PNS 2022 Abstract Supplement
Poster Session I
Sunday 15 May 2022
12.00 – 14.00
CKD-510, a Novel Non-Hydroxamic Acid Histone Deacetylase 6 (HDAC6) Inhibitor for Charcot-Marie-Tooth Disease Type 1A

Poster No:
1a

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Introduction:
Charcot-Marie-Tooth (CMT) disease is one of the most common hereditary peripheral neuropathies with no approved treatment to prevent the disease progression. CMT type 1A (CMT1A), which accounts for approximately 50% of CMT patients, is caused by duplication of peripheral membrane protein 22 (PMP22) gene and linked to the defective proteostasis with the accumulation of misfolded PMP22 aggregates in the myelin sheath of peripheral neuron. Histone deacetylase-6 (HDAC6) that removes acetyl group from various non-histone proteins, has been well known for its pleiotropic effects on proteostasis via unfolded protein response. Thus, HDAC6 has been proposed as a promising therapeutic target for various neurodegenerative diseases caused by abnormal proteostasis, such as CMT1A. Most of the HDAC6 inhibitors are hydroxamic acid (HA)-based compounds and previous researches have demonstrated their efficacy in both in vitro and in vivo CMT models. However, their clinical applications were limited to oncology due to the fast clearance in plasma, extensive metabolite generation, and safety issues. We identified a new non-hydroxamic acid HDAC6 inhibitor (NHA), CKD-510, with better pharmacokinetic and safety profiles. In this study, we described the preclinical efficacy results (CMT1A mice) of CKD-510.

Methods:
We evaluated the potency and selectivity of CKD-510 using HDAC enzyme panel assay and western blots as well as its therapeutic potentials using behavioral and electrophysiological testing in the C3 murine CMT1A model. Electron microscopy, semithin analysis and H&E staining were performed to evaluate histological improvement.

Results:
CKD-510 showed excellent inhibitory potency and selectivity for HDAC6. In the preclinical study, CKD-510 restored myelination, axonal integrity, and neuromuscular junction of the sciatic nerve, which led to behavioral, electrophysiological and histological improvements in C3 murine CMT1A model.

Conclusions:
CKD-510 is currently at clinical development stage and exhibited excellent oral bioavailability and tolerability in human. Based on the results from preclinical and clinical studies we are planning Phase 2 study for CMT 1A patients.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support:

**Keywords:** Non hydroxamic acid HDAC6 inhibitor, CKD-510, Charcot-Marie-Tooth disease, C3 mice
Novel Variant in the ATPase Module of MORC2 c.71C>A, p.Thr24Asn consistent with infantile onset Charcot–Marie–Tooth disease (CMT) type 2Z

Poster No:
2a

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Introduction:
Charcot–Marie–Tooth disease (CMT) type 2Z, an axonal form of Charcot–Marie–Tooth disease is associated with pathogenic mutations of the microrchidia family CW-type zinc finger 2 (MORC2) gene. We report an infant with profound hypotonia, generalized weakness, microcephaly, nystagmus, epilepsy, global developmental delay, cardiac conduction abnormality, respiratory failure requiring tracheostomy and failure to thrive requiring gastrostomy tube placement.

Methods:
Whole-exome sequencing identified the de novo MORC2 variant of uncertain clinical significance in the ATPase Module of MORC2 c.71C>A, p.Thr24Asn.

Results:
Electrophysiological studies demonstrated a severe axonal neuropathy. Frequent fasciculations were noted on muscle ultrasound further supporting a neurogenic process.

Conclusions:
Given these findings and phenotypic overlap with previously reported individuals, we conclude that this variant likely explains this individual's clinical features and propose the pathogenicity of this variant.

References:
Yes

References 1:
Duan, X. et al. Characterization of genotype-phenotype correlation with MORC2 mutated Axonal Charcot-Marie-Tooth disease in a cohort of Chinese patients. Orphanet J. Rare Dis. 16, 244 (2021)

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** Charcot–Marie–Tooth disease (CMT), MORC2, exome sequencing, axonal neuropathy, EMG
Evaluating The Causes Of Rapid-progressive Sensorimotor Polyneuropathy In A Patient With CADASIL And Plasmacytoma-associated Paraproteinemia

Poster No:
3a

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Introduction:
A 57-year-old female patient, previously diagnosed with Cerebral Autosomal Dominant Arteriopathy with Subcortical Infacts and Leukoencephalopathy (CADASIL) and IgG-lambda paraproteinemia, presented with a rapid-progressive, leg stressed and distally pronounced sensorimotor polyneuropathy.

