPLIT HAND SYNDROME IN CHARCOT-MARIE-TOOTH DISEASE TYPE X1 (CMTX1)

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The split hand (SH) syndrome is a dissociated hand atrophy pattern, typically observed in motor neuronopathies, particularly amyotrophic lateral sclerosis, and characterized by predominant wasting in the thenar muscles, with relative sparing of the hypothenar eminence. SH has been also reported in CMTX1 and considered related to a disproportionate involvement of the median compared to the ulnar nerve. We investigated SH in CMTX1 through clinical, neurophysiological, and neuroradiological evaluation.

We gathered a minimal dataset of clinical and neurophysiological data in CMTX1 patients, including hand dominance, disease severity (CMT Examination Score-CMTES), disease duration, strength (MRC) in abductor pollicis brevis (ABP), first dorsal interosseous (FDI) and abductor digiti minimi (ADM) muscles, and median (from ABP) and ulnar (form FDI and ADM) motor nerve conduction study. Clinical SH was defined by both ΔMRC (ADM-FDI)≥1 and ΔMRC (ADM-ABP)≥1. CMAP(ADM)/CMAP(ABP) ratio>1.7 and CMAP(APB)×CMAP(FDI)/CMAP(ADM) (SH Index - SHI)<5.2 defined neurophysiological SH. Neuroradiological atrophy pattern was evaluated using muscle MRI. Statistical analysis was performed through Mann-Whitney U Test, Fisher's exact test, or Spearman's rank correlation (rs), as appropriate.

Overall, we evaluated 13 right-handed CMTX1 patients (8 males, age 38.9±11.1) and 22 hands. All patients (13/13) showed ΔMRC (ABP-FDI)<1, reflecting an equal involvement of thenar eminence: of them 54% (7/13, 5 bilateral, 1 unilateral) and 58% (7/12, all bilateral) had clinical and neurophysiological SH respectively, the latter assessed by both SHI and ADM/ABP ratio. Patients with neurophysiological SH were older (44.6 vs 31.2, p<0.031), had longer disease duration (32.4 vs 10.2, p<0.005), and higher burden of disease (CMTES 12.8 vs 6.7, p<0.045). Males were not more prone to develop neither clinical (40% vs 63%, p=0.592) nor neurophysiological (57% vs 60%, 0=0.962) SH than females. We found a strong correlation between disease duration-SHI (rs=-0.67, p<0.001), CMTES-SHI (rs=-0.62, p=0.003), disease duration-ADM/ABP ratio (rs=-0.77, p<0.001), and CMTES-ADM/ABP ratio (rs=-0.58, p=0.006). MRI detected dissociated atrophy pattern (>in thenar eminence) in 2/2 patients, one of whom had tested negative either for clinical and neurophysiological SH.

More than 60% of CMTX1 patients develop an atrophy pattern in their hands which does not respect nerve trunk innervation as both FDI (ulnar) and ABP (median) are more involved than ADM (ulnar). In CMTX1, this dissociation in hand wasting is independentof sex, increases along with disease duration and severity, and can be detected early by MRI.

A CASE REPORT OF NON-SYSTEMIC VASCULITIC NEUROPATHY: AN UNDERRATED CLINICAL ENTITY?

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Non-systemic vasculitic neuropathy (NSVN) is usually a sensorimotor, asymmetric and painful polyneuropathy commonly related to systemic vasculitis. Cranial involvement is rarely reported.

A 53-year-old woman reports the onset, two years ago, of paresthesia and tactile hypoesthesia in the lower third of the left hemiface. Subsequently, progressive tactile hypoesthesia occurred in the left thigh together with deficit in plantar flexion of the feet, as well as widespread pain at four limbs. At clinical neurological examination severe muscle hypotrophy was observed at the level of the calves and intrinsic muscles of the hands. In her medical history she had undergone a left breast quadrantectomy followed by radiotherapy and tamoxifen therapy from 2015 to 2021. A diagnostic workup was carried out, including lumbar puncture, blood tests and electroneurography. The search for infectious diseases, rheumatology panel, anti-gangliosides and anti-neuronal antibodies revealed only a positive ANA title. Electroneurography showed an axonal sensorimotor polyneuropathy at four limbs. A whole-body PET scan excluded an oncological relapse. The presence of systemic autoimmune disease was not supported by biochemical data. In the suspicion of NSVN, asural nerve biopsy was performed, which revealed a peripheral axonal nerve damage with findings strongly suggestive of a vasculitic etiology. Initially, the patient received high-dose methylprednisolone therapy, which was soon discontinued due to poor tolerability. Methotrexate therapy was then started at a dosage of 10 mg per week, with significant pain relief and moderate improvement in motor impairment at four limbs.

Even in the absence of systemic signs of autoimmune disease, NSVN should be considered in cases of painful asymmetric neuropathies or cranial involvement. In particular, considering its typical clinical course, an accurate differential diagnosis with infectious and paraneoplastic forms is important.

CMT2A-PARKINSONISM SPECTRUM DISORDER AS EXPRESSION OF THE RARE HETEROZYGOUS C.262A>G MFN2 VARIANT: A CASE REPORT

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Mitofusin 2 (MFN2) is a 757 amino acids protein involved in mitochondrial fusion, endoplasmic reticulum stress apoptosis, axonal transport of mitochondria and mitophagy. *MFN2* gene mutations are associated with dominant Charcot–Marie–Tooth (CMT) disease-2A, which is characterized by complex phenotypes, not only including neuropathy-related features but also impairment of the central nervous system (CNS). To date, more than 100 *MFN2* mutations causing CMT2A have been described, preferentially located within the GTPase domain and in the downstream region before the HR1 domain. Even if the main clinical presentation is axonal polyneuropathy, CNS involvement was well described (pyramidal signs, encephalopathy, hearing loss, optical atrophy). Here we report a patient affected by late onset CMT2A due to the rare heterozygous c.262A>G *MFN2* variant.

A 58 year-old man came to our observation for gait impairment with difficulty in climbing and descending stairs, hand tremor, night vision impairment, hyposmia, REM behaviour disorder and hypoacusia. Neurological examination showed difficulty in toe walking due to bilateral hyposthenia of posterior leg muscles and bilateral pes cavus. An extrapyramidal syndrome with bilateral hand rest tremor (right>left), global bradykinesia, right dysdiadochokinesia, sialorrhea and hypomimia were also present. Tactile, nociceptive and vibration sensitivity was normal. Cutaneous plantar reflexes were down-going.

EMG/ENG revealed an axonal, length dependent, mild sensory-motor polyneuropathy with minimal denervation (positive sharp waves and rare fasciculations) in left medial gastrocnemius and tibial anterior muscle. Maximal MUPs recruitment was diffusely reduced especially in leg muscles. Brain MRI showed bilateral frontal-parietal-temporal atrophy. DAT-SCAN demonstrated presynaptic dopaminergic neuron loss. L-DOPA was ineffective. After excluding acquired causes of axonal neuropathy, NGS target sequencing was performed on peripheral blood DNA, using a custom panel specific for peripheral neuropathies. Sequencing analyses revealed the heterozygous c.262A>G variant in *MFN2* gene leading to the amino acid change p.Ile88Val located upstream the GTPase functional domain; this variant has never been described in literature, but it is reported in ClinVar database in a patient manifesting CMT phenotype.

MFN2 is involved in idiopathic PD, in fact pharmacological MFN activation partially reversed the mitochondrial abnormalities in a subset of Parkinson's disease patients. This is a peculiar case of late onset CMT in which axonal neuropathy and parkinsonism coexist in the same clinical spectrum disorder due to a rare MFN2 mutation.

GUILLAIN-BARRÉ SYNDROME IN A PATIENT WITH UNDIAGNOSED CHARCOT-MARIE-TOOTH DISEASE TYPE 1A: WHEN DIAGNOSIS BECOMES COMPLICATED

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Charcot-Marie-Tooth (CMT) is a heterogeneous group of multi-gene disorders characterized by a wide range of progressive motor and sensory neuropathy. Patients with CMT type 1A (CMT1A), the most common subtype, may present progressive gait difficulty with normal life expectancy. Limited evidence documented a possibleassociation between Guillain-Barré syndrome (GBS) and CMT.

A 75-year-old woman was referred for hyposthenia and amyotrophy of both hands, worse on the right, from an unspecified time, that had worsened after an episode of gastroenteritis occurred two months before with accentuation of difficulty in fine movements of the hands and uncertainty while walking. Neurologic examination revealed wasting of hands and feet muscles with flaccid weakness (4-/5 MRC

strength in the hands and 4+/5 inn the flexion-extension of the feet fingers. Reflexes were reduced and the Achilles absent. Sensory examination was normal. Bilateral pes cavus was noted. The ENG-EMG documented a chronic sensorimotor demyelinating polyneuropathy with secondary axonal loss. Serum anti-GD1b IgG were strongly positive, anti-GM1 IgM and IgG antibodies were also positive. Due to the distance from the symptoms worsening and the initial clinical improvement presented by the patient with the established rehabilitation process, diagnostic lumbar puncture and subsequent specific therapy was postponed. Finally genetic analysis was positive for CMT1A. Patient's daughters were also evaluated, one of whom presented pes cavus and chronic sensorimotor demyelinating polyneuropathy on EMG-ENG.

At t 6-months follow-up the patient showed clinical and neurophysiological improvement being able to walk without assistance.

Our case shows a possible occurrence of GBS in a previously undiagnosed CMT. Some authors suggested that CMT1A patients could present myelin structure alterations with abnormal exposure of nervous cell components to immune cells. Further investigations are needed to understand a possible susceptibility to inflammatory damage in CMT1A patients.

DEVELOPMENT OF ALLELE-SPECIFIC GENE-SILENCING SIRNAS FOR MPZ-D61N IN CMT1B

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Introduction: We recently generated a mouse model carrying the D61N heterozygous mutation in the *MPZ* gene, which encodes a structural protein of peripheral myelin. This mutation causes, in humans, a severe early-onset form of CMT1B, characterized by extensive demyelination. This model has been deeply characterized in our laboratory using a sequential protocol including evaluation of motor performance, ultrasonography, magnetic resonance imaging, and whole-body micro-PET imaging to monitor in-vivo the effects of any therapeutic intervention.

Methods: In this study, we investigated the sensitivity and specificity of short-interfering RNA (siRNA) treatment for CMT1B caused by MPZ-D61N heterozygous mutation, using exogenous expression constructs in HeLa cells. A panel of 19 MPZ-D61N-specific siRNAs was assessed by a dual-fluorescent reporter assay and suppression of mutant MPZ expression was confirmed by Western blot. We also plan to perform a rescue experiment using dorsal root ganglia myelinating cultures from $MPZ^{D61N/WT}$ heterozygous mice, which are characterized by severe myelination defects.

Results: Our screening identified several effective inhibitors for the mutant allele, which had no appreciable impact on wild-type MPZ.

Conclusions: Our results will hopefully provide proof-of-principle that allele-specific RNAi has potential therapeutic efficacy for CMT subtypes caused by gain-of-function and dominant-negative mutations.

MYELIN MATURATION DELAY AND ARREST OF AXONAL GROWTH IN CMT1A

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Introduction: Findings accumulated over time show that neurophysiological, neuropathological, and molecular alterations are present in CMT1A and support the dysmyelinating rather than demyelinating nature of this neuropathy. Moreover, uniform slowing of nerve conduction velocity (NCV) is already manifest in CMT1A children and does not improve throughout their life. Interestingly, CMT1A children under 1-year-old have almost normal NCV and structural organization of peripheral nerves comparable to healthy subjects equal in age. Therefore, NCV studies and neuropathological evidence support a defective PNS development in CMT1A likely involving both axon and myelin maturation. To shed light on these issues, and to investigate the relationship among axonal, myelin, and lipidome deficiencies in CMT1A, we extensively analyzed the evolution of both myelin lipid profile and myelinated fibers structure in WT and CMT1A rats.

Methods: We monitored the lipid profile of WT and CMT1A myelin during development from P5 to P365 using mass spectrometry and paralleled lipidomics with extensive quantitative advanced neuropathology to investigate whether CMT1A myelinated fibers experience a structural impairment while growing.

Results: Lipidomic analysis revealed a delayed maturation of CMT1A myelin already detectable at P10 characterized by deprivation of sphingolipid species such as hexosylceramides and long-chain sphingomyelins, whose concentration physiologically increases in WT, and an increase in lipids typical of unspecialized plasma membranes, including phosphatidylcholines and phosphatidylethanolamines. Consistently, advanced morphometric analysis on more than 130.000 myelinated fibers revealed a delay in the evolution of CMT1A axon and myelin geometric parameters, appearing concomitantly with lipid impairment.

Conclusions: Peripheral nerve development is a complex and dynamic process that is twisted at various levels in CMT1A neuropathy. In this study, we demonstrated a remarkable delay of myelin maturation and

an arrest of axonal growth at an immature-like stage in CMT1A. Our results corroborate the dysmyelinating phenotype for CMT1A and envisage CMT1A as a neurodevelopmental disease: in this inherited neuropathy, the PNS is arrested at early development stages and could be equated with that of a child.

CENTRAL AND PERIPHERAL MICROVASCULAR NETWORK IS ABNORMAL IN RATS WITH PAINFUL-CHEMOTHERAPY INDUCED NEUROPATHY: NEW PATHOPHYSIOLOGICAL MECHANISMS OVER THE HORIZON?

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Painful chemotherapy-induced peripheral neurotoxicity (CIPN), with paresthesia, numbness, dysaesthesia and neuropathic pain ranks among the most common dose-limiting toxicity of anticancer drugs. Beside peripheral neurons, for several years considered the only reasonable target for peripheral neuropathy studies, the recent evaluation of the microvascular angiogenesis reveals other important actors in neuropathic pain development and chronicization related to peripheral neuropathy. Many patients develop allodynia and hyperalgesia, experiencing neuropathic pain that originated from a peripheral sensitization then transmitted to the central nervous system where it determines structural and functional changes. An abundant microvascular angiogenesis was described in the primary somatosensory cortex, specifically on the hindlimb projection of rats with neuropathic pain with a compressive origin. To elucidate the relation between chemotherapy-induced neuropathic pain in CIPN and vascular alterations, we evaluated the microvasculature in central and peripheral nervous compartments of rats exposed to neurotoxic chemotherapy.

Rats were chronically treated with PTX 10 mg/kg once a week or with cisplatin 2mg/kg twice a week for 4 weeks to induce CIPN or with their vehicles. Animals were tested for neurophysiological abnormalities and behavioral pain and finally perfused with fixative and/or indian ink before collecting samples. Samples have been analyzed at synchrotron radiation resources by X-ray Phase-Contrast Tomography (XPCT) Imaging. Volume rendering allowed a detailed visualization of vasculature at the sub micrometric scale. A quantitative and morphological analysis of micro-vascular structures in the central and peripheral nervous system was performed. Complementarily, histochemical and molecular evaluations were performed to validate the results.

XPCT analysis revealed that rats exposed to paclitaxel (with painful sensory axonopathy) showed an increased vascular density (putative sprouting angiogenesis) in the crucial districts of the central (somatosensory cortex and lumbar spinal cord) and peripheral nervous system (lumbar Dorsal Root Ganglia and peripheral nerves). However, the complexity of the vascular network and the size of neo-formed vessels were significantly decreased in some specific regions. On the other hand, no significant changes were observed in rats exposed to CDDP (with a painless mild neuronopathy) suggesting a specific involvement of neo-angiogenesis in the development of neuropathic pain. Molecular and immunohistochemical analysis performed on the DRG and S1 cortex confirmed alterations in the expression of genes involved in the angiogenesis.

These results can contribute to shed light on new pathogenetic mechanisms and potential novel therapeutic approaches for neuropathic pain in CIPN.

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ANTI-MAG NEUROPATHY: ELECTROPHYSIOLOGICAL INSIGHTS INTO PATHOPHYSIOLOGY

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Anti-myelin-associated glycoprotein (MAG) neuropathy is a demyelinating neuropathy with a peculiar disproportion between nerve conduction slowing in distal and intermediate nerve tracts resulting in altered Terminal Latency Index (TLI). The pathophysiology of such electrophysiological feature remains unclear although the site of entrapment (e.g. carpal tunnel) might play a role in slowing conduction in anti-MAG neuropathy. Under this assumption, we investigated the median nerve in order to evaluate whether there were differences in the electrophysiological findings recorded distally (through carpal tunnel) from the abductor pollicis brevis muscle (APB) respect to those recorded proximally (outside carpal tunnel) from the pronator teres (PT) muscle.

We recruited 30 subjects (14 anti-MAG patients and 16 sex- and age-matched healthy controls). All anti-MAG patients had $\geq$7000 Buhlmann Titer Unit and subjects with history and signs of carpal tunnel syndrome were excluded. Median nerve responses were recorded from APB (stimulation at wrist and elbow) and PT muscle (stimulation at elbow and arm). Distal motor latency (DML), TLI, compound muscle action potential (dCMAP) and motor nerve conduction velocity (MNCV) were collected.

No significant differences between anti-MAG patients and controls were found for age (65.5$\pm$10.1 vs 67.1$\pm$13.8; p=0.37) and sex (78%

vs 75% of males; p=0.053). By recording from APB muscle, DML resulted longer (9.2±4.2 vs 3.4±0.3; p<0.001), MNCV slower (36.2 ±9.8 vs 52.2±2.4; p<0.001) and TLI lower (0.24±0.04 vs 0.40 ±0.04; p<0.001) in patients respect to controls. By recording from PT muscle, DML resulted longer (3.5±1 vs 2.7±0.3; p=0.012) and MNCV slower (42.4±9.8 vs 60.4±3.7; p<0.001) in patients respect to controls, while TLI was not significant different between the groups (0.71±0.42 vs 0.56±0.07; p:0.448). No difference was noted in CMAP amplitude.

Our data suggest that the disproportionate distal slowing that is typically observed in anti-MAG neuropathy could be influenced by compression at entrapment sites. One might assume that widely spaced myelin as observed in anti-MAG neuropathy might be more susceptible to damage in entrapment sites.

THE COMPLEMENTARY USE OF ULTRASOUND AND ELECTOMYOGRAPHY IN EVALUATION OF PERIPHERAL NERVE TRAUMA

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Background: Peripheral nerve ultrasound is a non-invasive method to provide morphological information on the state of the nerve. Despite the increasing use of it, the current literature presents little data on its diagnostic and prognostic contribution, associated with electromyography (EMG), in peripheral nerve trauma.

Methods: We collected data from patients with post-traumatic bone fracture and a consequent nerve deficit, who were sent by the orthopedic clinic of Trieste January 2022 to December 2023, to receive a neurophysiological study. The evaluation protocol included electroneurography-myography (ENG-EMG) and nerve ultrasound. The ENG-EMG alterations found were classified as follows: undetectable potentials and presence of denervation (pattern 1); detectable low-amplitude potentials and ± denervation (pattern 2). Ultrasound results were categorized into the presence or absence of nerve continuity.

Results: a total of 25 patients (13 males, 12 females, average age 56,5 years) were examined approximately 3-4 months after the trauma. 5 patients underwent osteosynthesis surgery before the analysis. 56% of patients presented pattern 1, 71,4% of which showed continuity of the nerve on ultrasound. The remaining 44% of patients, presented pattern 2, 90.9% of which showed continuity of the nerve on ultrasound.

Conclusions: Referring to pattern 1, in the majority of cases (71.4% of patients) the ultrasound showed continuity of the nerve, despite the EMG results suggested axonotmetic damage. Therefore, Nerve Ultrasound plays a fundamental role, associated with ENG-EMG, in the evaluation of nerve trauma, to acquire a more accurate diagnostic and prognostic results.

DRAMATIC CLINICAL RELAPSES TRIGGERED BY INFECTIOUS EVENTS IN ANTI-CONTACTIN1 AUTOIMMUNE NODOPAHY: A CASE REPORT

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Autoimmune nodopathies (AN) are characterized by heterogeneous onset, sometimes acute in a Guillain-Barré Syndrome (GBS) like manner and sometimes subacute or chronic, similar to a Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). From a clinical perspective, AN are sensory-motor neuropathies characterized by tremors, sensory ataxia, distal weakness and cranial nerve involvement, and respond less to standard immunomodulatory therapies. The disease course can be progressive or relapsing and is usually independent of any external events. Herein we report a case of anti-contactin1 (CNTN1) nodopathy characterized by relapses during infections.

In 2020 a 35-years-old man developed lower limbs weakness associated with pain and unsteady gait, with acute onset. Electroneuronography demonstrated a demyelinating sensory-motor neuropathy in the four limbs. Cerebrospinal fluid (CSF) analysis showed an albuminocytological dissociation. Serum test for antiganglioside antibodies was unremarkable.

A diagnosis of GBS (acute inflammatory demyelinating polyneuropathy – AIDP) was made and treatment with intravenous immune globulin (IVIg) was started with prompt recovery. A few months later a clinical relapse was observed, leading to the diagnosis of acute onset CIDP (A-CIDP). A treatment regimen with periodic cycles of IVIg and corticosteroid was set up, with partial clinical response. Serum test for nodal/paranodal antibodies was positive for CNTN1 antibodies, and treatment with Rituximab was started with full benefit. In 2022, after a paucisymptomatic SARS-COV-2 infection, the patient developed a severe relapse that led to hospitalization. He was treated with plasmapheresis followed by a course of oral corticosteroids with immediate recovery. Serum immunophenotyping demonstrated a depletion of CD27 B memory cells. After a period of symptoms remission, a new dramatic relapse was observed, characterized by severe weakness in lower limbs (the patient was unable to walk), occurring after an episode of hyperpyrexia with flu-like and urinary symptoms. A course of plasmapheresis and methylprednisolone IV in association with rehabilitation led to a full recovery.

This case describes an anti-CNTN1 nodopathy with relapsing-remitting course triggered by infections. Infections are known to

influence the course of some autoimmune diseases, either by acting as a trigger factor at onset or by participating in symptoms relapse. A relapsing-remitting course during infections has been previously reported in other autoimmune neuropathies, in relation to several possible mechanisms: nerve conduction abnormalities due to the induction of cytokine release by viral infection, the development of a direct viral neuritis, or an aggravation of sodium channel dysfunction at the level of the nodes of Ranvier. Further studies are needing to clarify these findings.

TRANSLATION OF PACLITAXEL-INDUCED PERIPHERAL NEUROTOXICITY FROM MICE TO PATIENTS: THE IMPORTANCE OF MODEL SELECTION

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Paclitaxel-Induced Peripheral Neurotoxicity (PIPN) is a potentially dose-limiting side effect in anticancer chemotherapy. Several rodent models have been proposed to reproduce PIPN, but their results are sometimes difficult to be translated into the clinical setting. We compared with an extensive multimodal approach two widely used PIPN models characterized by marked differences in their experimental design.

For the experiment, female C57BL/6JOlaHsd mice were treated only with paclitaxel vehicle (n. = 38), paclitaxel via intravenous injection (n. = 19, 70 mg/kg) once a week for 4 weeks (Study 1) or intraperitoneally (n. = 19, 10 mg/kg) every 2 days for 7 times (Study 2). At the end of treatment and after a 4-week follow-up period, mice underwent behavioral and neurophysiological assessments of PIPN. At the same time points part of the mice were sacrificed and dorsal root ganglia, skin, sciatic and caudal nerves samples were collected for pathological examination. Serum neurofilament light (Nfl) levels were also measured. The differences in the neurotoxicity parameters were analyzed using a nonparametric Mann-Whitney test, with significance level set at $p<0.05$.