Methods:
Analysis of cerebrospinal fluid (CSF), nerve conduction studies (NCS) and electromyography (EMG) as well as nerve ultrasound and spinal magnetic resonance imaging (MRI) were performed. Furthermore, a positron emission tomography-computed tomography (PET-CT) scan was performed to evaluate the cause of the monoclonal gammopathy. A sural nerve biopsy was taken and investigated using light and electron microscopy (EM).

Results:
CSF analysis, NCS, nerve ultrasound and spinal MRI hinted towards a primarily demyelinating and inflammatory neuropathy. However, EMG revealed early and substantial axonal involvement. After initially responding well to immunosuppression, the patient demonstrated a remitting and progressive course. The PET-CT scan revealed a solid plasmacytoma of the femur causing the monoclonal gammopathy; a common differential diagnosis in Guillain-Barré-like demyelinating neuropathies. Light microscopy of the sural nerve biopsy revealed pronounced axonal damage in presence of inflammatory infiltrates with no indications of amyloidosis. Consequently, the immunosuppressive therapy was escalated, and radiotherapy initiated. While the patient did not profit from the escalated immunosuppressive treatment, effects of the radiotherapy cannot be evaluated yet. Interestingly, additional EM demonstrated microangiopathic changes matching the histopathological alterations seen in CADASIL.

Conclusions:
Given the insufficient response to immunosuppression in a primarily demyelinating neuropathy with significant axonal involvement and the EM findings, we conclude that the clinical presentation and course are neither fully explained by an immune-mediated mechanism nor CADASIL. We assume that initial nerve damage may have been immune-mediated, but that CADASIL could have played a role in early axonal damage and overall poor response to immunosuppressive treatment. This an especially interesting case when it comes to evaluating the mechanisms of peripheral neuropathy under such complex conditions in the presence concurring causes.

References:
No
References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: polyneuropathy, plasmacytoma, CADASIL, nerve ultrasound
Low intensity pulsed ultrasound modulates axonal regrowth and remyelination after peripheral nerve injury

Poster No:
4a

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Introduction:
While they are quite common, peripheral nerve injuries can result in long term motor and sensory impairments that make them very challenging to treat. Low intensity ultrasound emits sound waves above the surface of the skin that are then absorbed and converted to vibrations to induce responses crucial to nerve regeneration and repair at the cellular level. In recent years, low intensity ultrasound has become a novel non-invasive treatment with the potential of remediating nerve injury through an unknown mechanism.

Methods:
We applied LIPUS to primary Schwann cells to assess optimal ultrasound parameters and the effect on Schwann cell proliferation. We then performed a comprehensive study and investigated the effect of LIPUS on peripheral nerve regeneration at 7, 20, 60 days post injury to understand the effect of LIPUS on Schwann cell dedifferentiation, proliferation, axonal regrowth and remyelination during their respective critical timepoints in a sciatic nerve crush model.

Results:
Here we show that low intensity pulsed ultrasound (LIPUS) at 0.3 W/cm² can potentiate Schwann cell proliferation which will directly impact peripheral myelination. Thus far, LIPUS plays a critical role in modulating axonal regrowth during nerve regeneration. Moreover, our lab has found LIPUS to increase myelin thickness and the number of myelinated axons after injury.

Conclusions:
Overall, we show that LIPUS application is beneficial to peripheral nerve regeneration when applied during the early stages following nerve injury. In future studies, we hope to examine downstream mechanosensitive effectors such as YAP/TAZ and extracellular matrix components in hopes of revealing the underlying mechanisms that intertwine mechanotransduction and peripheral myelination.

References:
Yes

References 1:

References 2:

References 3:
References 4:

Grant Support:

**Keywords:** Schwann cell, Myelin, Ultrasound, nerve regeneration
Functional characterisation of missense variants in the pro-survival gene NMNAT2

Poster No:
5a

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Introduction:
Dysfunction and/or loss of axons and synapses is a common pathological denominator across various neurological disorders. In fact, maintaining axonal health is highly dependent on a fine interplay between different proteins that majorly impact the NAD+ metabolome. One such protein is the pro-survival factor Nicotinamide mononucleotide adenylyltransferase 2 (NMNAT2). It is an NAD+ synthesizing enzyme crucial for axonal growth, without which axons cannot survive, dying through a mechanism called Wallerian degeneration (WD). WD is an evolutionary-conserved and druggable pathway triggering axonal death which we hypothesize contributes substantially to axon loss in human disease.