Study 1 showed significant and consistent behavioral, neurophysiological, pathological and serological changes induced by paclitaxel administration at the end of treatment, and most of these changes were still evident after the follow-up period. By contrast, the Study 2 evidenced only a transient small fiber neuropathy, associated with neuropathic pain.

Our comparative study clearly distinguished between a PIPN model that very closely reproduce all the clinical features of the human condition, and a model showing only a small fiber neuropathy with neuropathic pain induced by paclitaxel.

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USEFULNESS OF AUTONOMIC TESTING IN CLINICAL PRACTICE: THE EXPERIENCE OF TRIESTE

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Background: Autonomic testing is a simple and non-invasive method to evaluate the function of Autonomic Nervous System (ANS), although not often used. Aim of this study was to examine our case history in order to evaluate its real diagnostic contribution in the clinical setting.

Methods: The autonomic testing protocol, performed in our neurophysiology clinics, consists in three tests to evaluate the Parasympathetic function: 30.15 (immediate standing), Deep Breathing and Valsalva Ratio; two tests to evaluate Adrenergic Sympathetic function: Standing Blood Pressure (BP) and Sustained Handgrip BP; and the Sympathetic Skin Response test (SSR) to evaluate the Cholinergic Sympathetic function. We collected the autonomic exams performed in our clinic from March 2021 to December 2023 and divided the clinical questions into three macro-categories: Parkinsonism or suspected MSA (multiple system atrophy), suspected Small Fiber Neuropathy (SFN) and Syncope / loss of consciousness (LOC) of undefined diagnosis.

Results: A sample of 36 adult patients (17 males and 19 females; average age 57 years) were considered. A selective alteration of the Parasympathetic ANS (73% of cases) was found in the 11 patients with Parkinsonism o suspected MSA. In the 5 patients with suspected SFN, alterations in the adrenergic ANS were detected in 60% of cases and only in one case also in the cholinergic ANS. Finally in the 20 patients with Syncope or LOC, the Parasympathetic ANS was found to be the most affected by alterations (50% of cases).

Conclusions: Our data confirm the relevant information provided by Autonomic Testing in the diagnostic process of selected patients.

GUILLAIN-BARRÉ SYNDROME: IS ELECTROPHYSIOLOGICAL SUBTYPE CLASSIFICATION USEFUL IN THE CLINICAL MANAGEMENT?

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Current European guidelines on Guillain-Barré Syndrome (GBS) advise supporting the diagnosis with neurophysiological techniques, but state that electrodiagnostic partition into acute inflammatory demyelinating

polyradiculoneuropathy (AIDP) and acute motor (or sensory-motor) axonal neuropathy (AMAN or AMSAN respectively) is not helpful in management nor treatment of the condition. However, axonal subtypes that present with reversible conduction failure (RCF), which is a transient conduction slowing due to nodal/paranodal dysfunction resembling demyelination, have a better prognosis than those with axonal degeneration occurrence[1].

We revised the neurophysiological studies conducted on patients with a clinical suspect of GBS, performed in the Neurology Clinic of Trieste between 2018 and 2024, and re-classified the diagnoses according to the criteria proposed by Uncini and colleagues[2], with particular attention on the mechanisms in place in the axonal subtypes.

Forty-five patients were taken into consideration, for a total of 97 studies. Thirty-two patients (71% of the total) received an electrodiagnosis of GBS confirming the clinical suspicion. Among them, based on Uncini et al. classification criteria, 15 (47% of GBS-confirmed patients) were categorized as AIDP, 7 (21.8%) as axonal - of which 2 (6%) as AMAN and 5 (16%) as AMSAN - 1 (3%) as unexcitable, and 9 (28%) as equivocal. The percentage of axonal subtypes matches the frequency observed in another Italian center[3], while demyelinating subtypes align with the slightly lower frequency in European cohorts, in favor of a higher amount of equivocal studies in our analysis. Among the patients with axonal involvement (AMAN or AMSAN), all 7 (100%) show axonal degeneration, and 2 (40%) show RCF in the second study.

Even though current guidelines do not valorize the GBS subtypes, the classification criteria set proposed by Uncini et al. could help us give patients a more accurate prognosis about disease progression and recovery time, shed light on the etiopathology of the disease and possibly assist in personalize treatment according to the degree and quality of the nerve impairment.

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HEAD DROP (HD) IN NEUROLOGICAL DISEASES: AN OVERVIEW

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Introduction Dropped head syndrome (DHS) is defined by weakness of neck extensor muscles against gravity with or without weakness of neck flexor muscles. It can be an isolated clinic entity presenting with difficulty raising the head or it can be part of the generalized neurological diseases. Despite DHS is a possible clinical manifestation of many diseases, it remains a relatively rare condition and little is known about the differences between the presentation in different clinical entities.

Materials and Methods We retrospectively analyzed patients who came to Policlinico San Martino from 2003 to 2017 and then identified 35 patients (17F and 18M) who presented head drop. For each patient we described demographic data, clinical presentation and diagnosis and then we compared all the data.

Results We found 16 patients with Miastenia Gravis (3 with Ab AchR positivity, 3 with thymoma and 1 with extrapyramidal symptoms), 6 patients with amyotrophic lateral sclerosis (ALS) (1 with paraneoplastic syndrome), 8 patients with extrapyramidal signs (1 who developed motoneuron involvement over the time, 3 with atypical parkinsonism and 4 with Parkinson disease), 4 with muscular disease (2 myotonic dystrophies, 1 hyperkalemic miopathy and 1 axial myopathy) and 1 patient with scleroderma. The average age at symptoms onset was 67 years (range 14 to 87 years). Drop of the head was the first symptom in 54% of patients (9F and 10M) while the other patients developed this sign after averagely 42 months (range 0.5 to 156 months). Neurophysiological data were available in 57% of patients.

Conclusions Despite DHS is a manifestation of various neurological and neuromuscular entities, this is a relatively rare condition and there isn't a validated marker to distinguish between the two. Medical history, symptoms trend over the time, physical examinations and, most of all, investigations are all important tools to lead to a correct diagnosis. The future aim of our study is to characterize the different kind of DHS using neurophysiological and imaging data.

QUANTITATIVE MUSCLE ULTRASOUND IN THE EVALUATION OF RADICULOPATHY

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Lumbosacral radiculopathy represents a clinically significant condition that requires careful evaluation and management. This study investigated the utility of quantitative muscle ultrasound in the analysis of radiculopathy.

Twelve patients suffering from unilateral L4 or S1 lumbosacral radiculopathy underwent clinical and neurophysiological evaluation with needle electromyography and quantitative muscle ultrasound. For the latter, both the gray scale and the gray level co-occurrence matrix

(GLCM) were used. The ultrasound evaluation was performed on the muscle linked to the root damage (tibialis anterior for L4, gastrocnemius medialis for S1). In each patient, the ultrasound-assessed muscle was compared with the same contralateral muscle. The neurophysiological severity was classified in three degrees on the basis of the voluntary recruitment. The numerical ultrasound data of the two sides were compared using a non-parametric test for paired samples, while a comparison of the ultrasound data among the three electrophysiological severity groups was evaluated with a non-parametric test for more independent samples.

In the examined patients, no acute denervation potentials were observed. Seven patients presented S1 damage, five patients showed L4 damage. Concerning the electrophysiological severity, low level was present in three and medium level in five. The affected muscles showed a significantly greater level of whiteness, i.e. greater echogenicity, compared to the contralateral muscle. Significant differences were also detected in the parameters contrast and correlation levels, calculated through GLCM. The results also highlighted a strict relationship between neurophysiological damage and ultrasound. The level of echogenicity and the changes in the GLCM parameters were consistent with the neurophysiological severity.

These findings suggest the usefulness of quantifying muscle ultrasound as a monitoring tool and in supporting rehabilitation decisions in the management of L4-S1 lumbosacral radiculopathy. The ability to perform a real-time assessment of muscle alterations can provide fundamental information for optimal management of patients suffering from this pathology and to better define the most suitable rehabilitation protocol.

THE USE OF CHATGPT FOR THE DEVELOPMENT OF PATIENT-REPORTED QUESTIONNAIRES. THE EXAMPLE OF CHARCOT-MARIE-TOOTH DISEASE

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During the last year, chatbots based on artificial intelligence have invaded the world with a high impact in every field of life, including medicine. Among them, ChatGPT is showing promising results. Different applications of this tool have been proposed, especially to support doctors' training and clinical valuation. Our research explores the effectiveness of ChatGPT in creating questionnaires for evaluating patients with Charcot-Marie-Tooth (CMT).

We asked ChatGPT to produce a list of questions in the Italian language and able to assess the disability in CMT. The request aimed to create a patient-reported questionnaire. ChatGPT produced different but consistent questions, where increasing severity was translated with an increase in the numerical value of each individual response. Data explored different aspects, including demographic information, pain and tenderness, fatigue, disability, and access to care. Ratings were based on multiple choice and yes/no questions. However, human intervention was necessary to summarize the questionnaires and obtain a complete version that was free from redundancies and adequate for calculating the final score. For the latter, the values of the individual items were added together, except for those relating to access to care. The questionnaire was administered to 15 patients with CMT, and internal consistency was calculated. Finally, the final score was compared with the CMT Examination Score (CMTES) in these patients, and a correlation analysis was performed through the Spearman test.

The patients were able to complete the questionnaires without difficulty. The internal consistency of the questionnaire generated by ChatGPT was high (Cronbach's alpha > 0.9), and it highlighted a good correlation with CMTES ($r = 0.82$).

The study highlights not only the potential of ChatGPT as a medical support tool but also the importance of human intervention in data synthesis and interpretation. Furthermore, the interest shown by ChatGPT in evaluating access to care is significant. The evaluation of this latter data, although little attention is given by routine clinical questionnaires, should also enter medical practice due to the possible management and economic implications of taking care of patients suffering from CMT and other rare diseases.

CRITICAL ILLNESS MYOPATHY AND NEUROPATHY IN PATIENTS AFFECTED BY SEVERE ACQUIRED BRAIN INJURY: EPIDEMIOLOGY, RISK FACTORS AND CLINICAL DETECTION. A SINGLE CENTER STUDY

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Critical Illness MYopathy and NEuropathy (CRIMYNE) is a neuromuscular disorder acquired in the intensive care unit (ICU) in critically ill patients, characterized by diffuse muscular weakness and difficulty in weaning the patient from mechanical ventilation.

In patients with severe acquired brain injury (sABI), the coexistence of neurological conditions, such as coma and/or muscle weakness due to central nervous system damage, may complicate the diagnosis of CRIMYNE.

The aim of this study is to assess the prevalence of CRIMYNE in sABI patients admitted to our Neurorehabilitation Unit, identify the risk factors for CRIMYNE in this type of patient, and define the sensitivity and specificity of the clinical assessment in the diagnosis of CRIMYNE in sABI patients.

This is an observational study on sABI patients hospitalized at our Neurorehabilitation Unit. Demographic and clinical data were

collected. Each patient has been evaluated for clinical signs suggestive of CRIMYNE: bilateral hypoareflexia, bilateral paresis/plegia, bilateral hypo/atony, bilateral muscular hypo/atrophy. Patients underwent the neurophysiological study looking for the presence or absence of spontaneous activity in four muscles of the four limbs. The examination was considered suggestive of CRIMYNE when spontaneous activity was revealed in at least three muscles or in two muscles of the contralateral limbs. The prevalence of CRIMYNE was calculated. We calculated the sensitivity and specificity of the clinical signs when at least one, two, three, or four of them were present.

One hundred and four patients were included, and a neurophysiological diagnosis of CRIMYNE was made in 21 patients, with a prevalence of 20%. We found a statistically significant association between the intubation time and CRIMYNE (p 0.005) and between hyperglycemia and CRIMYNE (p 0.047). None of the single clinical signs were more sensible and/or specific than the others. The best relationship between sensitivity and specificity occurred in the presence of two of the four clinical variables (sensitivity 95%, specificity 71%).

Our findings suggest a high prevalence of CRIMYNE in sABI patients, and a simplified neurophysiological protocol could be useful for all patients admitted to rehabilitation units. Assuming that this approach is not easily sustainable, we checked the validity of a set of clinical signs in the diagnosis of CRIMYNE. It could be suggested to limit the neurophysiological study to patients who present with two of the four proposed clinical criteria or, if neurophysiological service is not available, to strongly suspect CRIMYNE based on the clinical pattern.

INVESTIGATING LOSS OF REPLICATION FACTOR COMPLEX SUBUNIT 1 (RFC1) FUNCTION IN CANVAS PATIENTS AND HETEROZYGOUS AAGGG EXPANSION CARRIERS

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CANVAS is a recessively inherited condition caused in most cases by biallelic AAGGG expansions in RFC1. Despite the recessive mode of inheritance, RFC1 transcript or protein expression appear unchanged. Yet, the identification of compound heterozygous null variants causing CANVAS suggests a role of RFC1 function in the disease pathogenesis. Here we show that pathogenic AAGGG expansions form stable nucleic acid structures compatible with G-quadruplexes in vitro and lead to transcription inhibition in vitro and in reporter assays in a repeat-length-dependent manner.

We confirmed that RFC1 transcript and protein expression are preserved in bulk post-mortem cerebellar tissue and IPSC neurons. Also, long-read RNA sequencing did not show changes in RFC1 transcript processing or splicing. Nonetheless, patient-derived lymphoblasts showed increased susceptibility to DNA damage, exhibiting reduced survival and earlier activation of apoptosis when treated with the DNA-damaging agents cisplatin or oxaliplatin. Furthermore, we found that neuron-specific knockdown of gnf1 - the fruit fly RFC1 ortholog - led to decreased survival, progressive motor impairment, and increased neuronal DNA damage in adult flies, and that these phenotypes were exacerbated by cisplatin treatment. Because of the known toxicity of platin on sensory neurons and given the key role of RFC1 in DNA damage repair, we speculated that AAGGG expansions might increase the susceptibility to chemotherapy-induced neuropathy in humans. Indeed, in a multicenter cohort of subjects who received oxaliplatin for an underlying neoplasm, heterozygous RFC1 expansion carriers showed an increased risk of developing severe neuropathy compared to non-carriers (25/34, 73% vs. 172/336, 52%, $p = 0.01$).

Although the exact mechanisms causing the selective neuronal loss in CANVAS remain unknown, our in vitro, fruit fly, and human data suggest that RFC1 function is relevant to the disease pathogenesis and that treatment with DNA-damaging agents may unmask a hypomorphic effect of AAGGG expansions.

AMINOLEVULINIC ACID DEHYDRATASE PORPHYRIA: A ULTRARARE EARLY-ONSET AXONAL NEUROPATHY

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Delta-aminolevulinic acid dehydratase (ALAD) deficiency porphyria (ADP; OMIM 612740) is the rarest acute hepatic porphyria. Deficiency of ALAD, which catalyzes the second step of heme biosynthesis, leads to the accumulation of the toxic porphyrin precursor ALA. ADP has a chronic course punctuated by acute attacks characterized by variable gastrointestinal, cardiovascular, and neurological manifestations. Only eight cases were reported worldwide.

We report the clinical, electrophysiological, and genetic findings of two siblings with ADP.

The two patients, aged 7 and 14 years, were born to consanguineous Moroccan parents. Their older sister had a severe intellectual disability (ID), axonal neuropathy, hypertension, and cyclic vomiting and died of renal and respiratory failure at the age of 10 years. Both presented with developmental delay and hypotonia due to axonal motor polyneuropathy. The younger girl was found to have moderate ID, and both had sensorineural hearing loss. From the ages of 5 and 12, respectively, they experienced recurrent acute neurovisceral crises defined by a range of autonomic, peripheral, and central manifestations. These included abdominal pain, nausea, vomiting, hypertensive crises necessitating intensive care, progressive weakness requiring wheelchair use and respiratory support, and severe drug-resistant neuropathic pain. The older brother also experienced depression, hallucinations, and severe sleep disorders. After each neurovisceral crisis, there was a partial improvement in clinical and neurophysiological findings. Whole exome sequencing analysis identified a homozygous ALAD variant (p.Arg147Leu) along with a PEPT2 polymorphism (p.Leu350Phe) reported to influence the severity and prognosis of porphyria-associated kidney disease. Interestingly, a homozygous PCDH15 variant (p.Leu1603Phefs*11) was also detected, possibly causing sensorineural hearing loss. Combined therapy with heme arginate and hydroxyurea to reduce the erythroid heme pathway significantly reduced protoporphyrins without reducing ALA, the metabolite responsible for the attacks, which remained frequent and severe. The new RNA inhibitor of ALAS1, Givosiran, recently approved by the FDA and effective in other porphyrias, was discontinued because it appeared to contribute to triggering attacks. Recently, using plasmaexchange or erytroexchange helped to resolve the acute attack as it resulted in a significant, albeit temporary, reduction in urinary ALA.

ADP should be considered in patients with triadic abdominal pain, neuropathy, and neuropsychiatric symptoms. Neuropathic signs can vary from focal neuropathy to acute or subacute axonal polyneuropathy with progressive quadriparesis, dysautonomia, and respiratory failure mimicking Guillain-Barré syndrome. Unfortunately, givosiran was not effective in treating or preventing attacks in these patients. However, combined treatment, including heme arginate, hydroxyurea, and plasmaexchange/erytroexchange, can prevent further neurological morbidity and mortality.

THE ROLE OF THE SYMPATHETIC SKIN RESPONSE TO DISCRIMINATING EARLY DISAUTONOMIC IMPAIRMENT IN IDIOPHATIC PARKINSON'S DISEASE AND ATYPICAL PARKINSONISMS

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Alpha-synucleinopathies are a class of neurodegenerative diseases characterized by misfolded α-synuclein aggregates, leading to clinically distinct disorders based on cellular location and pattern of deposition. Autonomic nervous system dysfunction is characteristic of synucleinopathies and can occur at all stages of the disease course. It can even be a prodromal marker.

We investigated the autonomic system (ANS) impairment in a cohort of 26 patients, 14 with idiopathic Parkinson's disease (iPD), 6 with multiple system atrophy (MSA), and 6 with dementia with Lewy bodies (DLB), using sympathetic skin response (SSR) and comparing naïve, not treated, and treated patients during the course of the disease (<1 year vs. >1 year from diagnosis).

Patients were consecutively enrolled and assessed by an extensive examination, including a neurological exam, the administration of disease-specific scales (i.e., MDS-UPDRS for iPD and DLB, UMSARS for MSA), and the scale for autonomic symptoms (SCOPA-AUT). In addition, age-matched healthy controls (HC) were enrolled. The exclusion criteria for both patients and HC included any condition potentially interfering with the ANS response. The SSR study was performed under resting conditions. The recording methods are the conventional ones used in clinical practice. The response to four different stimuli (electric, sound, pain, and the Valsalva maneuver) was evaluated. The response latency was indicated by the first continuous deflection from the baseline. Absent responses were defined when no consistent change from the baseline was observed. Asymmetric response was defined as a greater than 30% difference between the right and left sides. Statistical analysis was conducted by a t-student test for paired variables.

In our iPD cohort, we found an asymmetric impairment with increased latency and reduced amplitude, corresponding to the most affected clinical side. Otherwise, there was no clear asymmetry in MSA and DLB patients. In all patients' groups, however, a length-dependent pattern was found with a worse response (amplitude and latency difference of 50% or greater) in the lower limbs. In addition, patients with absent SSR displayed worse scores on specific clinical scales and SCOPA-AUT.

Our results highlight that autonomic dysfunction is length-dependent and strictly correlated to the severity of motor symptoms in

α-synucleinopathies, especially in iPD patients. In addition, our findings suggest that the presence of an asymmetric dysfunction could be an early marker to distinguish iPD from atypical parkinsonisms. As a future perspective, we intend to perform serial clinical and neurographic follow-up on our patients to find potential specific SSR patterns suggestive of certain phenotypes and prognosis.

AN AGGRESSIVE DEMYELINATING NEUROPATHY MIMICKING CHARCOT-MARIE-TOOTH DISEASE

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Neuronal Intranuclear Inclusion Disease (NIID) is an autosomal dominantly inherited neurodegenerative disorder linked to a GGC triplet expansion in the 5' non-coding region of the NOTCH2NLC gene. Adult-onset NIID presents diverse clinical manifestations, ranging from a predominant peripheral to a predominant central nervous system phenotype, and has been mainly described in subjects of East Asian origin. Age of onset has been reported to inversely correlate with repeat size, with the highest GGC counts associated with the so-called muscle weakness-dominant phenotype, primarily characterized by a demyelinating neuropathy.

This report describes a case of NOTCH2NLC-associated muscle weakness-dominant NIID in Italy.

In the proband, symptoms began at age 49, with distal lower limb weakness extending to the distal upper limbs within a year. Hand action tremors appeared at age 51, followed by bilateral hearing loss. Hoarse voice, dry cough, and dysphagia emerged at 53, while lightheadedness, constipation, and urgency developed at 54. Family history unveiled similar symptoms in six other members; notably, two cousins had been diagnosed with an atypical, aggressive demyelinating Charcot-Marie-Tooth disease (CMT) and had died 1-2 decades after onset due to dysphagia and respiratory insufficiency. At age 57, our patient exhibited mild facial weakness, bilateral hearing loss, wide-based stance, clumsy gait, a positive Romberg sign, prominent action tremor, distal limb weakness/atrophy, absent DTRs, non-length-dependent pain and touch sensory loss, and mild vibration sensory loss in the lower limbs. Electroneuromyography revealed a predominantly demyelinating sensorimotor neuropathy. The somatosensory evoked potentials showed a prolonged central conduction time; motor, visual, and retinal evoked potentials were normal. Autonomic tests revealed cardiovascular dysautonomia with orthostatic hypotension. Neuropsychological assessment uncovered long-term verbal memory impairment and disinhibition, despite an overall normal MoCA score. MRI showed minimal cerebral and cerebellar atrophy. A CMT gene panel and whole exome sequencing yielded negative results in the cousins. Eventually, NOTCH2NLC gene analysis revealed a heterozygous pathogenic GGC expansion.

NIID should be considered in the genetic workup of patients presenting with a CMT-like phenotype characterized by a predominantly demyelinating sensorimotor neuropathy, especially if they exhibit an aggressive disease course and develop bulbar symptoms, autonomic dysfunction, and CNS involvement. The GGC expansion in NOTCH2NLC should be specifically sought, as standard sequencing methods fail to detect it.

HETEROGENEOUS REAL-LIFE STRATEGIES IN THERAPEUTIC APPROACH OF CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

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Introduction: The European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guidelines for CIDP provide some general recommendations regarding therapeutic management, but uncertainty remains on several aspects related to the therapeutic strategy. This uncertainty is likely to be reflected in the heterogeneity in the choices of different centers regarding therapy in CIDP. Observational studies can address real-world questions such as the real-life patient pathways from diagnosis to and through treatment. This can generate a wide description of the existing unmet medical needs in CIDP, helping to identify areas where evidence-based recommendations are needed.

Methods: A comparative analysis was conducted, examining therapeutic strategies in 533 CIDP patients from tertiary referral centers included in a large national database.

Results: Intravenous immunoglobulins (IVIg) and steroids emerged as the most commonly used first-line therapies, with variability among centers ranging from 0 to 78% and from 0 to 79%, respectively. Plasma exchange was used as a first-line therapy in only 6% of the patients, with figures ranging among centers between 0 and 40%. A non-negligible proportion of patients (8%) received combined first-line therapy with IVIg and steroids or (2%) monotherapy with immunosuppressants. Overall use of immunosuppressant agents ranged from 0 to 60%, with differences among centers in their indication and choice of the specific immunosuppressor. The use of subcutaneous immunoglobulin ranged from 0 to 56% (mean 22%) and was associated with clinical worsening in 7% of the patients. Out of the initial 533 patients, 120 (22.5%) did not respond to first-line therapy, decreasing to 24 (4.5%) after the second line and 13 (2.5%) after the third. Overall, only 13 (2.5%) patients did not respond to treatment after undergoing a mean of 3 treatment lines (range 2–6). There were no distinctive features between responder and non-responder patients besides more frequent ataxia at onset and greater disability at enrollment.

Discussion: Considerable heterogeneity in CIDP treatment strategies exists among different centers, highlighting the need for studies aimed at better defining and individualizing therapeutic approaches. While current treatments yield clinical responses in the majority of patients, it seems that relying solely on clinical data may not be adequate for identifying treatment responders. Enhanced understanding of disease pathogenesis and the identification of biomarkers indicative of treatment response are likely essential steps toward achieving precision medicine in CIDP.

MULTIFOCAL MOTOR NEUROPATHY, MYASTHENIA GRAVIS, AND ANTI-GBM NEPHRITIS: OVERLAP AUTOIMMUNE SYNDROMES IN ONE PATIENT

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Objectives: Multiple autoimmune diseases are common in patients with a chronic autoimmune disease and are known as "multiple autoimmune syndrome". Rarely, autoimmune disorders may present with simultaneous onset triggered by different factors in genetically predisposed subjects. We present a case of the sudden onset of three autoimmune disorders: anti-GBM nephritis, Myasthenia Gravis (MG), and Multifocal Motor Neuropathy (MMN).

Case report: A 69-year-old man was hospitalized in our Neurology Department due to the subacute onset of tetra-hyposthenia, dysphagia, ptosis, and ophthalmoparesis. Nerve conduction studies showed peripheral motor trunk neuropathy with conduction blocks, while single-fiber EMG was suggestive of an altered neuromuscular junction. Screening tests for autoimmunity displayed positivity for ARAB, anti-GBM, ABTG, ABTPO, and ANA antibodies. The chest CT scan was normal, ruling out thymoma.

In a few days, a worsening in his clinical picture associated with an increase in gamma globulin and nonselective proteinuria was observed. The patient was admitted to the intensive care unit due to respiratory failure. Intravenous Ig were administered twice, with complete remission of the nephritic syndrome and progressive motor recovery. Steroids and azathioprine were started as maintenance therapy.

Conclusions: The concomitant occurrence of membranous glomerulonephritis and MG has been sporadically reported, usually associated with thymic pathology. In this case, the patient also presented with MMN without a putative trigger, suggesting a shared underlying immune mechanism involving autoantibodies, complement activation, and T cells.

FLUID BIOMARKERS OF ONSET AND DISEASE PROGRESSION IN ATTR-PN

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Introduction: The main tools for diagnosing and monitoring ATTRv-PN are neurophysiological studies. Nonetheless, these markers proved ineffective in monitoring the disease's progression, both in terms of a patient developing symptoms and assessing the treatment response.

Materials and Methods: In this study, we examined, using SIMoA, a Quanterix's digital biomarker detection technology, the potential role of serum total tau protein and neurofilament light chain (NfL) as biomarkers for early diagnosis and neurodegeneration in ATTRv-PN. We carried out a single-center observational, prospective, longitudinal study on 30 ATTRv patients and 10 carriers, including patients harboring four different mutations.

Blood samples were collected at 0, 6, and 12 months from healthy control, presymptomatic, and symptomatic subjects. The FAP stage, PND score, NIS-LL, and CADT were also performed. All patients were under treatment with stabilizers or RNA therapies.

Results and Conclusions: The results of our study support NfL potential as a clinically useful biomarker in ATTRv-PN. On the other hand, tau protein levels rose in parallel with the disease progression, without a direct correlation trend.

GAIT ANALYSIS IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: A VALUABLE TOOL IN CLINICAL PRACTICE

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated disorder clinically characterized by relatively symmetric proximal and distal weakness, reduction or loss of deep tendon reflexes and distal sensory disturbances. Gait impairment is evident in almost all patients.[1] Multiple factors contribute to such impairment, especially loss of proprioceptive information and muscle weakness of the lower limbs. Gait analysis (GA) is is a simple-to-perform, three-dimensional tool that provides a quantitative measure of human gait. It allows quantification of a series of measurable parameters and their interpretation provides a close-up and faithful picture of patients' clinical gait conditions. The aim of this work is to analyze the gait pattern of CIDP patients and correlate the data obtained with clinical scales and electrophysiological data.

Eight CIDP patients (seven male, one female; mean age: 63±7.2-years) fulfilling EFNS criteria[2] were recruited. Exclusion criteria were: concomitant diseases that affect walking performance, need of a crutch to walk. We performed clinical evaluation, nerve conduction study, several clinical scales, including Medical Research Council (MRC) sum score, Inflammatory Neuropathy Cause and Treatment (INCAT) disability score, Sensory sum score (SSS), Overall Neuropathy Limitation Scale (ONLS), and walk and swing analysis using BTS Gait Analysis system.[3]

Higher SSS was associated with with several balance-related gait alterations (i.e. reduced velocity and step length, reduced swing phase and increased stance phase). Reduced MRC sum score correlated with several gait parameters (i.e. increased stance phase, double support time and reduced swing phase), specifically associated with dynamic stability domain. When analyzing swing features with closed eyes, increasing swing parameters correlated with SSSand disability scores (ONLS and INCAT disability score). No significant correlation was found between electrophysiological parameters and gait variables. However, correlations between increased antero-posterior center of pressure (COP) displacement (a measure of reduced balance) and reduced amplitude of compound muscle action potential (CMAP) from lower limb nerves (peroneal and posterior tibial) were found.

Our data showed that sensory impairment at clinical evaluation (SSS) correlated with standing balance (sway), whereas dynamic stability during the gait cycle was inversely correlated with muscle strength (MRC sum score). Furthermore, increased sway parameters (with closed eyes) correlated with clinical disability (ONLS and INCAT disability score). GA could represent an objective, non-invasive and reproducible method providing additional data to the clinical evaluation and closely following the patient gait disability. Electrophysiological parameters were not correlate with any clinical scales, seeming unsuitable to follow clinical disability. Limitations of our study were: small number of patients and the recruitment of patients able to walk unassisted.

LONG TERM CLINICAL AND ELECTROPHYSIOLOGICAL OUTCOME IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY PATIENTS: A SINGLE CENTER EXPERIENCE

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Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) is an immune-mediated disorder characterized by damage of the myelin sheath of peripheral nerves. CIDP can exhibit a heterogeneous clinical presentation, with symptoms ranging from mild to severe.

Immunomodulatory therapies can avoid progressive course and disability burden. The aim of this study was to explore the long-term clinical and electrophysiological outcome of CIDP patients. We enrolled 34 CIDP patients followed at Federico II University of Naples between 2010 and 2024. We collected clinical data including gender, age at onset, disease duration, CIDP subtype (typical *vs* variants), treatment (scheduled maintenance *vs* none/on demand), and clinical worsening over time (i.e. ≥1-point deterioration in INCAT score at the last assessment compared to the first assessment). Moreover, we recorded electrophysiological data, and the number of electrophysiological findings fulfilling EAN/PNS demyelinating criteria was computed to define the "demyelinating burden" for each patient at first and last evaluation while, the sum of distal Compound Muscle Action Potential (dCMAP) was used as a surrogate marker of axonal degeneration. Most patients were male (76.5%), mean age at onset was 42.9±18.3 years (median 48.5; min 10 max 71), mean disease duration was 10.1±9.3 years (median 8; min 1 max 48) and half of the patients (52.9%) had typical CIDP. Over time, 11 patients worsened (≥1-point deterioration in INCAT), while 23 patients (67.6%) remained stable or improved. Fifteen patients (8/11 in worsened group and 7/23 in stable/improved group) were on maintenance treatment. Demyelinating burden decreased from the first to the last evaluation (-2.9; p=0.003), while the sum of dCMAP was not significantly different between the two assessments (-0.8; p=0.932). Worsened patients (n=11) had a higher age at onset (54.9±9.6 *vs* 37.2 ±18.9; p= 0.011), underwent treatment more frequently (p=0.02), and exhibited greater axonal loss at both evaluations (p=0.013; p=0.031) than stable/improved patients. There were no differences in sex (p=0.170), disease duration (11.3±11 *vs* 7.3±2.7; p=0.586), CIDP subtype (p=0.180), demyelinating burden at first (4.4±2.3 *vs* 3.3±1.7; p=0.176) and last evaluation (2.7±2.4 *vs* 2.1±1.8; p=0.561) between the group of worsened patients and the group of stable/improved patients. Most of our CIDP patients (70%) remained stable or improved, and interestingly, most of them were not on maintenance therapy. Consistently, demyelinating burden was reduced, while axonal loss did not increase over time. However, about one third of patients worsened: such patients were older and showed greater axonal loss from the first evaluation.

"PATISIRANITALY" MULTICENTER OBSERVATIONAL STUDY OF PATISIRAN IN ATTRV AMYLOIDOSIS WITH POLYNEUROPATHY

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Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) is a multisystemic, rare, inherited, and progressive adult-onset disease, affecting the sensorimotor nerves 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 its production. We report and discuss a multi-center real-life experience of patisiran in ATTRv-PN. We enrolled patients with genetically confirmed diagnosis of ATTRv-PN, from 30 specialized Italian centers. All subjects underwent neurologic evaluation, each obtaining a Familial Amiloid Polineuropathy (FAP) score, Neuropathy Impairment Score (NIS) scale, a quality-of-life assessment with the Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QOL-DN) questionnaire, and Compound Autonomic Dysfunction Test (CADT) at baseline and after 9 and 18 months of treatmentOne hundred seventy-seven ATTRv patients (70% males) have been recruited. Most patients presented with multisystemic involvement, and only 15% had isolated polyneuropathy. Neurological onset was observed in 62%. In 70% of patients patisiran was the first treatment, while in 30% it replaced a previous treatment based on tafamidis or inotersen. Mean NIS values were stable during follow-up, suggesting the absence of neuropathy progression. Patisiran was safe without side effects in 90% of patients. A significant positive correlation was demonstrated between age at patisiran onset and the severity of neuropathy assessed by NIS (R2=0.043) and quality of life assessed with Norfolk QOL-DN (R2=0.006).

Our data show that patisiran is effective and safe and that this drug stabilizes neurological symptoms, and QoL of ATTRv amyloidosis patients.

ASSESSMENT OF DIAGNOSTIC CRITERIA FOR MULTIFOCAL MOTOR NEUROPATHY IN PATIENTS INCLUDED IN THE ITALIAN DATABASE

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This study aimed to assess the diagnostic criteria, ancillary investigations, and treatment response using real-life data in patients with multifocal motor neuropathy (MMN).

Clinical and laboratory data were collected from 110 patients enrolled in the Italian MMN database through a structured questionnaire. Twenty-six patients were excluded due to the unavailability of nerve conduction studies or the presence of clinical signs and symptoms and electrodiagnostic abnormalities inconsistent with the MMN diagnosis. Analyses were conducted on 73 patients with a confirmed MMN diagnosis and 11 patients who did not meet the diagnostic criteria.

The European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) diagnostic criteria were variably applied. Applying the American Association of Electrodiagnostic Medicine (AAEM) criteria, an additional 17% patients fulfilled the criteria for a probable/definite diagnosis, while a further 9.5% missed the diagnosis. In 17% of the patients only the Compound Muscle Action Potential (CMAP) amplitude was measured, but not the area, which was subsequently recorded in the database by the treating physician. Additional investigations, including anti-GM1 IgM antibodies, cerebrospinal fluid analysis, nerve ultrasound, and magnetic resonance imaging, supported the diagnosis in 46-83% of the patients. Anti-GM1 IgM antibodies and nerve ultrasound demonstrated the highest sensitivity. Additional tests, outside the recommendations of the EFNS/PNS guidelines, were often performed. This study provides insights into real-world MMN diagnostic and management strategies, and highlights challenges in applying diagnostic criteria.

ELECTROMYOGRAPHY FINDINGS AND THEIR VALUE IN STIFF PERSON SPECTRUM DISORDER: A CASE SERIES

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Stiff person spectrum disorder (SPSD) is a group of rare autoimmune disorders characterized by stiffness of truncal and limb muscles with superimposed spasms and exaggerated startle response. Most SPSD

patients also present with psychiatric symptoms and other autoimmune comorbidities. Anti-glutamic acid decarboxylase (GAD) antibodies are the serological hallmark of SPSD, although less common antibodies can be found. Recently, a set of diagnostic criteria has been proposed for diagnosis of SPSD. Electromyography (EMG) is one of five items and is mandatory for diagnosis in seronegative cases. Herein, we reported EMG findings in our cohort of SPSD patients.

Patients referred for the diagnosis of SPSD at the Neurology Department of Careggi University Hospital, Florence, from 2016 to 2023 were identified. SPSD diagnosis was defined as the association of clinical SPSD manifestations confirmed by a neurologist and seropositivity for high-titer GAD65-IgG or for glycine receptor-IgG or amphiphysin-IgG, or as the co-occurrence of both clinical and EMG SPSD typical features. Electromyographic studies were recollected and compared, in order to characterize different patterns.

Of the 4 cases collected, 2 tested positive for GAD65-IgG at high titers, 1 tested positive for glycine receptor-IgG, and one is currently seronegative. All the patients had a positive anamnesis for autoimmune thyroiditis and other autoimmune comorbidities. Two also had a positive neurological history other than SPSD. The EMG study showed in 1 case the typical pattern of co-contraction of agonist and antagonist muscles, in 2 cases an exaggerated exteroceptive reflex, and in 1 case an exaggerated startle reaction. Burst of spontaneous repeating motor unit potentials, doublets, or triplets, with quasi-rhythmic or rhythmic activity, were present in two patients.

Like clinical manifestations, EMG findings are also heterogeneous in SPSD. Despite the lack of specificity, EMG is a very important tool for clinicians in diagnosing SPSD, especially in seronegative cases. In our small series, we have noticed the prevalence of some electromyographic signs. To better understand the association of these signs with the different serological status of patients, further investigations are needed.

A RARE CASE OF ACUTE PAINFUL SENSORY-AUTONOMIC GANGLIONOPATHY ASSOCIATED WITH THYROID CANCER

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Papillary thyroid cancer is rarely associated to paraneoplastic syndromes. Sensory-autonomic neuronopathies may occur primarily or secondarily to various underlying diseases. Dysautonomia is frequent in non-paraneoplastic sensory neuronopathies. Sensory-autonomic neuropathy may have a rapid and monophasic course mimicking Guillain-Barré syndrome (GBS). We describe a challenging case of sensory-autonomic ganglionopathy associated with thyroid cancer with an acute painful onset.

A 40 year-old woman with history of hypertension, irritable bowel syndrome, recent thyroid cancer undergoing surgical and radiometabolic treatment visited our hospital because of acute onset of widespread pain, itching, burning feet and mouth, dry skin and photophobia. One month later the symptomatology evolved in disabling paraesthesias and severe gait disturbance.

Clinical examination showed severe gait ataxia, positive Romberg sign, not length-dependent pinprick and tactile sensory loss, hyporeflexia, and distal hypopallesthesia. She also reported widespread burning pain, asymmetric numbness in upper and lower limbs, blurred vision, and constipation. We found increased cerebrospinal fluid proteins without oligoclonal bands. Neurophysiological exams showed a moderate non lenght-dependent axonal sensory neuropathy and abnormal visual evoked potentials with foveal involvement. Brain and spine MRI was normal. Initially, extensive assessment for secondary causes was negative, including infectious serology, vitamin deficiency, tests for transthyretin amyloidosis, Fabry disease, onconeural antibodies, radiological and laboratory screening for occult cancer. We found exclusively a not significant ANA positivity (1:100) and HLA B51 positivity in the absence of diagnostic criteria for Bechet's disease. Intravenous immunoglobulin therapy and subsequent steroid pulse therapy did not improve her symptoms except for blurred vision and hypertension. After six months, nerve conduction studies and somatosensory evoked potentials showed severe sensory axonal loss but normal visual evoked potentials. PET revealed recurrence of thyroid tumor with minimal extra-thyroidal extension.

The clinical picture is suggestive of a sensory-autonomic ganglionopathy. The acute onset resembles a sensitive GBS. The finding of mild ANA and HLA B51 positivity could suggest an inflammatory genesis. However, the history of cancer and poor response to immunomodulatory treatments suggest a paraneoplastic syndrome. The oncological follow-up showed cancer recurrence awaiting metabolic radiotherapy. Further investigations as neuro-vegetative tests and skin biopsy are scheduled. This case report suggests that it may be necessary to consider a paraneoplastic neurological syndrome even in a patient with acute sensory-autonomic neuropathy and history of a poor aggressive cancer. A close clinical and instrumental follow-up is mandatory to reach a correct etiological diagnosis and provide adequate therapy.

OCULOMOTOR FEATURES IN CANVAS

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Introduction: CANVAS (Cerebellar Ataxia, Neuropathy and Vestibular Areflexia Syndrome) is a late-onset, slowly progressive, autosomal-recessive disorder due to a biallelic intronic expansion in the *RFC1* gene. Vestibular areflexia caused by vestibular ganglia degeneration is considered a distinctive feature. The objective of this exploratory study is to assess the oculomotor system in a cohort of CANVAS patients.

Materials and Methods: Seventeen genetically confirmed CANVAS patients were assessed by bedside oculomotor examination, including

a "reading test" (with slowly sinusoidal head movements), and by video-oculography (EyeSeeCam), to explore lateral vestibulo-ocular reflex, smooth pursuit, optokinetic nystagmus, gaze holding and saccadic system.

Results: The patients were 6 males and 11 females (mean age: 66.9 years; range: 52-85; mean disease duration: 11 years; range: 1-33). The "reading test" was altered in 6/10 subjects (60%). The video-oculographic data were as follows: horizontal vestibulo-ocular reflex (VOR) impairment at video head-impulse test (vHIT) in 13/17 (77%), smooth pursuit impairment in 14/17 (82%); altered/absent optokinetic nystagmus (OKN) in 9/15 (60%); downbeat nystagmus (DBN) in 6/17 (35%), gaze-evoked nystagmus in 2/17 (12%), and mild-to-moderate saccadic dysmetria in 6/15 (40%). In 1 subject no clear oculomotor abnormality was found.

Conclusions: In CANVAS, characteristic oculomotor abnormalities consist of a varying combination of vestibulo-ocular hypo-/a-reflexia, marked reduction of smooth pursuit gain, reduction/lack of the OKN, and DBN. These changes indicate a wider involvement of the vestibule-cerebellar system, including the flocculus and vestibular nuclei, beyond the vestibular ganglia. The "reading test" can be a simple test to identify vestibulo-ocular abnormalities at bedside.

RNAI THERAPY IN ATTRV AMYLOIDOSIS WITH POLYNEUROPATHY (HELIOS-A): PATIENT-REPORTED EXPERIENCES AND PREFERENCES

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Background: Vutrisiran and patisiran are approved RNAi therapies for ATTRv amyloidosis with polyneuropathy. Vutrisiran is administered subcutaneously every three months (Q3M) and patisiran intravenously every three weeks (Q3W). We evaluated patients' experiences and preferences about treatment administration approaches.

Methods: In HELIOS-A, patients with ATTRv amyloidosis with polyneuropathy were randomized to vutrisiran (Q3M) or patisiran (Q3W) for 18 months with an extension phase where patients received vutrisiran (Q3M or Q6M) for 18 months. A 'Patient Experience Survey' (PES) evaluating study treatment convenience in all patients at baseline, 9 months and 18 months, and a 'Patient Preference Survey' (PPS) was administered during the extension phase to evaluate the preference between vutrisiran and patisiran.

Results: 113/122 vutrisiran-arm and 38/42 patisiran-arm patients completed the PES at 18 months; 95.6% and 99.1% of vutrisiran-arm PES respondents considered dosing frequency and time per dose administration, respectively, to be "somewhat", "quite", or "extremely" convenient, versus 71.1% and 57.9% of patisiran-arm respondents. PPS results at 9 months were available in 27/37 patients who switched from patisiran to extension-phase vutrisiran treatment; 92.6% preferred vutrisiran over patisiran, with dose frequency (80.0%) and administration time (52.0%) being the most commonly cited reasons for preferring vutrisiran. The location of administration (i.e., infusion center, doctor's office, home) was not a major factor driving vutrisiran preference (8.0%).

Conclusions: Majority of patients receiving vutrisiran or patisiran report favorable experiences regarding convenience, although vutrisiran is more commonly considered a convenient treatment option. The majority of patients switching from patisiran to vutrisiran prefer vutrisiran, primarily due to less frequent dosing; the location of dose administration has a limited impact on patient preference.

EVALUATION OF HISTONE DEACETYLASE 6 INHIBITORS AS POSSIBLE NEUROPROTECTORS AGAINST PACLITAXEL-INDUCED NEUROTOXICITY

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About 70% of treated cancer patients might develop Chemotherapy-Induced Peripheral Neuropathy (CIPN) during or after chemotherapy treatment. CIPN is an important therapeutic problem to solve, and it is mandatory to identify drugs able to counteract it, studying the mechanisms at the basis of the pathology. We focused our attention on the NMNAT2/SARM1 pathway, suggested by several studies to be associated with peripheral neuropathy and neurite degeneration. We investigated Paclitaxel, a microtubule-stabilizing agent that is widely used against breast cancer, which induces CIPN with high frequency. By binding microtubules, Paclitaxel reduces axonal transport (including NMNAT2 transport), consequently promoting activation of SARM1, a pro-degenerative protein. Histone deacetylase 6 (HDAC6) localizes predominantly in the cytoplasm and exerts the deacetylase enzymatic activity mainly on non-histone substrates. It is mainly involved in deacetylating tubulin, playing a crucial role in microtubule stability, and therefore emerging as a potential target to reduce Paclitaxel-induced neurotoxicity. The aim of this work was to investigate NMNAT2/SARM1 pathway as the possible molecular mechanism through which HDAC6 inhibitors protect against Paclitaxel-induced neurotoxicity.

The potential effect of three selected HDAC6 inhibitors (Ricolinostat, SW-100, Tubastatin A) was tested, evaluating neuronal viability and neurite length, in an *in vitro* model based on adult mice primary sensory neurons cultures. Neurons were treated with HDAC6 inhibitors

individually, as well as in combination with Paclitaxel, with increasing concentrations of the drugs; NMNAT2 and SARM1 protein expression was analyzed through Western blotting. Lastly, acetylated SARM1 levels were evaluated using immunoprecipitation assay, and NMNAT2 and SARM1 localization was assessed by immunofluorescence.