Methods:
Here, we present new functional data on a small set of artificial and natural NMNAT2 missense variants found in an important functional region of the protein among the general human population. We further report on a rare NMNAT2 variant identified through clinical exome sequencing in two young patients with neuropathy. The capability of these variants to support axon survival in mouse primary neuron cultures is functionally assayed when overexpressed. In vitro enzymatic assays are used to test protein stability and potential defects in NAD+ synthesis.

Results:
A number of NMNAT2 variants within this protein region confer loss-of-function (LoF), impairing axon survival and enzymatic function, and some are already associated with disease. Biallelic NMNAT2 LoF appears to be causal for some rare disorders, and we discuss what role monoallelic NMNAT2 LoF could also play in disease.

Conclusions:
We show that, despite being extremely rare, genetic variants in human NMNAT2 exist and alter axon vulnerability. We further discuss how these variations may influence axon vulnerability and disease susceptibility in some individuals.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:
Keywords: Wallerian degeneration, human NMNAT2, axon vulnerability, peripheral neuropathies
HELIOS-A: Impact of Vutrisiran on Quality of Life and Functional Status in Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy

Poster No:
6a

Authors:
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Introduction:
Hereditary transthyretin-mediated (hATTR) amyloidosis, also known as ATTRv amyloidosis, is associated with significant disability, worsening quality of life (QOL), and loss of function. The effects of treatment with vutrisiran, an investigational RNA interference therapeutic, on QOL and functional status were evaluated in HELIOS-A (NCT03759379).

Methods:
Patients with hATTR amyloidosis with polyneuropathy were randomized (3:1) to vutrisiran (25 mg subcutaneous [SC] injection q3m) or patisiran (0.3 mg/kg intravenous infusion q3w), a reference comparator. The APOLLO placebo group (n=77) provided an external control. HELIOS-A primary endpoint was change from baseline in modified Neuropathy Impairment Score +7 (mNIS+7) at 9 months vs. external placebo. Secondary and exploratory endpoints at 18 months included change from baseline vs. external placebo in measures related to QOL (Norfolk QOL-diabetic neuropathy [Norfolk QOL-DN], EuroQoL-Visual Analog Scale [EQ-VAS]) and functional status (Rasch-built Overall Disability Scale [R-ODS], gait speed [10-meter walk test; 10-MWT], Karnofsky Performance Status [KPS]).

Results:
HELIOS-A enrolled 164 patients (vutrisiran, n=122; patisiran, n=42). The primary endpoint was met. At 18 months, vutrisiran significantly improved Norfolk QOL-DN (least squares [LS] mean difference: −21.0; p=1.844 x 10−10) and EQ-VAS (13.7; p=2.214 x 10−7) vs. external placebo. Significant improvement was observed across all Norfolk QOL-DN domains vs. external placebo. Additionally, total score alongside the large-fiber function, symptoms, and autonomic domains improved vs. baseline. At 18 months, vutrisiran improved R-ODS (LS mean difference: 8.4; p=3.541 x 10−15) and 10-MWT (0.239; p=1.207 x 10−7) vs. external placebo. The majority of vutrisiran-treated patients (71.3%) had stable or improved KPS at 18 months vs. baseline.

Conclusions:
In HELIOS-A, vutrisiran q3m SC significantly improved multiple measures of QOL and functional status at 18 months vs. external placebo. Continued worsening of these measures was observed on placebo, highlighting the importance of effective treatment. The long-term effect of vutrisiran will be confirmed in an open-label extension study.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Supported by Alnylam Pharmaceuticals

Keywords: hATTR amyloidosis, vutrisiran, RNAi, quality of life, functional status
Metformin and Resistance Exercise Alleviate Stress-Induced Peripheral Injury in Type 2 Diabetes

Poster No:
7a

Authors:
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Introduction:
Sufficient evidence confirms that type 2 diabetes (T2DM) can damage both the peripheral and central nervous system precipitating concurrently diabetic peripheral neuropathy (DN) and depression. However, contributing factors remain poorly studied. Clinical retrospective analysis indicates that early psychosocial stress, namely post-traumatic stress disorder (PTSD) and diabetes, contributes to adverse neuropathic and depressive outcomes. Yet, the mechanism of injury remains poorly elucidated. The following study aims to investigate the impact of early life social stress as key player in the aggressiveness of the development of DPN in T2DM, and to assess the mechanistic pathways that could be involved.

Methods:
Male C57BL/6J were used receiving either a single hit or a double hit of social stress (using social defeat protocol) and T2DM. In parallel experiments, mice were treated with metformin or exposed to resistance exercise. Behavioral and molecular studies were conducted to assess peripheral injury and depressive-like symptoms and to explore the mechanistic role of AMPK and its crosstalk with ROS production and BDNF alteration.