Data demonstrate that Paclitaxel reduces neuronal survival rate and neurite elongation in a dose-dependent manner, while the co-treatment with Paclitaxel and each of the three HDAC6 inhibitors protects against Paclitaxel-induced neurotoxicity. Furthermore, no HDAC6 inhibitor showed interference with Paclitaxel antitumoral activity on MCF-7 cells. Paclitaxel decreases NMNAT2 and SARM1 protein expression, which is significantly restored by HDAC6 inhibitor co-treatment. Immunofluorescence experiments demonstrate that Paclitaxel induces neurite fragmentation and a redistribution of NMNAT2. Although neuroprotective, Ricolinostat does not restore the localization of NMNAT2 in control neurons. However, Ricolinostat treatment (alone or in combination with Paclitaxel), increases SARM1 acetylation, contributing to its inhibition.

Our results demonstrate that HDAC6 inhibitors modulate NMNAT2/SARM1 pathway suggesting that their protective effect against Paclitaxel-induced neurotoxicity may be mediated by this pathway.

COMPOUND MUSCLE ACTION POTENTIAL AMPLITUDE RATIO TO DISTINGUISH CHARCOT-MARIE-TOOTH 1A FROM CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY: A SINGLE-CENTER EXPERIENCE

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Introduction: Charcot-Marie-Tooth disease 1A (CMT1A) is the most common subtype of CMT, and it is characterized by demyelinating features related to a duplication in the *PMP22* gene. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated polyneuropathy that, in some cases, may present differential diagnosis challenges with CMT. Recent studies showed that the proximal/distal compound muscle action potential (CMAP) amplitude ratio (P/D ratio) could be a useful index in discriminating between demyelinating CMT and CIDP. Specifically, the tibial nerve P/D ratio has been demonstrated to be significantly lower in the CIDP group than the CMT1A group. The objective of our study was to investigate the potential utility of the P/D ratio in differentiating between CMT1A and CIDP in our patient population.

Patients and Methods: We analysed retrospectively 17 patients with CMT1A and 22 subjects with CIDP diagnosed between 2006 and 2021. The mean age at the diagnosis was 58 years for the CIDP group and 44 years for CMT; 18 were male and 21 were female. We determined the P/D ratio between the median and ulnar nerves of the electrophysiological study at the time of diagnosis. A comparison of the P/D ratio, calculated by dividing the proximal CMAP amplitude by the distal CMAP amplitude, was made between the two groups. A non-parametric analysis (Mann-Whitney U test) was conducted to compare electrophysiological variables.

Results: In our population, CMT patients exhibited a significantly higher P/D ratio compared to CIDP patients in both the median ($p = 0.038$) and ulnar nerves ($p = 0.047$).

Conclusion: Our study confirmed the observation that the P/D ratio could be an effective index for distinguishing CMT1A and CIDP. Specifically, we demonstrated significant differences between the P/D ratio of the median and ulnar nerves of CMT patients compared to the CIDP group. Further studies on a larger number of subjects will be able to better define its usefulness in clinical practice.

EARLY DETECTION OF AUTONOMIC NEUROPATHY THROUGH CARDIAC 123I-METAIODOBENZYLGUANIDINE (123I-MIBG) SCINTIGRAPHY IN TWO PAUCI-SYMPTOMATIC TRANSTHYRETIN CARRIERS

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Introduction: Hereditary transthyretin amyloidosis (ATTRv) is a rare progressive multisystem disease, usually manifesting as a length-dependent axonal polyneuropathy and progressive cardiomyopathy. Autonomic neuropathy could represent the first clinical manifestation. Since disease modifying therapies are available, the early detection of neuropathic involvement is of paramount importance. Herein, we report two cases of pauci-symptomatic patients who developed an autonomic neuropathy years before the predicted age of onset detected by cardiac 123I-metaiodobenzylguanidine (123I-MIBG) scintigraphy.

Materials and Methods: Two pauci-symptomatic ATTRv p.val50met carriers belonging to the same family underwent to an extensive neurological and cardiological assessment comprising nerve conduction study (NCS), skin biopsy with intraepidermal nerve fiber density (IENFD) determination, quantitative sensory testing (QST), Sudoscan®, electrocardiogram (EKG), trans-thoracic echocardiogram, cardiac MRI, NT-pro-BNP dosing, 99Tc-MDP bone scintigraphy, and 123I-MIBG scintigraphy.

Results: The first patient is a 56-year-old man with occurrence of chronic diarrhea, while the second is 62 years old woman, who

developed gastrointestinal symptoms (alternating constipation and diarrhea, excessive fullness after a meal). The closer affected relative developed symptoms at 73 years.

In both cases, the neurological examination and NCS were normal, as well as a complete small nerve fiber assessment (skin biopsy, QST and Sudoscan®). The initial cardiac assessment through EKG, trans-thoracic echocardiogram and NT-pro-BNP dosing was unremarkable. Cardiac MRI showed subendocardial late post-contrast enhancement in the woman.

99Tc-MDP bone scintigraphy showed cardiac uptake (Perugini Score 2) while 123I-MIBG scintigraphy showed myocadiac denervation confirming the autonomic neuropathy. Patisiran at 0.3 mg/kg every three week was started in both subjects.

Conclusions: In our cases, nuclear imaging allowed the detection of myocardial amyloid deposition and cardiac denervation in absence of other abnormalities enabling timely therapy initiation. In ATTRv subjects with mild autonomic symptoms and normal electrodiagnostic and small nerve fiber assessment tests, MIBG scintigraphy could identify autonomic nerve involvement years before expected onset.

COMPARISON OF THE DIAGNOSTIC ACCURACY OF THE 2010 EFNS/PNS AND AAEM DIAGNOSTIC CRITERIA FOR MULTIFOCAL MOTOR NEUROPATHY

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To compare the sensitivity and specificity of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) diagnostic criteria for multifocal motor neuropathy (MMN) with those of the American Association of Electrodiagnostic Medicine (AAEM)

Sensitivity and specificity of the two above-mentioned criteria were evaluated in 53 patients with MMN and 225 controls with axonal peripheral neuropathy or amyotrophic lateral sclerosis. Comparison of the utility of nerve conduction studies with different number of nerves examined was also assessed.

EFNS/PNS criteria had a sensitivity of 47% for definite MMN and 57% for probable/definite MMN, while the AAEM criteria had a sensitivity of 28% for definite MMN and 49% for probable/definite MMN. The sensitivity of the AAEM criteria was higher when utilizing area reduction to define conduction block compared to amplitude reduction. Using supportive criteria, the sensitivity of the EFNS/PNS criteria for probable MMN increased to 64% and an additional 36% patients fulfilled the criteria (possible MMN). Specificity of the EFNS/PNS criteria for definite MMN and probable/definite MMN was 99.5%, while the AAEM criteria had a specificity of 100% for definite MMN and for probable/definite MMN. More extended studies slightly increased the diagnostic sensitivity of both sets of criteria without significantly reducing specificity.

In our patient populations, the EFNS/PNS criteria were more sensitive and had a similar specificity compared to the AAEM criteria. Extended nerve conduction study is advised to achieve a slightly higher sensitivity while maintaining a very high specificity.

CONDUCTION BLOCK IN INFLAMMATORY NEUROPATHIES: EVALUATION OF THE BEST DIAGNOSTIC CRITERION

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In the literature, various criteria exist for defining motor conduction block (CB), resulting in different criteria for multifocal motor neuropathy (MMN) and partly explaining the presence of various criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) and Guillain-Barré syndrome (GBS). This study aims to evaluate which criterion for defining CB offers the best diagnostic accuracy in inflammatory neuropathies.

The sensitivity and specificity of the electrophysiological criteria for defining CB (definite and probable) outlined in the 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) for MMN, the American Association of Electrodiagnostic Medicine (AAEM) for MMN, and the 2021 European Academy of

Neurology/Peripheral Nerve Society (EAN/PNS) for CIDP will be assessed in patients with MMN, CIDP, GBS, and controls. The positivity of these criteria in at least one nerve was considered. Preliminary results are available from 53 patients with MMN, 56 with CIDP, 32 with GBS, and 225 controls diagnosed with axonal peripheral neuropathy or motor neuron disease.

In MMN, the EAN/PNS criterion (>30% reduction in amplitude) showed the highest diagnostic accuracy (sensitivity 77%, specificity 97.5%). This was followed by the AAEM criterion for probable CB (>30-40% reduction in area with TD <30%) and by the EFNS/PNS criterion for probable CB (>30% reduction in area with TD <30%) with comparable sensitivity (both 74%) and specificity (98% and 99.5%, respectively). In CIDP, the highest accuracy was shown by the EAN/PNS criterion with sensitivity 59% and specificity 97.5%. The other criteria showed lower diagnostic accuracy. In GBS, the EAN/PNS criterion for CB and the AAEM criterion for probable CB (>30-40% reduction in area with TD <30%) showed the highest accuracy with a sensitivity of 44% and a specificity of 97.5% and 98%, respectively.

CB defined as >30% amplitude reduction, with or without TD, in a single motor nerve demonstrate the highest diagnostic accuracy both in MMN, CIDP and GBS with good levels of sensitivity and exceptionally high levels of specificity. These findings warrant validation in a larger cohort of patients.

AN UNUSUAL CASE OF LARGE MYOKIMIA MIMICKING SPINAL SEGMENTAL MYOCLONUS OF LOWER LIMB

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Spinal myoclonus is a rare disorder characterized by myoclonic movements in muscles that originate from several segments of the spinal cord. Careful history taking and electrophysiological evaluation are important in differential diagnosis. The aim of this report is to evaluate the main clinical characteristics and treatment results, of a case with spinal lumbar segmental myoclonus and diffuse lower limbs myokimias, not responsive to decompressive laminectomy, probably triggered by previous intraforaminal root compression.

We report the case of a 63-year-old man with one-year history of involuntary twitching of left quadriceps muscle, without atrophy or weakness. The symptom was initially associated to back pain with sciatic territory irradiation and MRI showed L3-L4 and L4-L5 foraminal hernia stenosis. After decompressive laminectomy and posterior arthrodesis, the pain disappeared, in the absence of regression of involuntary movements.

He showed gross, semirhythmic contractions of right thigh muscles; some movements were large enough to produce slight knee joint movement, when the knee was flexed and the patient sat without foot support. Diffuse myokymia were also noted in left thigh flexor muscles. Neurological, systemic examination, motor evoked potential and cervical, dorsal spine MRI were normal. EMG and NCS revealed slight sensory nerve axonal abnormalities length-dependent while NCS of motor nerves with low amplitudes in left tibial and peroneal nerves. Needle examination revealed continuous, involuntary, repetitive motor unit activity consistent with myokymia in the quadriceps muscles. Florid active denervation, high-amplitude, broad and polyphasic motor unit action were found in all lumbosacral regions examined.

Polymyography was conducted recording duration, distribution of the stimulus of muscle jerk and a spinal lumbar segmental myoclonus was detect. First treatment with Clonazepam was unsatisfactory, so that valproic acid was started with partial mild response.

Local infiltration of xylocaine and botulinum toxin will be evaluated.

In rare occasions, spinal myoclonus can be observed after the peripheral nerve lesions. There is evidence that various pathological mechanisms could be involved: e.g. loss of inhibitory function of local dorsal horn inter-neurons, abnormal hyperactivity of local anterior horn neurons. We supposed, the present case of spinal myoclonus, started with lumbar root compression and persisted, although decompression surgery was performed, even increased. It did not affect only the femoral tract, as in peripheral myoclonus, but involved other segments. The underlying lesion is usually treatable and reversible in peripheral myoclonus, but spinal myoclonus usually persists though various treatments. Careful history taking and electrophysiological evaluation are important in differential diagnosis.

FOCALITY IN AMYOTROPHIC LATERAL SCLEROSIS: PATHOLOGICAL EVIDENCE FOR A SPECIFIC BIOMARKER OF THE DISEASE

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Introduction: Despite clinical focal onset is often reported in amyotrophic lateral sclerosis (ALS), its pathological counterpart has been poorly described in the literature, limited only to few post-mortem cases. Taking advantage of our repository of motor nerve biopsies, we sought for evidence of focality in motor nerves of ALS patients versus ALS-mimics.

Materials and Methods: semithin sections from motor nerve biopsies of patients with ALS (n=16) and motor neuropathies (MN, n=6) were

analyzed in this study. For each fascicle, a grid was applied, and fibre density was calculated for each frame within the grid. To evaluate asymmetry in fibre density across each fascicle, the coefficient of variation (CV) of the fibre densities for each frame within the same fascicle was calculated. Subsequently, the mean CV for fascicles belonging to the same nerve, as well as the highest CV, were computed. These values were then used for clinicopathological correlations.

Results: mean CV was significantly higher in ALS patients compared to MN (0.45 vs 0.28, p=0.0157), with a greater range of variability observed in the former group (0.27-0.65 vs 0.27-0.36). The highest CV did not show significant differences between the two groups (0.55 vs 0.38, p=0.067). Mean fibre density significantly correlated with mean and highest CV only in the ALS group (r=-0.58, p=0.02; r=-0.57, p=0.02) but not in the MN group. None of the focality parameters correlated with age of onset or disease duration in both groups. In ALS patients, mean CV significantly correlated with MRC sum score of proximal muscles of the lower limbs (r=-0.77, p=0.002), which appears to be higher for the iliopsoas muscle (r=-0.77, p=0.001) compared to the quadriceps muscle (r=-0.63, p=0.01), while no significant association was found with the MRC sum score of the distal lower limb muscles (r=-0.36, p=0.20). Similar results were also found for the highest CV in the ALS group. Instead, no significant correlations were observed between mean and highest CV with clinical scores in the MN group.

Conclusions: Focality of fibre loss in motor nerve biopsies appears to be a specific biomarker of ALS, distinguishing it from MN. Furthermore, focality correlates with markers of clinical severity in ALS patients but not in MN cases. This suggests that the presence of proximal involvement in the lower limbs may increase the likelihood of detecting focality in nerve biopsies.

A PROPOSAL FOR IMPROVEMENT OF ACMG GUIDELINES FOR VARIANTS EVALUATION IN CHARCOT-MARIE-TOOTH DISEASE MOLECULAR DIAGNOSIS

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The use of massive parallel sequencing technologies, for diagnostic purposes, in the molecular analysis of CMT has allowed the rapid and inexpensive identification of many potentially pathogenic variants. It is now clear that it is necessary to reduce their number and focus only on those variants with more consistent pathogenic significance. The 2015 ACMG guidelines help to achieve this purpose, but it is evident that a critical review of these rules is essential to avoid misinterpretations that could result from a blind application of the general pathogenicity criteria.

We started with the molecular analysis of a small cohort of 226 CMT patients using a 76-gene NGS custom panel. We then compared a "blind" application of the ACMG criteria with a critical review that integrates them with CMT-specific literature data and in-house laboratory experience. Finally, we reviewed the ACMG criteria based on current knowledge of CMT and our experimental data to provide some guidance to meaningfully adapting them to the peripheral inherited neuropathies.

Out of 226 index patients analyzed, we obtained a diagnostic yield of 20% with the identification of *GDAP1*, *GJB1*, *HINT1*, *HSPB1*, *IGHMBP2*, *MFN2*, *MPZ*, *PMP22*, *SH3TC2* and *SORD* as the most frequently represented genes (excluding duplication or deletion of *PMP22*). Interestingly, in about 9% of cases, the final diagnosis changed with the application of the revised criteria, usually losing the pathogenic classification of a variant.

The widespread availability of high-throughput sequencing technologies has made genetic testing accessible to laboratories without disease-specific expertise. The development of disease specific ACMG criteria may be a useful tool to avoid the proliferation of variants of unknown significance (VUS) and the misinterpretation of variants.

A CASE OF GUILLAIN-BARRÉ SYNDROME WITH ISOLATED BILATERAL WRIST DROP

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There are several forms of Guillain-Barré syndrome (GBS) defined by the clinical features. Some of these forms are considered GBS variants and have been well described. Herein we describe a case of an acute motor axonal neuropathy (AMAN) with isolated bilateral wrist drop.

A 58-year-old man developed a bilateral wrist extension deficit 8 days after an episode of diarrhea. He had a history of Bell's palsy and works as a mechanical. On neurological evaluation, a symmetric deficit in hand dorsiflexion (MRC 3) and fingers (MRC 4) was observed; deep tendon reflexes were present except for the right Achilles reflex. The patient reported a tick bite two months earlier.

Cerebrospinal fluid analysis was unremarkable (protein 0.5 g/L, cell count 2/mm3). Blood lead assay, performed in view of the work history (mechanical), was within the normal range. MRI of the cervical spine showed contrast-enhancement of the ventral neural roots bilaterally (C5, C6, C7, C8). Electroneuronography demonstrated a motor axonal neuropathy in the four limbs. Serum test for antigangliosides antibodies was positive for the presence of IgG GM1 and GD1b. Serologic tests for infectious disorders showed a reactivity for CMV IgM

(CMV IgG – negative). Considering the history of tick bite, serology for Borrelia burgdorferi and Western blot for Borrelia on CSF were performed, both negative. The patient was treated with intravenous immunoglobulin (2 g/kg) and later transferred to the Rehabilitation Department. At two months follow-up he showed initial improvement in wrist extension (MRC 4 bilaterally), while strength in finger extension had worsened (MRC 2); a bilateral hallux extension deficit was observed (MRC 4).

This case represents an atypical clinical variant of AMAN characterized by isolated bilateral wrist drop. It should be noted that the "finger drop sign" has already been described in the literature as a new variant of AMAN (Yoon BA 2020). The patient's work history was an important confounding factor in view of the risk of lead poisoning; indeed, cases of bilateral wrist drop derived from lead-induced neuropathy are well known. In this case, contrast enhancement of the ventral roots on cervical MRI suggested the hypothesis of an inflammatory-based radiculopathy, for which IVIg therapy was initiated. The finding of antigangliosides antibodies corroborated the diagnosis of GBS (AMAN). This case emphasizes the importance of an early diagnosis of GBS even when it presents atypically, to proceed rapidly with immunomodulatory therapy.

EVALUATION OF UPPER LIMBS IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS PATIENTS WITH HAND TEST SYSTEM -EULA MULTICENTER PROJECT

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Introduction: Hereditary transthyretin amyloidosis with polyneuropathy (hATTR) is one of the most severe, disabling hereditary neuropathies in adults. The main aim of the project is to collect measurements of hand functionality using Hand Test System (HTS), which allows objective and quantitative measurement of fingers movements, and standard outcome measures at baseline, after 6(T1) and 12(T2) months in patients at different stages of disease and healthy controls.

Methods: To date, 65 patients were recruited, of whom 49 (F:21; M:28; age:62.16±12.65y) and 30 healthy controls (HC) (F:17; M:13; age:49.50±16.80y) were analyzed. Performed at each time point: HTS with 2 tasks and eyes closed (Finger-Tapping (FT) and Index-Middle-Ring- Little (IMRL) sequence); 9-hole peg test (9-HPT); dynamometry (handgrip and tripod pinch); Thumb Opposition Test (TOT); Disability of the Arm, Shoulder and Hand (DASH); Norfolk Quality of Life (Norfolk QoL); Neuropathy Impairment Score (NIS).

Results: The FT and IMRL sequence showed a significant difference in various stages and HC (dominant-hand (DH) FT: P=0.01 and IMRL: P=0.0001; non-dominant-hand (NDH) FT:p=0.03 and IMRL: p=0.0001). Interestingly, the difference between stage 1 and HC in the DH in finger tapping is significant (P= 0.021), but no significant difference was observed between stages 0 and 1. Handgrip showed a statistically significant difference (p=0.05) between groups only in DH (stage 0 and HC p= 0.95; stage 1 and HC p=0.045; stage 2 and HC p=0.044; stage 0 and stage 1 p=0.37). The correlation between the parameters of HTS and 9-HPT; DASH; Norfolk QoL and NIS are significant in both hands. Additionally, HC resulted significantly stronger in the DH of the Handgrip compared to the patients (HC 102.98±35.01N; Patients 77.98±40.99N; p=0.028). NDH of the Handgrip and both hands of the tripod pinch showed non-significant differences. TOT showed a significant difference between HC and patients for both hands (DH p=0.0001; NDH p=0.0001).

Conclusions: In these preliminary data, DH seems sensitive to detect the differences between HC and patients for all the outcome measures. The evaluation of the DH flexors can discriminate between HC and patients. Moreover, TOT is a rapid and interesting test for hATTR patients and HTS tests provide a more accurate measurement of upper limbs function in hATTR and are able to detect a small and slight progression of the disease compared to standard techniques at different stages of the disease. The project is ongoing and more complete results in terms of patient numbers and follow-up will be presented.

REAL WORD STUDY ON SMALL INTERFERING RNA THERAPY IN HEREDITARY AMYLOIDOGENIC TRANSTHYRETIN AMYLOIDOSIS-MIXED PHENOTYPE: ROLE OF PATISIRAN IN CARDIAC OUTCOMES

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Hereditary amyloidogenic transthyretin amyloidosis (ATTRv) due to p.Glu109Gln mutation is characterized by onset in the 5th – 6th decade, distal paraesthesias/Carpal Tunnel Syndrome as presenting symptoms and early heart dysfunction. Heart failure and sudden

death are the major cause of mortality followed by dysautonomia and cachexia. Previously we reported a life expectancy of 7.6±3.7 (3–13) years and a worse prognosis in a cohort of 40 patients harboring this mutation. The introduction of RNA-silencing treatments has greatly modified ATTRv natural history. The objective of this single-center real world study is the description of cardiac function in a cohort of patients with p.Glu109Gln mutation treated with patisiran.

We enrolled 10 patients (7 females and 3 males, with mean age, at diagnosis, of 50.6 years-old) affected by ATTRv amyloidosis with polyneuropathy, harboring the p.Glu109Gln variant, and treated with Patisiran. All patients underwent cardiological assessment with echocardiogram, serum sampling of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and Troponin T. Those assessments were performed at baseline (time 0) and every 6 months. Neurological progression was assessed using the Neuropathy Impairment Score in the Lower Limbs (NIS-LL).

At time 0, five out of ten patients presented cardiac hypertrophy with preserved ejection fraction with a mixed phenotype and elevated troponin T and NT pro BNP values. One out of ten patients presented cardiac hypertrophy with reduced ejection fraction and elevated troponin T and NT pro BNP values. Four out of ten patients presented normal cardiac function parameters with only neuropathic phenotype and normal NTproBNP and Troponin T values. During a median of 27.8 months (6-54) follow-up, 8 patients showed stability of echocardiographic and serological parameters. One patient had a reduction in NT-pro BNP values, and stability of troponin and ultrasound parameters. Only one subject experienced a reduction of the ejection fraction with mild heart failure symptoms progression.

Use of patisiran allowed substantial stability of the cardiological parameters in the majority of patients with p.Glu109Gln ATTRv. A greater number of patients and a prolonged follow-up are needed.

DORSAL ROOT GANGLIA NEURONS MORPHOMETRY ANALYSING METHOD OPTIMIZATION

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Oxaliplatin (OHP) is an anticancer drug known for its peripheral nervous system toxicity. Indeed, it can be considered as a robust model of neuronopathy; therefore, it is the ideal setting in which the issue of tailoring and ameliorating the morphometrical analysis of dorsal root ganglia (DRG) neuron can be addressed. Usually, DRG morphometry relies on manual measurements acquired by a trained operator; even so, an improvement of the standard morphometry protocol could allow to rule out potential subjective measurement bias and, eventually, it could be the basis for an automated or semi-automated measurement development.