Results:
Our results show that mice with T2DM previously exposed to social stress present depressive-like symptoms combined with an aggravated onset of peripheral injury characterized by loss of sensation and motor deficits when compared to mice with T2DM only. The resulting injury was corroborated molecularly with increased ROS production, NOX activity, AMPK inactivation and lower levels of BDNF. Metformin and resistance exercise training were able to restore the observed sensorimotor deficits primarily through AMPK re-activation, attenuation of ROS production and regulating BDNF levels.

Conclusions:
Our findings shed the light on the negative impact of early life stress in aggravating diabetes associated peripheral nerve injury and central behavioral alterations. Our study also puts forward the neuroprotective effect of AMPK activation through metformin administration and resistance exercise as a potential therapy to alleviate peripheral neuropathy.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Diabetic peripheral neuropathy, PTSD, Metformin, Resistance Exercise, Oxidative Stress
Muscle Structure, Function, and Gait Patterns in Distal Hereditary Motor Neuropathy and the Effect of Carbon fiber Ankle Foot Orthosis on Gait

Poster No:
8a

Authors:
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Introduction:
Distal Hereditary Motor Neuropathy (dHMN) is an inherited neuromuscular disorder characterised by distal weakness. It is a disabling condition and eventually many patients need aids to walk. Research is needed to understand the muscle impairments that lead to altered gait patterns, and to develop interventions to correct walking gait conservatively. The preliminary data presented here focuses on relationships between intramuscular fat fraction, muscle volume, muscle strength and kinetics and kinematics of gait. We also explored the effect of bilateral carbon fibre ankle foot orthoses (AFO) on the kinetics and kinematics of gait of people with DHMN.

Methods:
Baseline measurements included: - MRI scan for quantitative and qualitative analysis of thighs, calf and one foot muscles. - Isometric and Isokinetic dynamometer of hip flexors/extensors, knee flexors/extensors, and foot plantar flexors and dorsiflexors. - 3D Gait analysis with and without carbon fiber ankle foot orthosis. - Other clinical assessments: Manual muscle testing, Range of motion, Foot posture index, pain and sensory examination, Walk 12 questionnaire, and CMT examination score. The collected data will be analysed to identify patterns of muscle involvement and altered gait, explore the relationship between Intramuscular fat fraction and muscle function, and to investigate effect of bilateral carbon fibre ankle foot orthoses on the kinetics and kinematics of gait of people with dHMN.

Results:
The target recruitment is 20 people with dHMN and 20 controls. Thus far, 11 dHMN and 5 controls have been recruited. Six dHMN (3 females) aged 44-75 (mean 59.5, SD 11.2) and 3 have HSPB1 genetic diagnosis (2 males) completed baseline measurements. We will present the preliminary, baseline analysis of the data.

Conclusions:
The presented preliminary data will help us understand how changes architecture of the leg muscles impacts muscle strength and gait patterns. We will also explore whether carbon fibre AFOs can compensate for muscle impairment and improve gait.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: DHMN, MRI, Gait analysis, Dynamometer, carbon fibre ankle foot orthoses
Morpho-functional characterization of the caudal nerve to refine assessment of peripheral neuropathy in rat models.

Poster No:
9a

Authors:
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Introduction:
Rat caudal nerve is a relevant site to study length dependent processes. However, the site of neurophysiological testing is crucial. We performed an anatomical and functional study to verify the most appropriate approach.

Methods:
We compared a control (vehicle [VEH] treated, n=8) and a paclitaxel (PTX) treated group (PTX 10 mg/Kg, 1qw4ws, n=8). We performed nerve conduction studies (NCS) at baseline and at end of treatment. Caudal nerve sensory nerve action potential (SAP) was obtained starting from the base and moving then distally. The reference and active recording electrodes (interelectrode distance: 1 cm) were placed at 3 cm of distance with respect to the cathode and anode (interelectrode distance: 1 cm); ground electrode was placed midway between the 2 dipoles. The first recording was performed with recording electrodes at the base of the tail; subsequently recordings were repeated translating the montage of 1 cm each time. At the end of treatment whole caudal nerves were harvested; after fixation, they were subdivided/included in segments corresponding to sites of recordings.

Results:
At the end of treatment a moderate difference (statistical difference for SAP amplitude) was demonstrated in PTX group at the base of the tail and at 2 cm from the base of the tail the damage was complete (statistical difference for both SAP amplitude and velocity). Starting from 4 cm from the base of the tail SAP was not recordable in all PTX animals with an increasing damage going distally, reaching a complete absence of SAP at 8 and 10 cm from the base of the tail.

Conclusions:
Caudal nerve is an ideal site to study damage (easily accessible) but the montage for SAP recording should be carefully evaluated. We obtained a set of values to describe the normal variation of NCS for the whole length of the tail.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: rat models, preclinical nerve conduction studies, caudal nerve, nerve morphometry
Allografts in combination with local immune suppression as a strategy to improve peripheral nerve regeneration

Poster No:
10a

Authors:
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Introduction:
Peripheral nerve injury (PNI) is a common consequence of trauma. It is difficult to treat because of complex etiology and relatively slow and incomplete success of natural regeneration. To improve the outcomes of peripheral nerve regeneration, the current clinical gold standard in PNI treatment is sensory autografting of the injured nerve. This treatment option is closely followed by biomaterial conduits and decellularized grafts as options that provide less regeneration but don't require the sacrifice of a sensory autograft.

Methods:
Allografting of fresh, living nerves is as effective as autografts but requires systemic immune suppression to reduce the risk of graft rejection. Research conducted by our group suggests that localized immune suppression provided by delivery of T regulatory cells to the graft gives the same, or in some cases superior, regeneration to an autograft.

Results:
This technique has also shown success in complex peripheral nerve injury where the injury is greater than the field standard, 10 mm, and when the injury includes a branch point.

Conclusions:
The success of local immune suppression makes allografting a unique and critical addition to the field of PNI regeneration.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: NIGMS 2P20GM103432 ALSAM Foundation University of Wyoming

Keywords: Allograft, Local immune suppression, Regeneration, Peripheral Nerve Injury (PNI)
Dysregulated microRNA profile in skin epidermis contributes to small fiber pathophysiology

Poster No:
11a

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Introduction:
Small fiber neuropathy (SFN) is a multifactorial condition affecting thinly myelinated Aδ and unmyelinated C-fibers. The typical clinical presentation includes symmetrical, length-dependent sensory or autonomic symptoms, that significantly interfere with patient's daily life. The pathophysiological mechanisms of SFN remain unclear, nevertheless, crosstalk dysfunction among axons and epidermal cells might play an important role. Emerging evidences suggest microRNAs (miRNAs) mediating nature in intercellular communication and their possible contribution to the pathogenesis of SFN. Our study was designed to investigate miRNA profiles of SFN patients and their possible correlation with underlying disease mechanisms.

Methods:
By using microfluidic array cards containing 754 miRNAs we performed discovery and validation profiling experiments in skin epidermis of 20 SFN patients and age- and sex-matched controls. After relative quantification analysis, significantly altered miRNAs were further analyzed by using distinct resources, including experimentally validated data and computational target predictions by miRTarBase, TargetScan and DIANA combined, to identify genes that represent putative targets. Following target identification, we carried out functional enrichment analysis of miRNA targets using pathway maps from the KEGG Database through ClueGO (Cytoscape) to explore possibly affected biological processes and molecular targets.

Results:
Our data analysis revealed validated differential expression of the group of miRNAs that showed the highest significance (p <0.05) for intergroup differences after Benjamini–Hochberg correction. Moreover, our computational analysis showed their involvement in fine-tuning of multiple pain and SFN-related genes, some of which already known drug targets.

Conclusions:
Our proof-of-concept study of microRNA profiling of human epidermis provided novel hints on epigenetic regulation of epidermal innervation and chronic neuropathic pain, while adding value to the dysfunction of axon-cell network in the contest of SFN.

References:
No
Grant Support: This study was supported by grants from European Union’s Horizon 2020 research and innovation programme Marie Sklodowska-Curie grant for PAIN-Net, Molecule-to-man pain network (grant no. 721841).

Keywords: microRNA, small fiber neuropathy, skin epidermis, epigenetic, epidermal innervation
Perception of Ankle Foot Orthoses by Individuals with Charcot-Marie-Tooth Disease

Poster No:
12a

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Introduction:
Many individuals with Charcot Marie Tooth disease (CMT) use ankle foot orthoses (AFOs) to address impaired balance and functional deficits. However, deficits persist even with AFO use, and a better understanding of how individuals with CMT perceive their AFOs and how their AFOs affect their function could inform future AFO refinement, prescription practices, and patient education.

Methods:
The Inherited Neuropathy Consortium Contact Registry was used to distribute an electronic survey to individuals with CMT. Participants provided free response answers to three questions. 1) What would you change about your orthosis if you could? 2) What activities does your ankle foot orthosis improve? 3) What activities does your ankle foot orthosis limit? Two reviewers evaluated the responses to each question using an inductive approach to identify major themes.