Analyses were performed on DRG from rats treated with OHP (3 mg/kg, i.v., twice a week for 4 weeks), and compared to control (CTRL) animals. Acquisitions of light micrographs of methylene-blue stained DRG sections were obtained, after sacrifice, both at the end of the treatment and after 6 weeks of follow up. Measurements were performed by two blinded operators. Manual tracing of neuronal soma, nuclei, and nucleoli outlines, along with the calculation of corresponding areas, were carried out using ImageJ software. We followed a specific algorithm to save and label the outlines each examiner traced, facilitating the subsequent validation of measurement accuracy and the verification of the correct identification of the targets of interest (i.e., soma, nucleus, nucleolus).

A statistically significant decrease has been identified by both examiners in all components in rats treated with OHP at the end of the treatment, compared to CTRL animals. At the end of the 6-week follow up, due to a partial recovery, the reduction was statistically significant only in the nucleolar area. Both examiners achieved the same level of statistical significance in their assessments for all parameters at all time points.

As there was minimal and non-significant variation between the examiners, we can suggest that our algorithm is adequately reliable. Therefore, the proposed algorithm enabling a persistent segmentation of soma, nucleus, and nucleolus areas will be subsequently used as the ideal starting point for the implementation of automated or semi-automated measurement methods, relying on machine learning algorithms.

PHENOTYPIC AND GENETIC SPECTRUM OF EARLY-ONSET CHARCOT-MARIE-TOOTH TYPE 1B IN ITALIAN PATIENTS

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Introduction: Charcot-Marie-Tooth type 1B (CMT1B) is a hereditary condition caused by mutations in the Myelin Protein Zero (MPZ) gene, leading to demyelinating peripheral neuropathy with a wide range of clinical manifestations. Clinical and genetic characterization in CMT1B is crucial, especially in the context of early-onset cases, to inform future therapeutic strategies. This is particularly relevant as research progresses on therapeutic approaches targeting the unfolded protein response (UPR), a cellular stress mechanism implicated in nerve damage in CMT1B. As potential treatments aimed at modulating the UPR

are being developed, characterizing the patient population is essential for the transition to clinical trials.

Methods: We present cross-sectional data of 47 Italian patients with early-onset CMT1B due to MPZ mutations. Data was collected through a dedicated online platform ("Istituto Virtuale Nazionale Malattie Rare") and required cooperation from five different "Istituti di Ricovero e Cura a Carattere Scientifico" (IRCCS).

Results: The cohort comprised 21 reported and 5 novel MPZ mutations, with 64% exhibiting autosomal dominant inheritance. The average age of onset was 3.2 years, with a wide range reflecting the heterogeneity of disease severity. Approximately 57% of patients required ankle foot orthotics or shoe inserts, 26% regularly used unilateral or bilateral walking support, while 10% were wheelchair dependent. 64% of patients experienced hand motor skill difficulties, 26% reported neuropathic pain and/or burning and tingling in feet or hands, and 66% had a positive Romberg sign and/or clinical ataxia. Reflex abnormalities and foot deformities were ubiquitous, present in more than 90% of patients. Other findings included tremor (15%), hearing loss (13%), and scoliosis (49%). Optic nerve atrophy was not reported in our cohort. The mean CMTES score was 9.8, but values ranged from 0 to 28, indicating wide phenotypic variability. CMTES score showed a significant positive correlation with age of assessment (Pearson coefficient = 0.376, $p = 0.024$), suggesting clinical progression in our cohort.

Conclusions: Our study provides a comprehensive overview of the clinical manifestations in a large cohort of Italian patients with early-onset CMT1B due to MPZ mutations. The data underscore the phenotypic variability and the burden of disease in this population and highlight a consistent number of patients with positive sensory symptoms and ataxic features. The characterizations of this patient population is fundamental for fast transition to clinical trials and requires longitudinal assessment.

EARLY DISEASE BIOMARKERS COMPARED: ARE SERUM NEUROFILAMENT LIGHT CHAIN LEVELS AND SMALL NERVE FIBRE DAMAGE PARAMETERS CORRELATED IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS WITH POLYNEUROPATHY (ATTRV-PN)

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Both serum neurofilament light chain (sNfL) levels and small fibre related variables, as skin biopsy and quantitative sensory testing (QST), are valuable disease biomarkers of hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN).

Our study aimed to explore the relations between sNfL and small fibre related skin biopsy and QST data in a cohort of ATTRv-PN patients and asymptomatic carriers.

We conducted a retrospective analysis of data from 34 individuals (13 ATTRv symptomatic patients and 21 pre-symptomatic carriers) who underwent sNfL dosage, skin biopsy, and QST, and analyzed correlations between sNFL, IENFD, and thermal cold (CDT) and warm detection thresholds (WDT).

We found that both sNfL and small fibre related skin biopsy and QST parameters significantly differed between carriers and patients (sNfL: $p<0.0001$; IENFD: $p=0.0008$; CDT, WDT: <0.0001). sNFL levels were normal in all carriers and altered in 85% of patients; IENFD was abnormal in 41% of carriers and 77% of patients, CDT and/or WDT were impaired in 19% of carriers and 54% of patients. sNfL negatively correlated with distal IENFD ($r=-0.47$, $p=0.005$) and significantly correlated with small fibre related QST parameters impairment (CDT: $r=-0.68$, $p<0.0001$; WDT: $r=0.57$).

Our study showed that sNfL reliably discriminates symptomatic ATTRv-PN patients from pre-symptomatic carriers, and found significant relations between sNfL, skin biopsy, and QST small fibre related parameters, suggesting that sNfL might be a supportive criterion for symptomatic disease transition.

GENOME-WIDE COPY NUMBER VARIATION ANALYSIS AS A TOOL TO DETECT NEW RISK FACTORS IN CHRONIC PAIN

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Chronic pain (CP) is among the most common noncommunicable disorders, characterized by diverse signs and symptoms. Its unexplored complex genetic landscape could account for clinical heterogeneity. Copy Number Variants (CNVs), which are DNA structural variations involving duplications or deletions of segments greater than 1000 kilobases, can encompass multiple genes altering gene dosage and expression. The aim of our study was to explore CNVs as novel genetic factors in CP.

We employed Genome Wide Association Study (GWAS) to detect known genetic variants across the entire genome. The study population comprised two separate cohorts recruited at Istituto Neurologico "Carlo Besta" and Maastricht University Medical Center, including 515 patients and 580 controls. Genotyping was conducted using the

Infinium Global Screening Array-24 GSAv3.0+MD (Illumina Inc.), covering over 650,000 SNPs. CNV calling was performed on raw luminescence data with multiple tools (iPattern, PennCNV, CNVPartition) to reduce false-positive identifications. CNVs were grouped to detect CNV regions (CNVRs), and an association analysis was conducted to discriminate cases from controls. A meta-analysis was performed to increase the statistical significance of CNVRs with similar effects. Deep phenotypic information was utilized to stratify patients, allowing correlation analyses between CNRVs and specific clinical traits. A comprehensive overview of the CNVR landscape was achieved through supervised and unsupervised machine learning models.

Preliminary analysis successfully identified and replicated a duplication in an intronic CNVR, associated with a three-fold increase in the risk for CP (p-value = 0.038). This duplication maps to the Neuroligin (NLGN1) gene, encoding a cell adhesion molecule expressed in excitatory glutamatergic synapses, crucial in pain sensitization. Recent studies highlight NLGN1 involvement in regulating motivational processes and decision-making, critical aspects in chronic pain patients. Alterations in NLGN1 expression due to genetic factors such as CNVs could contribute to differences in how individuals with chronic pain experience and cope with their condition.

This study represents the first genome-wide CNV analysis for chronic pain. Insights into synaptic mechanisms can guide interventions targeting pain management and comorbid depression, advancing personalized treatments.

BANNWARTH'S LYMPHOCYTIC MENINGORADICULITIS IN A NON-ENDEMIC AREA: IMPLICATIONS ON DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

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Lyme neuroborreliosis (LNB) is a nervous system infection caused by Borrelia burgdorferi (Bb), a common vector-borne disease. The presence of Lyme disease (LB) is also documented in southern Italy and the islands, with considerably lower incidence rates compared to northern Italy, where LB is endemic in some regions. Here, we describe a rare case of LNB, found in a non-endemic area (central Italy, Latium), in a 51-year-old patient, presented with acute onset cephalgia and with multiple cranial nerve involvement.

The patient was followed up with three lumbar punctures spaced over time, two brain and spinal cord MRI studies, nerve conduction study, and serological data.

The patients acutely manifesting with holo-cranial and cervico-dorsal headache, diplegia of the seventh cranial nerve (House-Brackmann score 5), and bilateral hypoesthesia affecting the V_2-V_3 branches of the fifth cranial nerve. The patient's history was negative for certain contact with ticks, evidence of migratory erythema, tache noire and fever. The first lumbar puncture revealed a CSF pleocytosis (33 leucocytes/mm3) characterized by a prevalence of mono-morphonuclear cells and hyper-protidorrachia (282 mg/dl), in the absence of identification, by PCR-DNA, of a specific neurotropic pathogen (including Bb). MRI showed an enhancement of cranial nerves (III-V-VII-VIII-IX-X) and involvement of spinal roots in the cervical segment and cauda. Electroneurography showed diffuse radicular involvement with increased minimum latency of F responses and "A" responses. IgG antibodies specific for Borrelia were tested in CSF by ELISA test on a single antigen (VIsE) which resulted positive. Treated with empirical antibiotic therapy for 21 days, doxycycline 400 mg/day and ceftriaxone 4 gr/day, an improvement of clinical, CSF (10 leucocytes/mm3 and protidorrachia 186 mg/dl) and electroneurographic parameters was observed.

In Europe, the most common manifestation of Early-onset LNB is Bannwarth Syndrome, characterized by painful meningoradiculitis, lymphocytic meningitis, and cranial mononeuropathy. Less frequent manifestations include headache, plexus neuritis, and mononeuritis multiplex. In our patients, the differential diagnosis in the early stages of the clinical course was complicated due to the unlikely medical history for vector-borne disease. The definitive diagnosis of Early-onset LNB with Bannwarth syndrome, based on the EFNS criteria (A. Mygland et al. 2009), was made subsequently, given the finding of specific Borrelia IgG in CSF and serum, by ELISA test on a single antigen (VIsE) and the good therapeutic response to specific antibiotics.

PACHYMENINGEAL INVOLVEMENT IN POEMS SYNDROME: LONGITUDINAL FOLLOW-UP AND CORRELATION WITH VEGF LEVELS AND THERAPY RESPONSE

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POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin changes) syndrome is a systemic disease considered by some authors paraneoplastic due to the presence of an underlying plasma cell disorder. Polyneuropathy is one of the mandatory diagnostic criteria, but central nervous system may also be involved with ischemic lesions or pachymeningeal involvement. Vascular Endothelial Growth Factor (sVEGF) is highly increased in POEMS syndrome, mirrors disease course, and is among the diagnostic criteria. Although pachymeningeal involvement is common in POEMS, changes in response to therapy and correlation with sVEGF, neurological and hematological findings have rarely been reported.

We report on a longitudinal prospective study of 18 POEMS syndrome patients (9 men) median age at diagnosis 58 years, median disease duration at first MRI 9 months, followed at our Center since disease onset (median follow-up 4.3 years). Brain MRI was performed at diagnosis (before therapy) in 16 patients. All patients had IgG or IgA/lambda monoclonal protein, one an IgM/lambda paraprotein. MRIs were analyzed qualitatively from an expert neuroradiologist and classified according to the extent of pachymeningeal thickening. INCAT (Inflammatory Neuropathy Cause and Treatment) disability score was used to assess patients' disability. Hematological response was based on the recent criteria [1]. Neurological and hematological evaluations were performed the same week as MRI. sVEGF levels closer to brain MRI were considered. Bortezomib/dexamethasone were used in 11 patients as first-line therapy and 4 of them underwent autologous stem-cell transplantation (ASCT). One patient underwent daratumumab-bortezomib before ASCT. Lenalidomide was used in 10 patients. Only 3 patients received 3 or more lines of therapy. One patient received radiation therapy for an isolated osteosclerotic lesion.

The overall hematological response rate was 75% after first-line therapy with 50% (8/16) patients achieving at least a very good partial response. All patients pachymeningeal thickening after gadolinium administration was detected at baseline. After treatment, the pachymeningeal thickening decreased in 9 (53%) patients including 2 (12%) patients with complete resolution), remained stable in 5 (29%), increased in 1 (6%) and is still not assessed in 2 (12%). Among patients with a decrease of pachymeningeal thickening, 56% showed a decrease of sVEGF while in 33% it remained stable; in the only patient with pachymeningeal thickening increased after treatment, also VEGF increased.

In conclusion, in this longitudinal prospective study pachymeningeal changes seem to mirror hematological response in patients with POEMS syndrome supporting the pachymeningeal involvement as a useful marker of the disease.

PAINFUL SMALL FIBER NEUROPATHY: A NOVEL MUTATION IN THE SCN10A GENE

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We describe the case of a 35-year-old patient with severe painful small fiber neuropathy, early onset of symptoms and a long history of clinical and instrumental examinations who underwent over time several aggressive and ineffective treatments for a putative rheumatological disease.

Symptoms started at the age of 21 with paraesthesia and burning pain in pectoral and periscapular area and at the hands. Shortly thereafter pain gradually spread to involve both feet and pelvic area. Twelve years after onset of symptoms, the patient reported generalized burning pain affecting also face and tongue. The pain was so severe he could only walk with the help of crutches. He also complained of gastroesophageal reflux, early satiety, bloating and severe constipation. Neurological examination was normal except from mechanical allodynia at both feet. He underwent functional and morphological assessment of small fibers.

Spine and brain MRI, nerve conduction study, blood examination for dysmetabolic and dysimmune disorders were not relevant.

Quantitative sensory testing showed abnormal thermal thresholds. Sympathetic skin response was abnormal and dynamic sweat test showed a non-length-dependent hypohidrosis.

Cardiovascular reflexes were normal. Skin biopsy revealed a moderate non-length dependent loss of sensory and autonomic nerves. Exome sequencing revealed a heterozygous VUS mutation (c.4852A>C; p.-Met1618Leu) in the SCN10A gene.

The same clinical and instrumental features were present in a sister and in the father of our patient who carried the same mutation.

Awareness of the genetic causes of SFN is crucial for providing correct diagnosis and treatment for patients and their family.

EARLY NOCICEPTIVE EVOKED POTENTIALS (NEPS) IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS AND CHARCOT-MARIE-TOOTH DISEASE TYPE 1A

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A recent publication has described early nociceptive evoked potentials (NEPs) recorded from the scalp after selective electrical stimulation of

the free intraepidermal nerve endings using an interdigitated electrode with rail gaps of 150μm only (150IDE). The first negative component (N40) has been considered to reflect the activation of the primary sensory cortex by nociceptive afferents, comparable to the somatosensory N20. This technique allows for an objective assessment of the nociceptive pathway from the periphery to the primary cortex, quite different from the endogenously generated late vertex responses. In this study, we used the NEP technique to investigate some neuropathic conditions in comparison to age-matched healthy volunteers.

The study involved 20 healthy individuals, 9 with Charcot-Marie-Tooth disease 1A (CMT1A), 6 with hereditary transthyretin (ATTRv, v for variant) amyloidosis, and 3 presymptomatic Phe64Leu carriers. Standard nerve conduction velocity studies, Sudoscan for Electrochemical Skin Conductance (ESC), and 150IDE-NEPs were conducted. Data from affected and control subjects were compared using the Student's t-test or Mann-Whitney U test, as appropriate.

In healthy individuals, we confirmed that early NEPs are evoked after stimulation with the 150IDE. NEPs demonstrated statistically significant ($p<0.05$) abnormalities in all CMT1A patients, with non-recordable or delayed N40, P50, N60, and P80. ESC was normal in CMT1A subjects but in two, confirming the expected prevalent Aδ rather than C fibre involvement in CMT1A. Regarding ATTRv, half of the patients (3/6) had abnormal NEPs, while 5 subjects exhibited reduced ESC. The interpatient variability in NEPs may be attributed to the varying involvement of Aδ fibers with different TTR variants. Taken altogether, the ATTRv group showed significant differences at P50, N60, and P80 when compared to normal subjects. Presymptomatic ATTRv carriers were more than 10 years away from the predicted age of disease onset and displayed normal ESC and 150IDE-NEPs. Analyzing all patients together, individuals with neuropathic pain showed significantly longer N40 and N60 latencies compared to those without, and subjects with thermal hand hypoesthesia exhibited lower N60 amplitude than those without hypoesthesia.

In all healthy individuals, we confirmed the presence of early potentials following rhythmic stimulation with the 150IDE, which may represent a valuable tool for small fiber neuropathy (SFN) detection. In CMT1A, we confirmed the involvement of Aδ fibers. Early SFN detection could help identify the early transition to symptomatic disease in ATTRv.

CHRONIC PAIN SUSCEPTIBILITY: INSIGHTS FROM A TWO-STAGE GENOME-WIDE ASSOCIATION ANALYSIS

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Our study delves into the complex and heterogeneous nature of Chronic Pain (CP), employing a genome-wide untargeted approach to explore the impact of genetic variants on CP susceptibility and to unravel the missing heritability.

The two-stage GWAS included an Italian cohort (315 CP patients, 308 healthy controls) and an independent European sample (200 CP patients, 200 controls) for replication. Genotyping employed the Infinium Global Screening Array-24+ v3.0 GSA v3.0+MD, with imputed data from 1000 Genomes v3. Rigorous quality controls and ethnic stratification correction were applied. Association analyses comparing CP to healthy controls have been conducted at various levels: 1) Single variant analysis to assess the impact of individual genetic variations 2) Epistasis analysis to explore interactions between different genetic variants in multiple genes to identify combined effects and 3) gene-level analyses to aggregate multiple variants, considering the overall contributions of the genes. Stratified analyses were performed based on phenotypic sub-groups. Gene-ontology and pathways analyses provided insights into potential biological mechanisms.

The epistasis analysis significantly identified and replicated 3 interaction pairs of polymorphisms associated with the risk of chronic pain compared to healthy controls (meta-analysis odds ratio (OR) from 2.26 to 4.21, p-values ranging from 1.2X10-8 to 3X10-28) and 4 protective pairs (meta-analysis OR from 0.26 to 0.42, p-values ranging from 1.03x10-3 to 2x10-69). Our gene-level analysis revealed multiple genes (NELL1, GPRIN2, EDNRA) significantly enriched in risk variants within the neuron projection guidance biological function. Moreover, the intergenic locus between ANXA10 and DDX60 genes is enriched with 53 rare variants (P= 5.5X10-5) with a protective role against CP, with Annexin A10 already described as implicated in neuropathic pain development.

The study advocates for the strength of gene-level aggregation and epistasis analysis, over the single variant approaches, to unravel the chronic pain susceptibility, given its complex nature. However, future work should investigate the functional role of these variants, frequently localized in intergenic or intronic regions.

PROTEASOME INHIBITORS-BASED CHEMOTHERAPY INDUCED NEUROTOXICITY: FOCUS ON CYTOSKELETAL AND MITOCHONDRIAL DYSFUNCTION

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The proteasomal system is involved in the turnover of damaged proteins and it is responsible for their degradation. Because of its role in oncogenesis, the inhibition of the proteasome system is a promising therapeutic target for neoplastic treatment. The accumulation and deleterious effects of toxic proteins are frequently induced by exposure to chemotherapeutic drugs and 20S proteasome inhibitors, such as bortezomib (BTZ) and carfilzomib (CFZ), which have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of multiple myeloma (MM) and some other liquid tumours. Although the survival of MM patients has been improved by the introduction of both drugs-based therapies, these proteasome inhibitors have several limitations, including chemotherapy-induced peripheral neurotoxicity (CIPN). Since it is becoming increasingly clear that cytoskeletal integrity and mitochondrial function are intricately linked, we compared these targets after BTZ and CFZ treatments *in vitro*. Primary culture of dorsal root ganglion (DRG) sensory neurons isolated from adult mice were treated with BTZ 10 nM and CFZ 60 nM for 24 hours, and measurement of energy metabolism were investigated using XFe24 Seahorse Analyzer, while a morphological analysis of mitochondria was performed *in silico* using the toolset MiNA (Mitochondrial Network Analysis). Moreover, by immunoblotting we have evaluated drug-induced alterations of proteins involved in cytoskeleton, mitochondrial oxidative phosphorylation, and molecular motors transport.

BTZ was shown to induce several cytoskeletal damage in terms of increased levels of delta2-tubulin, acetylated tubulin and MAP2 expressions compared to both CFZ-treated cells and untreated cells. Conversely, the evaluation of the bioenergetic mitochondrial metabolism revealed a reduction in basal and maximal respiration for both chemotherapeutic drugs. Similarly, both BTZ-and CFZ cultures showed a decrease in ATP production compared with the untreated cells. These alterations were associated with a disruption in the organization of the mitochondrial network. These findings suggest that BTZ-induced neurotoxicity mechanism is correlated with peculiar cytoskeletal alterations, while changes in mitochondrial skeleton morphology along with reduced mitochondrial respiration may be a common mechanism underlying cell toxicity. Understanding these pathways may provide specific therapeutic targets for the treatment of BTZ-induced CIPN.

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Keywords: neurotoxicity, bortezomib, carfilzomib, microtubule stability, mitochondria biogenesis, mitochondrial network

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY AND OPTIC NEUROPATHY: A CHANCE ASSOCIATION?

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Combined central and peripheral demyelination (CCPD) is a rare entity characterized by chronic inflammatory demyelination of peripheral nerves (CIDP) and central nervous system (CNS) involvement, usually associated with NF155 antibodies (1,2,3). We report two cases of CCPD patients with CNS involvement characterized by optic neuritis (ON).

Case 1. A 59-year-old woman was admitted to our department because of acute onset of burning pain in lower back, lower limb paresthesias, and bilateral peripheral facial weakness occurring 15 days after administration of the first dose of COVID-19 vaccine ChAdOx1-nCov-19. She also reported low visual acuity and pain during movements of left eye. Cerebrospinal fluid examination (CSF) was consistent with CSF albumin-cytologic dissociation (protein 256 mg/dl, 1 cell). Nerve conduction study revealed demyelinating sensori-motor polyradiculoneuropathy consistent with the diagnosis of acute onset of immunomediate polyneuropathy. Anti-gangliosides and nodal/paranodal autoantibody screening was negative. IVIG treatment slightly improved symptoms. Brain MRI showed left monolateral ON. High dosage of IV steroid did not improve visual acuity. She received a diagnosis of CIDP according to definite European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria associated to ON (3). Peripheral neuropathy was under control with steroid treatment, while no improvement was observed in visual function at follow-up visits.

Case 2. A 70-years-old male, with Sars-cov2 infection about 2 months earlier, was admitted to our department for progressive generalized hyposthenia, painful and tingling-type paresthesias at the lower limbs. He got progressively worse becoming chairbound in 3 months, and at the same time he complained of low visual acuity in left eye. CSF examination revealed albumin-cytologic dissociation (protein 187 mg/dl, 3 cells). Brain MRI demonstrated recent signs of left ON. Neurophysiological study was performed after six months from clinical onset and fullfied CIDP criteria according to EFNS/PNS. Neither anti-gangliosides nor nodal/paranodal autoantibodies were found. IVIG and steroids treatment drastically improved motor and sensory symptoms, but visual loss didn't.