Results:
310 individuals participated, and primary themes were identified for each question. Responses to question one included text such as 'Better fitting, lighter, not as visible, flexible' and generally addressed primary themes such as device comfort or fit, durability, appearance, compatibility with shoes, and ease of use or functionality. Questions two and three included responses like 'Stability and I can walk further with them on and not so much pain' and 'Cannot wear continuously all day or else I develop sores on my feet' respectively. AFOs were described as beneficial for walking, standing, balance or stability, daily activities, and physical health or mobility. Limitations included mobility, shoes or clothing, balance or inclines, comfort or long-term use, and everyday activities.

Conclusions:
Results from this study identify areas of common benefit from AFO use and can inform future work to enhance AFO design and prescription. Additionally, the results provide a patient-centric perspective on AFO use which will aid in providing devices that better meet the needs of individuals with CMT.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support: Research reported in this publication was supported by the National Center For Advancing Translational Sciences of the National Institutes of Health under Award Number ULITR002537.

Keywords: Charcot Marie Tooth disease, Ankle Foot Orthosis
Use Of Intravenous Immunoglobulin In Patients With Chronic Inflammatory Demyelinating Polyneuropathy: A Systematic Literature Review

Poster No:
13a

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Introduction:
Intravenous immunoglobulin (IVIG) is recommended as first-line therapy for chronic inflammatory demyelinating polyneuropathy (CIDP), for both induction treatment and maintenance of response. This systematic literature review identified and summarized randomized controlled trials (RCTs) of IVIG in CIDP.

Methods:
Systematic searches were conducted (March 2020) of electronic databases (MEDLINE, Embase, BioSciences Information Service, Cochrane Library; no date restrictions) and selected congress and society websites (2017–2020) to identify RCTs of IVIG products, either placebo-controlled or head-to-head comparisons, in patients with CIPD. Efficacy, safety and health-related quality of life (HRQoL) data were extracted and summarized descriptively.

Results:
Seven eligible RCTs were identified (five placebo-controlled and two IVIG head-to-head comparison studies; 11 articles). IVIG was administered as 50 or 100 g/L infusions, or at 0.4–2 g/kg over 24 hours to 9 weeks. Versus placebo, IVIG was generally associated with statistically significant improvements in outcome measures of disability (4 of 5 studies reporting relevant data), muscle-strength (3 of 4 studies) and nerve-conduction (3 of 5 studies; p≤0.035) and in all domains of the Short Form 36 Health Survey and Rotterdam Handicap Scale (n=1; p≤0.044 and <0.001, respectively). The head-to-head RCTs (comparing Gammagard S/D 5% vs Kiovig 10%, and Clairyg 5% vs Tegeline 5%) reported that the different therapies were generally equivalent in efficacy, based on disability measures. Across RCTs most AEs were mild; few serious AEs were reported.

Conclusions:
In this recent systematic literature review of RCTs in patients with CIDP, IVIG use was generally confirmed to result in statistically significant improvements in disease symptoms and HRQoL measures versus placebo, and IVIG was shown to have a favourable safety profile. This review highlighted that few head-to-head comparisons exist of IVIG products/regimens, but those available have demonstrated no meaningful differences between the therapies evaluated. Study/medical writing support funder: Takeda Development Center Americas, Inc.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: Intravenous immunoglobulin, Chronic inflammatory demyelinating polyneuropathy, Randomized controlled trials, Systematic literature review
Comparison of different diagnostic criteria for atypical CIDP

Poster No:
14a

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

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

Results:
Patients with multineuropathic Lewis-Sumner syndrome (LSS) and those with length-dependent sensory demyelinating acquired distal symmetric (sensory DADS) neuropathy had distinct demographic and clinical features, less frequent response to treatment and to intravenous-immunoglobulin (IVIg) compared to patients with typical CIDP. There was no relevant difference when non-multineuropathic asymmetric CIDP or distal but non-length-dependent sensorimotor CIDP (distal CIDP) were compared with typical CIDP. Patients with a length-dependent sensory CIDP (sensory DADS) but not those with a non-length-dependent sensory CIDP (sensory CIDP) had a lower response to treatment and to IVIg compared to typical CIDP. When splitting DADS in sensory and sensorimotor DADS, only the former group showed lower response to treatment and to IVIg compared to typical CIDP.