We report two CIDP patients who also developed ON. These forms of CCPD were not linked to NF155 autoantibody (2). In both cases, the peripheral phenotype improved regardless severity, while the visual loss did not respond to treatment (IVIG and steroid), and remained the major disability. Further studies are needed to clarify if this is a chance association or a new entity related to immunomediate response against to SARS-COVID2 antigens.

PHOSPHORYLATED TDP-43 ACCUMULATES IN THE SKIN OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

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Aggregates of phosphorylated TAR-DNA binding protein-43 (pTDP-43) in the cytoplasm of neurons and neuroglia in the central nervous system represent the main pathological hallmark of ALS. Currently, in the peripheral nervous system, pTDP-43 has been detected in axon and Schwann cells of motor nerves in ALS patients. In the last decade peripheral sensory involvement has been demonstrated in ALS through skin biopsy. In addition, we recently demonstrated morphological changes of sensory cutaneous nerves paralleling disease severity and prognosis.

Therefore we aim to investigate if pTDP-43 deposits are present in the skin of ALS patients and if this finding correlates with nerve abnormalities and disease severity.

We applied indirect immunofluorescence technique and confocal microscope on skin samples from leg, thigh and fingertip to search for deposits of pTDP-43 in 20 controls and 20 patients (median age (IQR): 65,5 (16,5), 8 woman, 12 man), with a diagnosis of "probable", "probable laboratory-supported" or "definite" ALS, as per the revised El Escorial criteria. According to ALS King's scale, 10 patients were in the I-II and 10 in III-IV stage.

In the skin of ALS patients we observed pTDP-43 immunoreactivity in both nucleus and cytoplasm of keratinocytes, in the cytoplasm of dermal cells, in dermal nerve fascicles with no colocalization with PGP and in the capsule of Meissner corpuscles (MC) with no co-localization with PGP-ir neural component of the receptors. Using Image J software, we quantified the PGP-ir neural component of Meissner corpuscles and the pTDP-43 deposits in the capsule in each receptor. The ratio pTDP-43/PGP tended to be higher in patients belonging to advanced disease stages (0.9(0.8)) compared with patient at early disease stage (0.7(0.8)). pTDP-43 immunoreactivity was not found in the skin of controls.

Our work showed for the first time, in the skin of ALS patients, pathological pTDP-43 deposits that correlated with disease severity. This finding suggests a possible role of pTDP-43 skin deposits as in vivo specific biomarker of ALS and of disease aggressiveness.

MOBILE HEALTH TECHNOLOGIES IN MONITORING TREATMENT RESPONSE TO IMMUNOGLOBULINS IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY: A PILOT LONGITUDINAL STUDY

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Background: Response to treatment in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is defined using disability and impairment scales, despite their limited accuracy in detecting minimal changes in the clinical setting. Objective of the study was to explore the role of mobile health technologies (MHT) as potential outcome measure to evaluate treatment response in CIDP patients treated with intravenous immunoglobulin (IVIg).

Patients and Methods: Seven patients with a diagnosis of CIDP according to EAN/PNS criteria treated with IVIg and fifteen age- and sex-matched healthy controls (HC) were enrolled. Patients were asked to stand up from a chair, maintain the Romberg position, perform the Timed Up and Go (TUG) test and walk 20 metres at normal and fast speeds using wearable sensors attached to the lower limbs. Digital mobility assessments were performed at drug administration (T0) and at 21 (T1) and 45 days (T2). INCAT, I-RODS and grip strength data were also collected at each visit. Differences between CIDP and HC in postural transition, balance, turning and gait MHT parameters were assessed using non-parametric tests. Comparison of the three time points was evaluated by repeated measures ANOVA.

Results: Compared to HC, CIDP patients showed greater jerks, longer step time and turn duration, and lower angular and peak angular velocity at T0 (all p values <0.05). At follow-up, CIDP patients showed an improvement in the TUG peak and mean angular velocity at T1 compared to baseline (all p values <0.05), while no significant differences were found between T1 and T2. No statistically significant changes in clinical scales were observed across the three assessments.

Discussion: MHT assessment, compared with classical clinical scales, was able to detect minimal changes in mobility in CIDP patients and to track the effects of IVIg treatment on several mobility components, especially in the early phase after drug administration. Therefore, MHT may be a useful tool to monitor patients and their response to different treatment strategies.

NERVE TORSION AS A PATTERN OF PARSONAGE-TURNER SYNDROME: LITERATURE REVIEW AND TWO REPRESENTATIVE CASES

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Parsonage-Turner Syndrome (PTS) is a rare peripheral nerve disease characterized by different degrees of nerve impairment. The recent development of nerve ultrasound has enabled the use of new data to support disease diagnosis.

A review of the last 10 years literature about ultrasound evaluation in PTS was performed. In addition, two cases of PTS patients on whom nerve ultrasound was performed at the first evaluation and after the specific treatment were described.

The results of our review show that although PTS is defined as a plexopathy, it is most often a form of multifocal neuropathy. We also report the most frequently used ultrasound classification and possible prognostic correlations and report our experience with the description of two paradigmatic clinical cases.

Further studies are needed to understand the true prognostic power of each degree of nerve impairment and the possible implications in clinical practice regarding treatment indications.

MULTIDISCIPLINARY UNCONVENTIONAL TOOLS IN PRE-SYMPTOMATIC PATIENTS WITH MUTATION FOR TRANSTHYRETIN AMYLOIDOSIS

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Hereditary transthyretin amyloidosis (ATTRv) is a rare, autosomal dominant, multisystemic and devastating disease. If untreated, the disease is fatal within 4–15 years from onset. Thus, diagnosis in the early stages of ATTRv is crucial to start treatment, preventing or halting disease progression. However, the diagnosis of converted ATTRv in *TTR* gene mutation carriers may be challenging. We aimed identifying early indexes of multisystemic involvement in a cohort of pre-symptomatic subjects (carriers) harbouring *TTR* gene mutation.

Sixteen TTR-mutation carriers (mean age 51±9 years, 6 males) with normal nerve conduction study, maximal left ventricular thickness <12 mm and negative (Perugini 0) 99mTc-labeled bisphosphonate (HMDP) scintigraphy constituted the study populations. Subjects underwent tactile and thermal quantitative sensory testing (QST) at foot and comprehensive cardiological assessment including echocardiogram with evaluation of global longitudinal strain (GLS).

Seven carriers harboured Val30Met and the remaining 9 Phe64Leu mutation. Among the 16 subjects, tactile threshold was abnormal in 4/15 (26.6%) carriers, Cold Detection Threshold in 11/15 (73.3%), Warm Detection Threshold in 10/15 (66.6%), Cold Pain in 11/15 (73.3%) and Heat Pain in 11/15 (73.3%). Abnormal GLS (>-20%) was observed in 50% of asymptomatic carriers, independent of age and cardiovascular risk factors. GLS correlated with cold pain abnormalities ($p<0.05$).

As already know QST can evidence small fiber dysfunction in the most of patients. GLS reduction in presymptomatic carriers suggests early cardiac dysfunction unrelated to traditional measures. Interestingly, cardiac impairment seems to parallel that of small nerve fibers, at least in the earliest stage of disease: all 8 patients with abnormal GLS had at least one abnormal QST parameter as well. However, the role of GLS is still uncertain: can these 8 carriers be considered as "converted"? Can they access to a ATTRv treatment? Are they at risk of soon conversion? These questions are still unsolved and only the follow-up of these patients can clarify the usefulness of a combined approach with GLS and QST in the "conversion" diagnosis.

THE ROLE OF TECHNOLOGICAL REHABILITATION IN PATIENTS WITH INTENSIVE CARE UNIT WEAKNESS: A RANDOMIZED CONTROLLED PILOT STUDY

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Intensive-Care-Unit-Acquired Weakness (ICU-AW) is the most common neuromuscular disorder in critically ill patients and can have a significant impact on long-term disability. Early rehabilitation has been suggested to facilitate the natural recovery process. This is a pilot, randomized, single-blind study that aimed to evaluate the effectiveness of intensive combined technological rehabilitation treatment including focal muscle vibration and non-immersive virtual reality for patients with severe acquired brain injury (sABI) and ICU-AW. Twenty-four patients were randomized into the conventional group, which performed only conventional rehabilitation, and the experimental group, which also performed technological treatment. Assessments of motor function, autonomy, disability and quality of life were conducted at baseline, and after 3 weeks of treatment. At the end of the intervention, both groups showed significant improvement. However, patients in the experimental group achieved greater improvement in disability ($p = 0.001$) and quality of life ($p = 0.001$). The results show that intensive structured rehabilitation is effective in improving the motor function, disability, and quality of life of patients with severe acquired brain injury and weakness. The combination of non-immersive virtual reality training and focal muscle vibration can result in a significant improvement in overall disability and quality of life compared with conventional treatment alone. These are preliminary data, further feedback is needed to confirm the starting hypothesis so the study is carrying on to enlarge the sample size.

NEUROPHYSIOLOGIC EVALUATION IN PATIENT WITH ATAXIA AND ACOUSTIC NEURINOMA. EXTENDING ELECTRODIAGNOSTIC STUDY TO IDENTIFY NEURONOPATHY IN CEREBELLAR ATAXIA, NEUROPATHY AND VESTIBULAR AREFLEXIA SYNDROME

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Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) is a recognized cause of late-onset hereditary ataxia characterized by vestibular and cerebellar impairment and neuropathy. The pathological background of CANVAS neuropathy is a non-length-dependent dorsal root ganglionopathy.

A 78-year-old woman was admitted to our department referring a 10-year history of progressive imbalance, ataxia and cerebellar dysarthria. Since 1986, she complained of dry cough ascribed to gastroesophageal reflux. In 2016, she underwent brain MRI that revealed left acoustic neurinoma. In 2022, she was diagnosed of ataxia in sensory neuropathy and acoustic neurinoma; genetic causes of spinocerebellar ataxia were excluded. Neurological examination showed mixed sensory and cerebellar ataxia, cerebellar dysarthria, horizontal gaze-evoked nystagmus, oscillopsia and diplopia, distal lower limb amyotrophy, hypopallesthesia. Upper-limb and knee jerks were preserved, ankle jerks were absent. Neither sensory and autonomic complaints nor hypoacusis were referred.

Brain MRI showed cerebellar atrophy and small left acoustic neurinoma. Cerebrospinal fluid and serological investigation for acquired ataxias were negative. Sensory action potentials were absent in four limbs at electrodiagnostic studies (EDx); motor EDx showed mild axonal lower-limb neuropathy with normal F-wave latencies. Tibial H-reflex was retained. Somatosensory evoked potentials were not recordable. Brainstem auditory evoked responses were normal. Vestibular-evoked myogenic potentials showed delayed left responses compared to the contralateral, consistent with left acoustic neurinoma. Trigemino-cervical reflex was normal, bilaterally. To evaluate small nerve fibers and autonomic function, we used Edx performed during routine neurophysiology. Blink reflex (BR) and masseter inhibitory reflex (MIR) were tested stimulating the trigeminal nerve at 5, 10, and 15 times the perceptual threshold (5x, 10x, 15xPT). The BR showed increased latency of the R2 component. Normal silent period component 1 (SP1)of MIR was obtained stimulating mental nerve 10xPT. Delayed SP2 component appeared at 15xPT stimulation. Median nerve silent periods were recorded after mixed nerve (MNSP) and cutaneous (CSP) stimulation. CSP was not recordable whereas MNSP was normal. Sympathetic skin responses (SSR) were obtained with electrical stimulation. Nevertheless, acoustic and respiratory stimuli failed to evoke SSR. Skin biopsy showed non-length-dependent small fiber neuropathy. Head impulse test confirmed severe bilateral vestibular dysfunction. Biallelic intron 2 expansion in the replication factor complex subunit 1 (RFC1) was identified.

Sensory neuropathy involving cranial nerves and small diameter fiber dysfunction, with relatively preserved Ia afferents, led to the consideration of CANVAS diagnosis. This case highlights the importance of unconventional neurophysiological tests, besides routine EDx protocol, to investigate large, medium, and small size fibers in cranial and spinal districts.

EVALUATION OF SATELLITE GLIAL CELLS CHANGES IN DORSAL ROOT GANGLIA IN CHEMOTHERAPY-INDUCED NEUROTOXICITY MODELS

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Chemotherapy-induced peripheral neurotoxicity (CIPN) is one of the most frequent disabling side effects associated with the administration of commonly used antineoplastic drugs such as anti-tubulins (paclitaxel, PTX) and platinum derivatives (cisplatin, CDDP). Due to the incomplete knowledge about the underlying pathophysiology of CIPN, to date no effective therapies are available for CIPN prevention. Most of the molecular mechanisms related to the onset of neurotoxicity proposed so far mainly focused on sensory neurons in dorsal root ganglia (DRG) as principal target. In this study, we explored CIPN investigating the changes of satellite glial cells (SGCs) in the DRG and their crosstalk with neurons, induced by chronic administration of PTX or CDDP in rats.

Morpho-functional analyses, including neurophysiological analysis and behavioural tests as well as neuropathological investigations, were performed to verify the features of CIPN both at the end of chemotherapeutic treatments and after 4 weeks of follow up. Qualitative and quantitative immunohistochemistry, 3D-immunofluorescence, immunoblotting, and transmission electron microscopy analyses were also performed to detect alterations in SGCs and their interconnections.

We observed that after 4 weeks of treatment with PTX, but not CDDP, SGCs in DRG showed an extensive upregulation of GFAP demonstrating a strong glia activation. A similar level of activation persisted at the end of follow up period, when the painful component of neuropathy, but not the nerve damage, was resolved. In addition, non-physiological connections between SGCs and/or SGC-neuron were evident in rats treated with PTX. In fact, activated SGCs surrounding different adjacent neurons were found, and an increase in the contact between SGCs and their associated neurons displaying a peculiar pattern of glial cytoplasmic projections was present. Moreover, PTX increased the expression of Connexin43 with perineuronal localization and the expression of the adhesion molecule L1-CAM in the cytoplasm and plasma membrane of neurons.

We conclude that SGCs could have a key role in the onset of PTX-induced peripheral neurotoxicity, paving the way for the identification of new druggable targets for CIPN prevention and treatment.

TELE-COACHING PHYSICAL EXERCISE FOR PATIENTS WITH CHARCOT-MARIE-TOOTH DISEASE: AN ITALIAN MULTICENTRIC STUDY "EFTELCMT23"

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Charcot-Marie-Tooth disease (CMT) is the most common inherited disorder of the peripheral nervous system characterized by slow and progressive sensorimotor impairment of the legs and hands. The disease course is variable because of genotypic and phenotypic heterogeneity. To date, there are no effective treatments for CMT and rehabilitation therapy and functional surgical are the only available options. Physical exercise may be beneficial to maintain strength, balance and other functions, however, only a few studies on the benefits and risks of exercise have been conducted. The aim of this study was to evaluate the effectiveness of telecoaching-mediated aerobic physical exercise three times per week in patients with confirmed CMT diagnosis.

We planned a multicenter, prospective, randomized, single-blind, controlled study. The clinical endpoints including body mass index, CMT Neuropathy Score (second version), Modified Rankin Scale, handgrip strength and balance assessment (Berg Balance Scale and Timed Up & Go Test) as well as patients reported outcomes including Pittsburgh Sleep Quality, International Physical Activity Questionnaires, Walking Impact Scale (Walk-12), Graded Chronic Pain Scale-Revised, and Short Form Health Survey 36. All participants will be assessed at screening visit (T0), after 3 months (T1), after 6 months (T1), and after 9 months (T3). The overall duration of this study will not exceed 24 months. Furthermore, we also aim to explore the safety and tolerability (i.e., pain, strength reduction) of physical exercise in patients affected by CMT.

To date, we recruited 71 outpatients affected by CMT. From the analysis of the data concerning the patients who completed T2 - which represent only a part of the sample of the research project - and by comparing the results in the three-time intervals, improvements emerged for almost all the characteristics evaluated. Progressive improvements also emerged from the questionnaires. The results suggest that over the 6 months of our research, the limitation in walking, the pain, the quality of sleep and the quality of life progressively improved, especially following the 3 months of training.

The tele-coaching program demonstrated great compliance from the patients and displayed to be useful in a short-term followup period in terms of patients management, high motivation maintenance over time, and great flexibility.

GENETIC SCREENING FOR HEREDITARY TRANSTHYRETIN AMYLOIDOSIS WITH POLYNEUROPATHY IN WESTERN SICILY: FOCUS ON THE CITIES OF CAMMARATA AND SAN GIOVANNI GEMINI

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Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) is a rare, inherited, progressive disease caused by mutations in the transthyretin (TTR) gene, leading to misfolded monomers that aggregate generating amyloid fibrils. Previous studies demonstrated that ATTRv-PN is not uncommon. Furthermore, genetic screening for ATTRv-PN showed the presence of a different genetic background in the population of Sicily. Among these studies, a genetic screening for ATTRv-PN was proposed in Cammarata and San Giovanni Gemini, two countries of western Sicily, with 5,839 and 7,463 inhabitants respectively, in the province of Agrigento. The population of Cammarata and San Giovanni Gemini will be subjected to a screening on a voluntary basis. The presence of specific "red flags" will be investigated through a detailed questionnaire. The subjects will be screened if they present two or more "red flags" among the following: family history of polyneuropathy or cardiopathy, bilateral carpal tunnel syndrome, cardiac insufficiency, renal amyloidosis, lumbar tract stenosis, autonomic dysfunction, idiopathic gastrointestinal disease, amyloid deposits on biopsy, and vitreous opacities. For screening, we proposed a molecular genetic test according to expert consensus statements and updated guidelines. We found that a systematic screening for ATTRv-PN yields an increased recognition of the disease in our neurological clinic. A focused approach for the screening of ATTRv-PN could lead to an earlier diagnosis and identification of asymptomatic carriers, who will be promptly treated after a strict follow up at the clinical onset. Furthermore, general practitioners and clinicians can have a key role in the screening and initial management of ATTRv, but they need the right tools to do so.

IMMUNE EVENTS PRECEDING NEURALGIC AMYOTROPHY

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Infections and vaccinations have been identified as potential immunological triggers preceding neuralgic amyotrophy (NA), but the exact type and frequency of the agents involved are unknown.

We planned amulticenter, prospective, observational, matched case-control study. NA was diagnosed by neuromuscular experts according to existing clinical criteria and electrodiagnostic studies. Clinical data and biological samples of NA patients were collected within 90 days from onset. Serological tests and PCR diagnostics for Hepatitis E virus, Human Immunodeficiency Virus, Severe acute respiratory syndrome coronavirus 2, Epstein-Barr virus, Cytomegalovirus, Parvovirus B19, Varicella-zoster virus, *Borrelia burgdorferi*, *Mycoplasma pneumonia and Bartonella Henselae*, were performed in the same laboratory. Each patient was matched for age, gender, and place of residence with a healthy control.

We included 57 patients and corresponding controls. The mean age was 45 years for both groups. We found that NA onset was preceded by an infectious trigger in 16/57 (28.1%) patients, mostly of viral origin (26.3% of total cases). COVID-19 vaccination was considered a potential trigger in 6/57 (10.5%) subjects. A viral trigger was associated with a bilateral involvement of the brachial plexus (p=0.003, Cramèr's V=0.43).

Immune triggers (infection or vaccination) preceded 22/57 (38.6%) of the NA cases. We suggest to test acute NA patients for HEV, *Mycoplasma pneumonia*, SARS-CoV-2, EBV, VZV, and Parvovirus B19.

MONOCLONAL-GAMMAPATHY-OF-UNDETERMINED-SIGNIFICANCE ASSOCIATED NEUROPATHIES: CAREGGI HOSPITAL (FLORENCE) OUTPATIENT EXPERIENCE

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The association between neuropathy and monoclonal gammapathy of undetermined significance (MGUS) has been widely investigated in literature, although leaving some uncertainty. In most cases It is possible to identify a disimmune process, for example, the serum reactivity towards the Myelin-Associated Glycoprotein (MAG) or gangliosides (i.e., GM1). Less clear, instead, the role of MGUS when a specific auto-reactivity is not detected.

The aim of the study was to characterize patients with neuropathy and concomitant MGUS.

Clinical and instrumental (ENG/EMG) data were collected from patients who had different types of neuropathies and MGUS (or without MGUS as control-population) followed by the NeuroMuscular Disorders Neurology Department in AOU Careggi, Florence, from 2008 to 2023.

We identified 114 patients with a MGUS-associated polyneuropathy (37 women and 77 men, M/F=2.1) with mean neuropathy onset age of 66.6 years (range 38-90 y) and with a mean modified-Total Neuropathy Score (mTNS) of 7.2. Of these, 63 (55.2%) either have anti-MAG antibodies (39 cases, 34.2%) or anti-ganglioside/sulfatides (24 cases, 21%); the remaining 51 patients have no specific reactivity. Patients with anti-ganglioside/sulfatide antibodies present a slightly higher M/F ratio (3), an earlier onset of the neuropathy (62 years) and a higher mTNS (11.7), compared with the other groups. The group of patients without any specific reactivity doesn't differ significantly from those with anti-MAG positivity as for M/F ratio, age of onset, and mTNS. Within this seronegative population, 23 (45%) individuals have an IgM-M protein and 28 have a non-IgM MGUS (IgG or IgA). We obtained clinical and electrophysiological diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) in 17 cases (33%, 9 with IgM-MGUS, 7 with IgG and 1 with Free Light Chains and of multifocal motor neuropathy (MMN) in 1 case (2%, with IgM MGUS). The remaining 33 patients present with unspecific axonal and/or myelinopathic, sensory or sensory-motor polyneuropathy. Patients with both CIDP and MGUS, compared with other 27 outpatient CIDP subjects without MGUS, have a slightly higher mean age (61.5 vs 55.3) and significantly lower mTNS (7.2 vs 10.1, p=0.04). Conversely, 33 patients with polyneuropathy and MGUS, compared with other 39 patients having idiopathic polyneuropathy without MGUS, show similar age (72.5 years vs 70.6) and clinical score (5.1 vs 4.1)

The association with MGUS characterizes a subpopulation of seronegative CIDP with a less aggressive clinical evolution. The high incidence of MGUS in CIDP cases (38.6%) indicates this hematologic condition as a risk factor independently of specific antibody reactivity.

RILP, A RAB7A EFFECTOR, INTERACTS WITH TDP-43 AND ITS DOWNREGULATION IN A FAMILIAL CASE OF AMYOTROPHIC LATERAL SCLEROSIS COMPROMISES THE AUTOPHAGY-LYSOSOMAL PATHWAY

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The autophagy lysosomal pathway (ALP) is the main mechanism responsible for the degradation of intracellular macromolecules which are carried into lysosomes for degradation and recycling. Fusion events between autophagosomes with components of the endocytic pathway lead to maturation into autolysosomes, in which degradation of cargo takes place.

Ras-related in brain 7 (RAB7A) is a small GTPase belonging to the Rab family, and it is important for transport to late endosomes and lysosomes. This protein has also important roles in some events related to

final autophagosome maturation which requires autophagosome movements from cell periphery to the perinuclear region. RAB7A is involved in this process recruiting RILP Rab-interacting lysosomal protein (RILP), which recruits the dynein-dynactin motor.

The role of another protein in the ALP recently emerged: TDP-43 TAR DNA-binding protein 43 (TDP-43) participates in RNA metabolism and some of the mRNAs regulated by TDP-43 are involved in the autophagy pathway.

We previously studied amyotrophic lateral sclerosis (ALS) fibroblasts obtained from patients belonging to an Italian family carrying a mutation in *TARDBP*, which results in the G376D aminoacidic substitution, demonstrating that they are characterized by increased oxidative stress, reduced viability, and cytosolic TDP-43 aggregates. The formation of TDP-43 aggregates interferes with TDP-43 normal nuclear functions, and their appearance could be related to alterations in the autophagy pathway.

We tried to clarify the role of RILP on autophagy using western blot analysis, confocal microscopy, and immunoprecipitation.

Here, we found that TDP-43 and RILP silencing strongly affects the autophagy pathway. Moreover, we demonstrated that RILP, TDP-43 and RAB7A are interacting partners, the interaction between RAB7A and TDP-43 is mediated by RILP, and the TDP-43^{G376D} mutation alters the interaction between RILP and TDP-43. The expression of RILP in ALS fibroblasts resulted decreased compared to control cells and we also found compromised lysosomal activity and reduced autophagic flux. Therefore, we hypothesized that RILP could have an important role in the alterations of autophagy observed in ALS cells. Thus, we overexpressed RILP in ALS fibroblasts and we observed the rescue of the autophagic flux in these cells, highlighting the importance of this protein in ALS disease, as its downregulation could be responsible for altered autophagic flux and consequent neurodegeneration.

These data suggest that the dysregulation of RILP expression and function may be responsible for autophagy disfunction which characterized ALS but also other neurodegenerative disorder, possibly highlighting a new pathogenic mechanism.

CHRONIC ATAXIC NEUROPATHY WITH DISIALOSYL ANTIBODIES: A THERAPY CHALLENGE

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Chronic neuropathies with anti-disialosyl ganglioside IgM antibodies are rare immune-mediated sensory-ataxic neuropathies with antibodies against disialosyl gangliosides. They include Chronic Ataxic Neuropathy Ophtalmoplegia IgM paraprotein cold Agglutinins and Disialosyl antibodies (CANOMAD) and Chronic Ataxic Neuropathy with Disialosyl Antibodies (CANDA). Given the rarity of the diseases, there is no consensus about treatment, but intravenous immunoglobulin (IVIg) and Rituximab (RXT) seem to be efficacious. Recently subcutaneous Ig (SCIg) have also been shown to maintain clinical stability, avoiding end-of-dose fluctuactions.

We describe the disease course and response to treatment in a CANOMAD patient.

A 41-year-old man went to the Emergency Room for acute onset of lower limb weakness, ataxic gait, distal limbs and oral paresthesia, bilateral ophthalmoparesis. Cerebrospinal fluid analysis revealed immune-cytologic dissociation. Nerve conduction studies disclosed a sensory-motor polyneuropathy with signs of acquired demyelination. Miller-Fisher syndrome was diagnosed and the patient was treated with IVIg with benefit. After nine months, a subacute worsening led the patient to hospital admission. Serum was positive for anti-GD1b IgM antibodies. The patient was treated with IVIg (1,2 g/Kg in five days) every four weeks, with partial improvement. The disease however became relapsing-remitting with IVIg dependance and significant end-of-dose fluctuations. Oral prednisone (0.75mg/kg/day for two months) was ineffective. Two courses of RXT (four infusions of 375 mg/m^2 weekly) were administered with no benefit. The 20% reduction of the IVIg dosage attempted four months after the RXT course was followed by clinical deterioration. Plasma-exchange was ineffective and worsening of ataxia with the reappearance of ptosis, ophthalmoparesis, and dysarthria occurred. Treatment with IVIg (1,4 g/Kg for five days) every four weeks led to slow improvement of weakness and ophthalmoparesis. Wearing-off fluctuations reappeared. Subcutaneous immunoglobulin (SCIg) achieved a stable response without fluctuations.

The pathogenesis of CANOMAD is not fully understood. Disialosyl antibodies have different targets (dorsal root ganglia, large myelinated fibers, nodal axolemma and nodes of Ranvier) and may be produced from an antigen-dependent B cell proliferation. The antibodies activate complement with destruction of voltage-gated sodium channels and paranodal junctions, leading to a failure in saltatory nerve conduction.

In our patient, RXT was ineffective, demonstrating that, besides B cells, there may be other players in immunopathophysiology. Relapsing-remitting course suggests there might be a persistent underlying pathogenic trigger. In our patient, responsive to IVIg but with frequent relapses and end-of-dose fluctuations, SCIg were able to maintain clinical stability, and may be considered an ideal therapeutic option.

MAGNETIC RESONANCE NEUROGRAPHY OF BRACHIAL AND LUMBO-SACRAL PLEXI IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS POLYNEUROPATHY

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INTRODUCTION The therapeutic advances in hereditary transthyretin amyloidosis (ATTRv) require quantitative biomarkers of nerve involvement to support an early diagnosis and to monitor treatment response. We recently identified, through magnetic resonance neurography (MRN) of the sciatic nerve morphological (cross sectional area, CSA) and ultrastructural (diffusion tensor imaging derived measures) differences between ATTRv patients affected with polyneuropathy (ATTRv-PN), pre-symptomatic carriers (ATTRv-C) and healthy controls. In this study we quantitatively assessed with MRN brachial and lumbo-sacral plexi in the same cohorts.

PATIENTS AND METHODS Nineteen subjects with a *TTR* gene mutation (mean age 62,32), including 13 ATTRv-PN patients and 6 pre-symptomatic carriers (ATTRv-C) were prospectively evaluated with 3 Tesla brachial and lumbosacral plexus MRN and compared with 10 healthy controls (mean age 61.36). The normalized signal intensity (NSI) and the CSA of the cervical roots of the brachial plexus and of lumbar and sacral roots of the lumbar plexus were assessed.

RESULTS ATTRv-PN patients had significantly increased CSA of the right and left C5-C8 roots of the brachial plexus compared to healthy controls ($p<0.0001$), and significantly increased CSA of right and left C6-C8 roots compared to carriers ($0.0001<p< 0.05$). No significant differences of C5-C8 nerve roots CSA were found between carriers and healthy controls. NSI of C5-C8 nerve roots was significantly increased in ATTRv-PN patients compared to healthy controls ($0.001<p<0.05$), NSI of C5-C7 nerve roots was significantly increased in carriers compared to controls ($0.001<p<0.05$). ATTRv-PN patients had significantly increased CSA of the right and left L3-S1 roots of the lumbosacral plexus compared to healthy controls ($0.011<p<0.0001$), and significantly increased CSA of right and left L4-S1 roots compared to carriers ($0.0001<p < 0.05$). Carriers had significantly increased L5 and S1 nerve roots CSA compared to controls ($0.003<p<0.042$). NSI of L3-S1 nerve roots was significantly increased in ATTRv-PN patients compared to controls ($0.001<p < 0.05$). No statistically differences in NSI were found between carriers and healthy controls and between ATTRv-PN and carriers.

CONCLUSIONS The combination of quantitative MRN (CSA and NSI) measures of brachial and lumbo-sacral plexi and nerve roots can reliably differentiate ATTRv-PN, ATTRv-C, and healthy controls, thus representing a potential tool for early diagnosis and disease monitoring.

PERIPHERAL MYELIN PROTEIN-22 POINT MUTATIONS: ASSOCIATED CLINICAL PHENOTYPES AND POTENTIAL PATHOMECHANISM

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Charcot-Marie-Tooth disease type 1E (CMT1E), is a rare and severe dysmyelinating neuropathy caused by point mutations in the peripheral-myelin-protein 22 *(PMP22)* gene (<1% of all CMT cases); the more severe cases are also classified as Dejerine-Sottas syndrome (DSS). The underlying molecular mechanisms are still unknown but previous studies in different models suggested that mutant PMP22 protein mistrafficking and activation of the unfolded protein response (UPR) may play an important role.

Here, we investigated four *PMP22* mutations (S72L, L80P, A106V, A113P) associated with DSS/CMT1E by performing: clinical and neurophysiological characterization of patients; studies on *in vitro* models; molecular modelling evaluation of mutant PMP22 proteins; collection of patients' skin biopsies for fibroblasts and immunohistochemical analysis (IHC); we have also collected serum and plasma for wet biomarkers' assessment.

To date, we have clinically characterized four patients (two males, two females, aged 22-25 years), each carrying one of the aforementioned *PMP22* mutations. Three subjects (S72L, L80P, A113P) showed early-onset and moderate-to-severe phenotype (CMTES range 9-20/28). Their motor nerve conduction velocities (MCV) were in the DSS range (2.1-7.3 m/s). The A106V patient was characterized by later onset (~14 years) and a still very mild phenotype (CMTES=1, MCV=49.8 m/s), though 2 of 3 affected family members showed an aggressive demyelinating neuropathy. For *in vitro* studies, we have generated plasmids expressing the HA-tagged and Myc-tagged version of PMP22-S72L, PMP22-A113P, and PMP22-A106V and in parallel, vectors for PMP22-wt, PMP22-L16P (associated with DSS, and known to be intracellularly retained) and MPZ-S63del (associated with CMT1B, and shown to be ER-retained and causing UPR activation) as

controls. Transfection of RT-4 cells (a rat Schwannoma cell line), followed by staining for ER (KDEL, calnexin) or Golgi (GM130) compartment markers, showed that while the PMP22-wt reaches the cell membrane, the mutant proteins are intracellularly retained and colocalize with both ER and Golgi markers. Co-transfection with a Xbp1s-GFP reporter confirmed that all mutant PMP22 proteins activated the UPR. Accordingly, molecular modelling suggested that the mutations alter aminoacidic interactions, possibly increasing protein rigidity, with a negative impact on plasticity and functionality. The observed results strongly suggest that *PMP22* mutations causing DSS/CMT1E likely share a common pathomechanism linked to mistrafficking. Ongoing experiments on patients' derived fibroblasts and IHC on skin biopsies (for CHOP and other UPR modulators' expression) will be crucial to confirm the hypothesis of the UPR activation in humans.

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IMMUNE CHECKPOINT INHIBITORS-RELATED MYASTENIA GRAVIS, MYOCARDITIS AND MYOSITIS: A SYSTEMATIC REVIEW OF CASES

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Introduction: Immune checkpoint inhibitors (ICIs) have had a major impact in treating a growing number of advanced malignancies. Among immune-related adverse events (irAEs) the rare triple-M syndrome (Myasthenia Gravis, Myositis, Myocarditis) has a high morbidity and mortality rate.

Materials and Methods: Studies reporting triple-M syndrome were identified in Pubmed, Scopus and Web of Science. Only published case reports and case series were included. We are conducting a systematic review according to the PRISMA Harms guidelines. We entered 345 articles on the Rayyan platform; once duplicates and irrelevant abstracts were removed, we proceeded to examine 167 articles.

Results: Our goal was to find an association between different ICIs, different malignancies and phenotype and severity of the adverse event. The neurological toxicity is overall rare (grade >3 in 1% of monotherapies and 2-3% in combinations); from a preliminary analysis of the data, we found that the greatest grade >3 neurological toxicity is with the combination with anti-CTLA4 and PD(L)1 drugs (>50%), followed by monotherapy with anti-CTLA4 with 33% and finally anti-PD(L)1 with 14%. We also aimed to stratify patient by a demographic, oncological, and neurological point of view and so identify subjects who could benefit from more aggressive immunosuppressive treatments. The most frequent indication for administration of ICIs is metastatic melanoma (38%) followed by lung cancer, but the range of treatable tumors is expanding. Risk factors for irAEs include male sex, high disease burden, high BMI, previous heart or neuromuscular diseases; in particular, a pre-existing autoimmune disease significantly predisposes to the development of this adverse event. Curiously though, regarding cases with previous negative history, studies demonstrate that only a small percentage of triple-M syndrome shows antibody seropositivity.

Conclusions: Management of these complications often requires stopping the ICIs and, in most cases, early use of plasmapheresis/intravenous immunoglobulins or steroids; there are no clear guidelines for the choice of other immunosuppressive drugs, which are often slow-acting. In this scenario we also speculate a role for new generation drugs with faster effect, such as complement inhibitors. Further longitudinal studies are needed to clarify the pathogenesis and get to early recognition and treatment of this complication, as well as identify clinical and/or biochemical risk factors to propose a watchful neurological follow-up when necessary.

POLYNEUROPATHY IN WILD-TYPE TRANSTHYRETIN AMYLOIDOSIS

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Transthyretin amyloidosis (ATTR) is a systemic disorder characterized by the extra-cellular accumulation of amyloid fibrils. It is classified as either mutant or wild-type (ATTRwt), based on the genetic sequence of the transthyretin (TTR) protein. While hereditary ATTR typically involves the cardiac and/or peripheral nervous system, ATTRwt primarily manifests with cardiac and osteo-articular involvement. Nevertheless, evidence of peripheral neuropathy and not only carpal tunnel syndrome (CTS) can still be found in ATTRwt patients. Although neurological complications of hereditary ATTR have been extensively studied, to date information regarding the PNS involvement in ATTRwt remains limited. In particular, the prevalence of polyneuropathy and its correlation with amyloid deposits have not been appropriately investigated.

Patients with diagnosis of ATTRwt confirmed by cardiological investigation (echocardiography and cardiac scintigraphy with bone tracers) and negative genetic test for TTR gene mutation underwent

neurological examination and nerve conduction studies (NCS). In patients with confirmed polyneuropathy we offered a sural nerve biopsy in order to detect amyloid deposits.

We examined twenty-three men and five women with a mean age of 80.6 years. None displayed motor signs of neuropathy. Absence of distal tendon reflexes of the lower limbs, consistent with age, was shown in 30% of cases. Unilateral or bilateral CTS was present in 68% of cases. NCS revealed a sensory polyneuropathy in eighteen patients (64%). Among those with neuropathy, three patients agreed to undergo sural nerve biopsy: in one patient histological examination showed the presence of Congo red-positive amyloid deposits.

We observed a sensory neuropathy in almost two third of enrolled ATTRwt patients, further supporting the systemic nature of this disease. However, the unclear pathogenesis of a sensory neuropathy in elderly patients, given their demographic characteristics and comorbidities, underscore the need for further exploration. Histological confirmation of amyloid deposits in nerve tissue may confirm a causal link between amyloidosis and PNS involvement.

DOUBLE PATHOGENIC VARIANT IN AN ATTRV PATIENT WITH MIXED PHENOTYPE

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Transthyretin-related amyloidosis (ATTR) is a systemic disease in which either mutant or wild-type transthyretin assembles into insoluble amyloid. Two different types of ATTR fibrils have been described: type A, a mixture of full-length TTR and C-terminal fragments, and type B, composed of full-length TTR only. The phenotypic presentation may be variable with the two most common systems affected, the peripheral nervous system and the heart, showing different involvement among diverse mutations and sometimes even within the same mutation.

We describe the case of a 77-year-old Caucasian woman who came to our attention on clinical suspicion of transthyretin-related (TTR) cardiac amyloidosis. An echocardiographic evaluation showed increased left ventricular mass (end-diastolic interventricular septum thickness of 17 mm), and cardiac MRI documented diffuse subendocardial late gadolinium enhancement. Laboratory tests showed increased levels of troponin and B-type natriuretic peptide. 99mTechnetium-methylene-diphosphonate (99mTc-MDP) bone scintigraphy was negative for myocardial uptake.

At first examination, the patient was symptomatic for dyspnea on moderate exertion and xerophthalmia. Neurological examination revealed sock-like hypoesthesia and decreased distal tendon reflexes at lower limbs, but baseline nerve conduction studies (NCS) did not show signs of polyneuropathy. TTR gene sequencing was performed, revealing two pathogenic variants (V122I/F64L).

Cardiological follow-up showed atrial tachycardia with variable conduction recorded by Holter ECG monitoring. Loop recorder implantation lead to the identification of paroxysmal atrial fibrillation, treated with anticoagulant therapy. NCS follow-up revealed a mild sensory neuropathy, so the patient could start gene-silencing therapy with Patisiran.

To date, more than 130 different amyloidogenic mutations in the TTR gene have been described, while the occurrence of a compound heterozygosity is extremely rare. We have reported on a patient with the coexistence of two pathogenic TTR variants (V122L/F64L) and a prominent cardiological phenotype with negative 99mTc-MDP bone scintigraphy. In our patient clinical phenotype was a late-onset hypertrophic cardiomyopathy which is typical of the V122I variant; however, these patients show significant myocardial uptake on bone scintigraphy. Bone tracer scintigraphy has low sensitivity in patients with TTR F64L mutation, and given the presence in our patient of two pathogenic variants, we can speculate that the absence of myocardial uptake at scintigraphy might be expression of a F64L prevalence in cardiac tissue. Additionally, in our patient NCS was negative at baseline but showed mild neuropathy at the first follow-up one year later. We therefore underline the importance of neurological and neurophysiological follow-up also of ATTRv patients with cardiac phenotype, in order to broaden treatment options.

HISTONE DEACETYLASE 6 INHIBITORS AND NEUROPROTECTION: EVIDENCES AND MOLECULAR MECHANISMS

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Histone deacetylase enzymes (HDACs) are a family of epigenetic regulators, able to act on both histones and non-histonic proteins, as well as on some cytoskeletal proteins. Since a deregulation of epigenetic control, as occurring after an increased activity of HDACs, is a common event in tumor development and progression, molecules able to inhibit the HDACs have been firstly tested as anti-proliferative agents. However, HDACs are known to play a crucial role also in neurodegeneration, mediating both neurotoxic and neuroprotective effects, depending upon the inhibited HDAC. In particular, HDAC6 inhibitors seem to be the best candidates for a neuroprotective role.

Aims of this study are i) to verify the greater neuroprotective effect of HDAC6 inhibitors than those targeting other HDACs, and ii) to shed light on the molecular mechanisms of their action.

We analyzed the neuroprotective effect of different non-specific (*pan*-inhibitors) and specific HDACs inhibitors on a very reliable neurotoxicity assay, represented by E15 rat embryo-derived Dorsal Root Ganglia (DRG). In particular, we evaluated the neurite length of DRGs treated with the different HDACs inhibitors alone, to test their neurotoxic/neuroprotective potential, or in combination with Oxaliplatin (OHP), a well-known neurotoxic drug, to test their ability to protect from a damage.

We found that the pan-inhibitors showed a slight neurotoxicity on DRGs, while SW100, an inhibitor targeting specifically HDAC6, not only did not induce any toxicity on DRGs, but it also resulted able to counteract OHP neurotoxic effect. We are now investigating the molecular mechanisms that make SW100 so unique among the different HDACs, focusing our attention on those pathways mediating neuroprotection. Preliminarily, Immunoblot and immunofluorescence analysis showed that only SW100 was able to preserve tubulin-acetylated form, pivotal for axonal integrity and transport.

The identification of the molecules mediating the protective effect of HDAC6 inhibitors could provide new targets for more effective strategies to fight neurotoxicity.

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INTRANEURAL SCIATIC NERVE LESIONS IN A PEDIATRIC CASE SERIES: FROM CLINICAL SUSPICION TO THE DIAGNOSIS

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Intraneural perineurioma (INP) is a rare benign peripheral nerve sheath tumor most commonly involving the sciatic nerve. Sciatic INP is responsible for localized nerve hypertrophy and motor-predominant neuropathy, leading to lower limb distal weakness and muscle atrophy. INP is further rare in pediatric patients, where the diagnostic delay causes often severe disability.

In this study we retrospectively analyzed data from 7 pediatric patients diagnosed with intraneural sciatic nerve lesion, and describe their clinical presentation, neurophysiological and imaging features, including Magnetic resonance (MRI) and Ultrasound (US) techniques.

Our pediatric cohort consists of 5 males and 2 females. The age at onset ranged from 3.5 to 12.5 years (mean age 7.3 years); the age at diagnosis ranged from 4.2 to 17 years (mean age 11.4 years), with a significant diagnostic delay in some cases.

In all patients the disease onset was characterized by gait impairment and frequent falls; in addition, a limb dysmetria and foot deformity was noticed in 2 cases respectively, and ankle pain in other 2 patients. At our first neurological examination the presence of distal muscle atrophy and foot drop, associated with foot deformity and joint retraction, was noticed in all patients. The left lower limb was involved in 5/7 cases and limb-length discrepancy was revealed in 6/7. Sensitivity testing showed superficial foot hypoesthesia in two children. Almost all patients required assistive devices like ankle-foot orthoses.

Neurophysiological studies disclosed variable but significant reduction of CMAPs and SAPs amplitude in the external popliteal sciatic nerve and of SAPs in sural nerves, together with signs of chronic denervation in the biceps femoralis muscle in all patients.

MRI of the lower limbs allowed us to detect in all cases the presence of an intraneural lesion of the sciatic nerve characterized by fusiform enlargement of the nerve fascicles of variable length, isointense in T1-weighted and hyperintense in T2-weighted images, with variable contrast enhancement after gadolinium injection. US was performed in 3/7 patients, showing thickening and hypoechogenic appearance of the affected sciatic nerves. These features were considered compatible with INP.

The report of INP is scarce in early pediatric age and is probably under-recognized. The diagnosis of this condition requires clinical suspicion, expert neurophysiological and imaging evaluations. Our case series underlines the key signs and symptoms that represent red flags to address a prompt diagnostic path; the early diagnosis avoids unnecessary treatments and allows to the appropriate management.

BROADENING THE CLINICAL SPECTRUM OF MME RELATED NEUROPATHIES

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In the last decades the number of genes causally related to hereditary neuropathies has exponentially grown. One of the most recently identified is *MME* gene, coding for a metalloprotease (neprylisine), abundantly expressed in the peripheral nervous system and whose function remains to be understood. Recessive *MME* mutations, resulting in a truncated and non-functional protein (loss of function), have been linked to late-onset, predominantly distal CMT2 phenotype. Heterozygous *MME* mutations have been associated to: 1) AD-CMT2 with age-

dependent penetrance (1) and a genetic susceptibility to late-onset axonal neuropathy, in the absence of a clear co-segregation with CMT (2,3). We reported a patient harboring a homozygous *MME* mutation presenting a distal motor hereditary neuropathy (dHMN).

A 52-year-old man, from 45 years, complained of balance disturbances, distal leg weakness and mild hand difficulties. His parents were first-grade cousins, apparently healthy. Clinical examination showed: mild pes cavus, slightly right steppage, marked calf hypotrophy, bilateral strength reduction of foot (MRC 4/5) and toes (MRC 3/5) dorsiflexion, absence of DTRs. Sensory examination, cranial nerves were normal. Nerve conduction study (NCS) showed reduced CMAPs in lower limbs (peroneal nerve: R 2.8 mV, L 1.64 mV; tibial nerve: R 1.17, L 2.1 mV) and normal MCV. Sensory nerves were spared. Evoked motor and somatosensory potentials were normal. Genetically, he had a homozygous *MME* mutation (c.1946T>G, p.Ile 649Ser). His 46-year-old-sister presented a normal neurological examination except for mild pes cavus. NCS showed severe axonal motor neuropathy (peroneal nerve: R 0.31 mV with NCV 26 m/s, L 1 mV; L tibial nerve 3 mV). His 18-years-old son, affected by autistic spectrum disorder, showed normal neurological examination and the neurophysiological testing revealed findings at the lower limits of the norm for his age, rising the suspicion of an axonal neuropathy. His 16-years-old daughter showed normal neurological and neurophysiological examination.