Conclusions:
The use of different diagnostic criteria for atypical CIDP leads to a discrepant identification of patients groups. In this large series of CIDP patients, only those with multineuropathic LSS or with length-dependent sensory CIDP had clinical and therapeutic features that distinguished them from patients with typical CIDP, possibly suggesting different pathogenic mechanisms.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Chronic inflammatory demyelinating neuropathy, CIDP, Peripheral neuropathy, diagnostic criteria
Electrodiagnostic Subtyping In Guillain-Barré Syndrome: Application Of Criteria By Neuromuscular Specialists In Current Clinical Practice

Poster No:
15a

Authors:
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Introduction:
Nerve conduction studies (NCS) are helpful in diagnosing, subtyping and predicting outcome of Guillain-Barré syndrome (GBS). Published criteria for GBS subtypes focus on cutoff values, but certain aspects are underexamined, such as required minimal number of examined nerves, in-/exclusion of compression sites and requirements for distal CMAP amplitude. We aim to obtain insight into how neuromuscular experts deal with these different facets and make a comparison between various published electrodiagnostic (EDx) criteria regarding these aspects.

Methods:
An extensive questionnaire was developed and sent to 49 members of the electrophysiology expertise group in the International GBS Outcome Study (IGOS). Questions concentrated on 4 topics: (1) extensiveness of EDx testing, (2) nerve specific dilemmas, such as in- or exclusion of compression sites, (3) distal CMAP amplitude requirements and (4) criteria for conduction block and temporal dispersion. Literature containing GBS EDx criteria from six different authors were analyzed for these items.

Results:
Response rate was 49%. The indicated minimal number of motor nerves to be studied varied among experts and tended to be more extensive in equivocal rather than normal studies. Experts varied
considerably regarding usage of compression sites for subtyping (median at wrist, ulnar at elbow, peroneal at fibular head): 29% used all variables from all sites, 13% excluded all sites, and 58% used only a selection of sites and/or variables. In 38% for distal motor latency and 58% for motor conduction velocity, experts did require a minimal distal CMAP amplitude to classify these variables as demyelinating. For proximal/distal CMAP amplitude ratio and F wave latency, a requisite minimal CMAP amplitude was more often required (79%). The study comparing the requirements between various published criteria also showed differences on these aspects.

Conclusions:
Methodological aspects of EDx criteria for subtyping GBS and their application vary extensively between neuromuscular experts, potentially lowering reproducibility of GBS subtyping.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain-Barré Syndrome, Electrodiagnostics, Compression neuropathy
Use of SUDOSCAN in The Diagnostic Work Up of Small Fiber Neuropathy: Experience From a Large UK Single Centre Cohort.

Poster No:
16a

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Introduction:
Small fibre neuropathy (SFN) is a prevalent, often idiopathic condition pathologically characterised by distal damage to small diameter neurones. This leads to a variety of symptoms, predominantly neuropathic pain, paraesthesia, and dysesthesia. These patients are often misdiagnosed or denied of correct diagnosis. The current informal diagnostic criteria for SFN requires obtaining a skin biopsy to determine the intraepidermal nerve fibre density (IENFD), completing a thermal threshold test (TTT) and clinical evidence from the history and exam. SUDOSCAN is a point of care device often used in some clinical settings although its exact use is not investigated in a large unselected independent cohort. We used the SUDOSCAN in our clinic in addition to the golden triad of SFN investigation as an adjunct to measure the Electrochemical Skin Conductance (ESC) to determine the autonomic nerve dysfunction in SFN.

Methods:
We recruited all patients who attended SFN clinic and at least had TTT, SUDOSCAN, and detailed clinical assessment. Data were gathered in accordance with ethics and review board requirement of our hospital.

Results:
Our study was aimed at producing a detailed analysis of the sensitivity and specificity of quadruple testing for SFN, consisting of a skin biopsy, SUDOSCAN assessment, TTT together with clinical assessment for SFN. Total of 440 patients were included. 120 of the 440 patients who received a SUDOSCAN test also had skin biopsy examination. Sometimes abnormal SUDOSCAN was not supported by abnormal IENFD.

Conclusions:
SUDOSCAN assessment cannot support the diagnosis of SFN on its own, however it is useful as an adjunct. It was particularly helpful to counsel patients when a negative diagnosis is expected from IENFD.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

**Keywords:** Neuropathic pain, Small Fiber neuropathy, SUDOSCAN, Diagnostic criteria, Skin biopsy
The International CIDP Outcome Study (ICOS): An Update

Poster No:
17a

Authors:
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Introduction:
The diagnostic process of chronic inflammatory demyelinating polyneuropathy (CIDP), a rare immune-mediated polyneuropathy, is complicated by heterogeneity in clinical presentation and electrodiagnostic features. Improved description of typical CIDP and CIDP variants, relevant CIDP-mimics, and their characteristics could enhance future therapeutic considerations and prediction of long-term outcome in patients.