The *MME* mutations belong to rare CMT causative gene and few reports are present in current literature. The mutation described has already been reported by Senderek et al. (3) as a probably pathogenic variant, recessively transmitted and associated to CMT2. In our patient such recessive mutation resulted in a dHMN phenotype. However, this phenotype was already associated to compound heterozygous mutations (compound heterozygous variants c.1342C>T and c.2071_2072delGCinsTT and c.1416+2T>C with c.2027C>T) (2). Regarding heterozygous MME mutations, further data needs to be collected to clarify a possible pathogenetic role in determining AD-CMT2.

HEREDITARY NEUROPATHIES IN THE NEXT GENERATION SEQUENCING ERA: A CHALLENGING DIAGNOSIS

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The hereditary neuropathies (HN) are genetic disorders of the peripheral nervous system characterized by high genotypic and phenotypic heterogeneity. In recent decades, Next Generation Sequencing (NGS) technologies have identified over 100 causative genes of HN, improving diagnostic confidence. Nevertheless, many patients with clinically suspected HN remain without genetic diagnosis, especially when new variants of HN-associated genes are found and the familial co-segregation study cannot be performed. The aim of our study is to point out genetic diagnostic challenges of using NGS for adult patients with clinically suspected HN.

We reviewed the medical records of all patients with suspected HN who underwent NGS at Careggi Hospital from January 2017 through January 2022. Patients with variants reported as pathogenic or likely pathogenic were included for further clinical review.

We ordered NGS on 52 patients, 27 males (52%). Median age at onset of disease was 48 years old. Genetic tests resulted in single mutations/deletions/duplication of genes in accordance with clinical and electrophysiological data of 38 patients (61%): 22 (58%) had deletion (14 patients) or duplication (8 patients) of PMP22 gene. Five patients (13%) had GJB1 mutation; 4 patients (10.5%) had a homozygous mutation of MME gene and 3 (8%) had MP0 mutated. Single patients had heterozygous mutations of TTR and MFN2 gene and homozygous mutations of SORD and SH3TC. Fifteen patients (24%) had new pathogenetic or likely pathogenetic monoallelic variants in 10 different genes (MME, LRSAM1, BSCL2, ATP7A, FBLN5, KIF5A, MED25, GDAP1, SCN9A). The pathogenicity of these variants was however undetermined, mostly due to lack of co-segregation studies.

NGS panels provide specific genetic diagnoses for most patients with suspected HN, improving disease and genetic counseling. Despite these advancements, a significant proportion of cases remain without a specific genetic diagnosis especially when patients are adult and the familiar co-segregation study is not feasible.

UNRAVELING RARE GENETIC VARIANTS BURDEN IN CHRONIC PAIN

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We investigated the diagnostic challenge of Chronic Pain (CP) disorders, exploring the burden of rare variants in genes to discern differences between patients and healthy controls (HC). The neurological work-up included nerve conduction studies, intra-epidermal nerve fiber density, Doleur Neuropathic 4 and ID-PAIN questionnaires, and the evaluation of positive and negative signs.

In this study, 640 CP patients and 216 HC underwent targeted NGS sequencing of 107 pain-related genes. Only rare coding variants (GnomAD frequency <0.01) were considered, collapsed through Gene-Wise Aggregation Analysis. The SKAT-O test was then employed to explore any excess of rare variants in CP patients

compared to HC. Additionally, for genotype-phenotype correlation, patients were categorized into "neuropathic" or "nociplastic" pain subgroups based on the presence or absence of neuropathy, respectively. The gene-wise aggregation test revealed PTPRZ1 gene as significantly enriched (p-value= 4.77E-02, rho=1) with rare coding variants in patients (97 variants) compared to HC (15 variants), with approximately 2-fold higher risk based on the simple burden test (p-value= 3.63E-02, OR=1.73). *PTPRZ1* variants were identified in 65 patients and 7 HC. According to pain phenotype, patients with PTPRZ1 variants were more likely affected by "neuropathic" pain (72%) than "nociplastic" (28%), and 61% of carriers were female.

PTPRZ1, encoding Protein Tyrosine Phosphatase Receptor Type Z1, is a transmembrane receptor predominantly expressed in the CNS, influencing axonogenesis, myelin regulation, cell adhesion, and signalling. Recent studies highlighted PTPRZ1 protein expression in PNS regions linked to CP in both human tissue and animal models. Notably, its up-regulation was observed in fibromyalgia syndrome. Our study unveils novel genetic variants contributing to CP which can contribute to a differential diagnosis among phenotypes and provide insights for the design of clinical trials.

PHENOTYPING CANDIDATE REPLICATION FACTOR C SUBUNIT 1 (RFC1) AGGGC EXPANSION

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Replication Factor C subunit 1 (RFC1) biallelic AAGGG expansion has come to relevance as the genetic hallmark of Cerebellar Ataxia with sensory Neuronopathy and Vestibular Areflexia Syndrome (CANVAS). Recent advances in long-read sequencing led to the identification of different conformations possibly relevant for disease. We aim to describe the clinical characteristic of patients carrying the alternative AGGGC expansion.

The register of the neurogenetic laboratory was reviewed for adult patients tested for RFC1. According to local practice, cases showing an absent product by flanking PCR were tested for four distinct repeat-primed PCR (AAAAG, AAAGG, AAGGG, AGGGC). Nanopore Cas9-targeted sequencing was obtained in a subset of AGGGC patients. Clinical, paraclinical and histology characteristics were collected.

We identified 7 AAGGG/AGGGC and 116 AAGGG/AAGGG out of 198 patients with biallelic expansion. Long-read sequencing confirmed the compound AAGGG/AGGGC expansion in all patients tested. Median age at onset for AAGGG/AGGGC was 55 years (IQR 50-57), all patients presenting with sensory disturbances, in particular distal pain, and paresthesia in 10 patients as well as limited motor disturbances in 2 and autonomic disturbances in 5. Chronic cough was lamented by all patients. Cerebellar disturbances were not observed in any patient after a mean disease duration of 8 years (IQR 5-10). Nerve conduction studies revealed a diffuse decrease in sensory nerve action potential amplitude in all patients and motor involvement in three. High-definition nerve ultrasound and skin biopsy investigations are ongoing.

Clinical characteristics in AAGGG/AGGGC expansion are consistent among identified patients and reminiscent of the neuropathy observed in the reference biallelic AAGGG expansion, apart from the distinctive trait of a greater frequency of motor involvement.

NEUROINFLAMMATION AS A POTENTIAL TARGET FOR CIPN DIAGNOSTIC AND TREATMENT

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Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent side effect of various cancer chemotherapy treatments. Typically, CIPN manifests itself in patients as numbness, tingling, altered sensation, usually associated with neuropathic pain and, therefore the adjustment of chemotherapy dosages or even discontinuation of the treatment. Despite the widespread occurrence and adverse impact of CIPN, obstacles also persist in its diagnosis and treatment. Although various chemotherapeutic agents induce neuropathy, they do so by targeting different cellular processes and having different mechanisms. Neuroinflammation is one of the host defensive mechanisms and tends to be one of the most common pathological outcomes in most neurological and neurodegenerative diseases, making it the promising target.

In our study we aimed to compare two rat models of CIPN induced by different chemotherapeutic drugs, namely paclitaxel (PTX) iv 10 mg/kg two times a week for 4 weeks, and oxaliplatin (OXP) two times a week for 6 weeks, in order to identify its mechanism of action and characterize the neuroinflammation process as a source to identify possible biomarkers for potential diagnosis or treatment. In this study we proved that both PTX and OXP treated rats develop CIPN, as showed by dynamic test, caudal and digital amplitude and velocity analyses. However, further analysis showed that only PTX-induced CIPN is accompanied by neuroinflammation processes. Immunohistology analysis of CD68 marker showed a significant increase of macrophage infiltration in the proximal and distal part of the caudal nerve at the end of PTX treatment. We analyzed the presence of neuroinflammatory marker proteins in central and peripheral tissues, such as inflammasome protein NLRP3, interleukin IL6 and chemokine CCL2 in order to identify the inflammatory components in the pathology of CIPN development.

All three proteins showed a significant increase in the caudal nerve in PTX treatment over 4 weeks. IL6 has been also identified in the spinal

cord after both 24 hours and 2 weeks of PTX treatment. Moreover, serum analysis showed an increase in IL6 and GRO/KC proteins in PTX treated rats after 2 weeks of treatment.

Despite two chemotherapy treatments resulting in neuropathy development, we were able to demonstrate distinct pathological processes and biomolecular patterns in disease progression. The detection of elevated levels of IL6 in animal serum suggests its suitability for additional investigation as a potential biomarker in the diagnosis and prevention of CIPN.

CHRONIC ATAXIC NEUROPATHY WITH DISIALOSYL ANTIBODIES: DIFFERENT CLINICAL FEATURES AND THERAPY RESPONSE

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Ataxic neuropathies with anti-disialosyl antibodies are immune-mediated disorders called either CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies) or CANDA (chronic ataxic neuropathy with disialosyl antibodies), depending on the spectrum of symptoms/signs.

We present two patients with IgM paraproteinemic neuropathies and anti-disialosyl antibodies presenting different clinical presentations and therapy responses.

A 57-year-old heavy smoker man came to our attention for a one-year history of relapsing-remitting episodes of weakness at four limbs, unintentional weight loss preceded by infection episodes. Neurophysiological studies demonstrated sensory-motor axonal polyneuropathy. An IgMk monoclonal gammopathy of undetermined significance (confirmed by bone marrow biopsy) with MYD88 mutation was present. Antinuclear antibodies were present at low titer, anti-myelin associated glycoprotein (MAG) antibodies were absent. Paraneoplastic work-up (total body CT scan, anti-neuronal antibodies) was negative. Anti-ganglioside antibody panel resulted positive for high titers IgM anti-GD2, GD3, GT1a, GT1b, GQ1b. Serum cold agglutinins were also detected. The symptoms recovered spontaneously in several weeks. When we first saw the patient, he was in remission and neurological evaluation was unremarkable, apart from loss of Achilles tendon reflexes. A 62-year-old-man started complaining, since 2018 of sensory symptoms in his hands and feet extending over time to the knees and elbows. Nerve conduction studies were consistent with sensory axonal ganglionopathy at four limbs. Blood tests revealed an IgMλ paraprotein expression of a Waldenström's macroglobulinemia (confirmed by bone marrow biopsy). Anti-MAG and anti-neuronal antibodies were negative. Tests for anti-ganglioside antibodies revealed the presence of high titers of serum IgM anti-GD1b (1:100000), and of GD1a (1:3200), GM2 (1:1600), GM1 (1:12800). Neurological examination disclosed pinprick, and tactile hypoesthesia with stocking-glove distribution. The patient was responsive to intravenous immunoglobulin (IVIg) but reported end-dose fluctuations. Rituximab was started but soon discontinued for clinical worsening so IVIg therapy was resumed.

Our patients represent two different manifestations of the heterogeneous group of sensory ataxic neuropathies with anti-disialosyl IgM antibodies. None exhibited the full spectrum of CANOMAD, both had high titers anti-disialosyl IgM antibodies, and one also cold agglutinin. One patient had several relapses triggered by infectious, and reversible despite lack of therapy. The second patient became IVIg dependent, and rituximab worsened the clinical picture. Recently, subcutaneous Ig have been shown to maintain clinical stability, and daratumumab has been used in a refractory CANOMAD patient. The rarity of the diseases does not allow controlled studies, and tailored therapy may be necessary.

ANTI-HU AND ANTI-CV2 ANTINEURONAL ANTIBODIES NEUROPATHY AS CLINICAL ONSET OF SMALL CELL LUNG CANCER

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Paraneoplastic neurological syndromes (PNS) are rare neurological disorders occurring in people with malignancy that may develop months before the cancer becomes clinically overt. In most cases, PNS are associated with high-risk antibodies (previously known as onconeural antibodies) suggesting an immune-mediated pathogenesis. An early diagnosis and timely therapy are crucial for the outcome. Small cell lung cancer (SCLC) is the tumor most associated with PNS and anti-Hu or anti-CV2 the high-risk antibodies often present. Subacute sensory neuronopathy (SSN) is a classical high-risk phenotype PNS. We present a patient with anti-Hu and anti-CV2/CRMP5 antibody neuropathy as clinical onset of SCLC.

A 68-year-old man, with 6 months history of progressive walking difficulty, weight loss, mood changes, and acral painful was admitted to our Neurology Unit. The patient underwent a complete workup, including neurophysiological study, lumbar puncture, antibody serology, whole-body CT, endoscopic biopsy and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), whole-body PET/CT.

At neurological evaluation, the patient had ataxic gait, tactile hypoesthesia from elbows and knees down, acral paresthesia and allodynia, proximal and distal asymmetric weakness at all limbs, severely reduced vibration sense, and areflexia. Nerve conduction studies detected sensorimotor axonal polyneuropathy, with denervation signs. Cerebrospinal fluid analysis revealed hyperproteinorrhachia

(105 mg/dL), mild pleocytosis (16 lymphocytes/μL) and "mirror pattern" with additional oligoclonal bands. Serum anti-Hu and anti-CV2 anti-neuronal antibodies were detected. Whole-body CT scan showed a left lung suspect nodule, and mediastinal lymphadenomegaly, that showed hypermetabolism at PET/CT scan. A pulmonary embolism (PE) secondary to a deep vein thrombosis (DVT) was also detected and rivaroxaban started. Methylprednisolone 1g/die for 5 days partially lowered pain. Pregabalin was also introduced. EBUS-TBNA of mediastinal lymph nodes was suggestive of SCLC. The patient is currently in oncological management.

Neuropathy with Anti-Hu, and less frequently with anti-CV2 antibodies are the most common paraneoplastic neuropathies in patients with SCLC. The two antibodies rarely occur in the same patient. Anti-Hu is usually associated with SSN. Motor neurons may also be affected presenting with sensorimotor polyneuropathy more frequently associated with anti-CV2. Our patient is a rare case of double positive high-risk antibodies sensorimotor polyneuropathy. Moreover, in our patient also DVT was likely paraneoplastic, pointing to a rare case of double paraneoplastic syndrome.

INTERMEDIATE CHARCOT-MARIE-TOOTH DISEASE: FOOD FOR THOUGHT ON ELECTROPHYSIOLOGICAL APPROACH

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Charcot-Marie-Tooth disease (CMT) is a hereditary neuropathy characterized by heterogenous genetic, clinical and electrophysiological features. According to Berciano et al. CMT may be classified into demyelinating (< 25 m/sec), intermediate (25-45 m/sec) and axonal (>45 m/sec) CMT type on the basis of motor conduction velocity in the median nerve. However, when distal Compound Muscle Action Potential (CMAP) amplitude in median nerve is significantly reduced (>50% of lower limit normal value), exploring proximal segment of median nerve is required. Since distal median CMAP may be often reduced due to entrapment neuropathy as well split-hand phenomenon and proximal nerve conduction of median nerve is not routinely investigated, the aim of our study was to evaluate if ulnar nerve may be informative for electrophysiological characterization of CMT subtypes.

One-hundred twenty-seven genetically confirmed CMT patients was recruited from 2017 to 2023. Each patient underwent motor nerve conduction velocities of median and ulnar nerve. Median nerve CMAP was recorded distally from abductor pollicis brevis (ABP) e when required proximally (from pronator teres) while ulnar CMAP was recorded only distally from Abductor Digiti Minimi (ADM). Patients were classified into intermediate or axonal forms according to Berciano criteria. To explore the presence of split-hand we used the cutoff <0.6 for the ABP/ADM CMAP ratio. Concordance between median and ulnar nerve was considered.

Seventy-two patients were classified as axonal and 55 patients as intermediate by using median nerve. Twenty-four patients required proximal recording due to severely reduced median CMAP. Seventy-seven patients were classified as axonal and 50 patients as intermediate by using ulnar nerve. A concordance of 96.1% between median and ulnar nerve was proven. A total of 40 patients (31%) had a reduced ABP/ADM ratio compatible with a split hand. Among these patients, 47.5% (19/40) carried *GJB1* mutation. The remain cases was due to *MFN2*, *MPZ* and *MME* (7.5%), *MYO9B*, *RAB7* and *SORD* (5%) and *ATP1A1*, *LITAF*, *MORC2*, *PLEKHG5*, *REEP1* and *TRPV4* in one case.

Our study demonstrated that ulnar nerve evaluation is equally informative in the CMT subtype classification. We suggest that the CMT classification can be performed also through the study of ulnar nerve, since the median nerve can be severely affected, and thus proximal segment evaluation is required. However, adding the median nerve study can offer the possibility of also exploring the presence of the split hand, which can help to better deepen the electrophysiological features of patients.

SORD AND SORD2P INVERSION: LONG READ SEQUENCING IDENTIFIES A NOVEL GENETIC MECHANISM UNDERLYING INHERITED NEUROPATHY

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Despite the best efforts, over 50% of axonal CMT cases do not receive genetic confirmation. Notably, current short read technologies, including whole exome (WES) and whole genome sequencing (WGS), present major shortcomings in the study of structural variants and repeated regions, contributing to the missing heritability in CMT.

Here we leverage long read sequencing (LRS) and non-sequencing based optical genome mapping (OGM) to identify a large structural variant involving *SORD* and its pseudogene *SORD2P*, which disrupts *SORD* reading frame and causes autosomal recessive *SORD*-CMT in multiple families.

In three unrelated patients with axonal CMT exhibiting elevated serum sorbitol and carrying a heterozygous c.757delG *SORD* variant, LRS and OGM detected a 200Kb inversion with breakpoints spanning the highly homologous *SORD* intron 4 and *SORD2P* intron 5. Interestingly, this structural variant was invisible to previous WES or WGS. In addition, we screened by inverse PCR 37 CMT cases carrying a heterozygous pathogenic variant in *SORD* and identified four patients (~10%) carrying the same *SORD/SORD2P* inversion. In one family, the inversion occurred *de novo*, while in another family it was inherited from the unaffected parent. Clinical features were similar to previously described *SORD*-CMT cases. Notably, analysis of 3D chromatin structure from public databases showed that *SORD* and *SORD2P* are in close proximity within the nucleus, which may facilitate the occurrence of recombination events between them.

In conclusion, the possibility of *SORD/SORD2P* inversion should be considered in axonal CMT cases carrying a single pathogenic variant in *SORD*, particularly if serum sorbitol is elevated. Also, the study highlights the power of LRS or OGM in genetic studies of unsolved CMT cases and illustrates a novel mechanism of how structural variants involving one of the ~3000 gene/pseudogene pairs in the human genome can lead to genetic disease which can be missed by current diagnostic short read technologies.

CORRELATION BETWEEN ULTRASONOGRAPHIC AND ELECTRODIAGNOSTIC PATTERNS IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY - PRELIMINARY RESULTS FROM A MULTICENTRIC PROSPECTIVE STUDY

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Introduction Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) is a rare immune-mediated neuropathy diagnosed through clinical and demyelinating nerve findings. Nerve ultrasound (US) has recently gained attention as a non-invasive tool for disease detection and monitoring. CIDP patients often display regional, focal, or non-homogeneous alterations in nerve cross-sectional area (CSA), particularly observable in limbs without apparent neurophysiological abnormalities. Despite the reported associations between disease duration and US alterations, the relationship with clinical and electrophysiological study (EDX) data remains partly controversial and is not sufficiently explored on large, prospective study. We designed a prospective multicenter longitudinal study aimed to investigate EDX and US findings in CIDP patients.

Materials and Methods Consecutive CIDP patients from 10 centers underwent standardized assessments at baseline, 1-year, and 2-year follow-ups, focusing on baseline findings in these preliminary results. The study included neurological examinations, questionnaires, and EDX and US assessments. EDX studies covered various motor and sensory nerves, and CSA was measured at predetermined sites. In cases of diffuse focal swelling nerve patterns, data on the number of swelling sites, focal CSA for each site, and mean CSA of such focal swellings were recorded. Baseline EDX and US assessments were correlated with clinical variables (disease duration, gravity scales) using univariate and multivariate analyses.

Results The study enrolled 49 patients (mean age 52.5±33 years, 73.4% males, disease duration 73 ±57 months). Univariate analysis revealed correlations between various EDX and US variables and disease duration/severity scales. Notably, all motor conduction velocities (MCV) showed an inverse and significant correlation with CSA and

multifocal nerve swelling at corresponding sites. In multivariate analysis, disease duration inversely correlated significantly with MCV of median, ulnar, and peroneal nerves (P<0.001). Additionally, the RODS scale significantly correlated with CSA in all motor and sural nerves (P=0.003), as well as with peroneal Compound Motor Action Potential (CMAP) (P=0.002). The MRC scale demonstrated a direct correlation with CMAP of all motor nerves and MCV of the peroneal nerve (P<0.001). The INCAT score exhibited an inverse correlation with sural sensory action potential, peroneal CMAP, and multifocal nerve swelling alongside the sural nerve (P=0.002).

Conclusions This study establishes correlations among clinical, EDX, and US data, providing valuable insights into the relationship between disease severity and specific neurophysiologic and sonographic nerve patterns in CIDP. Future research and ongoing and follow-up aim to incorporate dynamic data, further enhancing the understanding of the role of US when combined with EDX in monitoring CIDP patients.

TRANSTHYRETIN AMYLOID DEPOSITION IN THE LIGAMENTUM FLAVUM IN AN ITALIAN COHORT OF PATIENTS WITH LUMBAR SPINAL STENOSIS

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Transthyretin amyloidosis (aTTR) is a disorder characterized by extracellular accumulation of misfolded transthyretin (TTR). As TTR deposition potentially occurs in every tissue, it also can lead to lumbar spinal stenosis (LSS), a clinical syndrome determined by hypertrophy of ligamentum flavum (LF) and narrowing of the lumbar spinal canal. Several studies report a strong association between LSS and TTR amyloid deposits in the LF. In this study, we prospectively investigated the frequency of TTR amyloid deposits in material obtained at LSS surgery performed at our Center.

LF specimens were provided from patients who underwent surgery for LSS in the Neurosurgery Department of Policlinico Gemelli, Rome, from June 2023. Demographic, clinical, and radiological data were collected. Extensive pathological analysis to detect possible amyloid deposits was performed in all specimens.

The study included 30 patients. Males/females ratio was 18/12. The mean age at the time of surgery was 64 ± 12.75 years. We detected amyloid deposits in 1/30 cases, which also resulted positive at immunohistochemistry with anti-TTR antibodies. Genetic investigations yielded a negative result for hereditary aTTR.

Lumbar canal stenosis is a common spinal condition in elderly patients. Although previous studies have shown a relevant frequency of amyloid deposits in LF hypertrophy, suggesting a possible role in LSS pathogenesis, in our cohort this occurrence was extremely rare. This result should be confirmed in different populations of the same non-endemic country in order to better define a possible geographic contribute to occurrence of amyloid deposits in LSS.