Methods:
The International CIDP Outcome Study (ICOS) is a prospective, observational, multicenter study, including all eligible patients fulfilling the EFNS/PNS 2010 criteria for CIDP. The EAN/PNS 2021 criteria will be incorporated in the next protocol amendment. In ICOS, clinical data, including diagnostic and treatment data, are collected, as well as biomaterials (DNA, cerebrospinal fluid, and serial serum samples). After the first two years, where follow-up visits are scheduled every 6 months, follow-up can be continued annually. Validated disability scales and patient reported outcomes, such as RODS, R-FSS, and EQ-5D-5L, are assessed each visit.

Results:
By January 1st, 2022, a total of 271 patients are enrolled in three Dutch university hospitals (66% men, median age at diagnosis of 59 years). Of 72 patients enrolled before January 2017, 22 completed a follow-up visit at five years. Acute-onset CIDP is reported in 29% of patients. Following the EFNS/PNS 2010 criteria, 70% of patients in ICOS are diagnosed with typical CIDP and 28% of patients have a CIDP variant (15% asymmetric, predominant motor 6%, -sensory 3% or predominant distal involvement 4%).

Conclusions:
The aim of ICOS is to improve the diagnostic process and optimize treatment strategies for CIDP. With follow-up extending over five years, we aim to identify determinants of long-term outcome. Results of applying the EAN/PNS 2021 criteria in the ICOS cohort will be presented at the PNS 2022 meeting. Harmonization of study protocols will allow close collaboration of ICOS with other registries, including INCbase.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, chronic inflammatory demyelinating polyneuropathy, long-term outcome, prospective cohort study
CIDP Mimics (CIMS) study protocol: improving the diagnostic process in CIDP.

Poster No:
18a

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Introduction:
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a disease with effective treatment options, but an extensive differential diagnosis. Correctly distinguishing CIDP from its mimics has proven to be difficult in clinical practice resulting in misdiagnosis of CIDP and a delay in initiation of appropriate treatment. Fast and accurate diagnosis of CIDP and subsequent treatment initiation will prevent unnecessary secondary axonal damage and might improve long-term outcome. The primary objective of the CIDP mimics study is to identify clinical factors and biomarkers that allow neurologists to distinguish between CIDP and its mimics early in the diagnostic process. Secondary objectives will be to identify the most common mimics, and what causes delay to a correct diagnosis and the start of treatment.

Methods:
This is a prospective observational multicenter cohort study. All patients aged 18 years or older in whom CIDP is considered in the differential diagnosis after first contact in the outpatient clinic, emergency room, hospital department, or after additional diagnostic testing, are eligible. After informed consent is obtained, clinical data, such as patient history and neurological examinations, are collected. If performed, results from additional diagnostic testing, such as nerve conduction studies, cerebrospinal fluid and laboratory testing, are also collected. Patients will not undergo additional testing for the purpose of this study. The diagnosis registered in the patient file at 3, 6 and 12 months after inclusion will be noted and evaluated based on the current EAN/PNS 2021 CIDP guideline by an expert panel.

Results:
Approval from the medical ethical committee has been obtained, and the study will commence shortly.

Conclusions:
An update of the preliminary results of the CIDP mimics study will be reported at the upcoming annual PNS meeting.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: CIDP, chronic inflammatory demyelinating polyneuropathy, CIDP mimics, Improving diagnosis
Investigation Of Sensors To Identify Gait Biomarkers In Individuals With Charcot-Marie-Tooth Disease Type 1A (CMT1A).

Poster No:
19a

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Introduction:
Purpose: Develop and optimize algorithms to derive gait and balance parameters from wearable sensors to identify existence of gait biomarkers to indicate impact of disease process in individuals with CMT1A. Background: Recent knowledge gains regarding the genetics, pathomechanisms and natural history of CMT1A, as well as emerging therapeutic candidates, highlight the need to prepare for clinical trials by identifying valid and responsive outcome measures. Body worn sensor technology has been used and validated with healthy individuals, but have shown to be less accurate when worn by individuals with gait deviations and therefore it may be useful to develop disease specific algorithms to capture gait metrics. The resultant parameters of gait may serve as useful functional biomarkers in future clinical trials.

Methods:
Methods: Participants and healthy controls donned MC10 sensors (containing triaxial accelerometers) during an in-person research visit. They completed the CMT Functional Outcome Measure (CMT-FOM) including the 6-minute walk test (6MWT). Gait and mobility assessments were video recorded and analyzed using video 2D pose software. Disease specific algorithms were used to calculate gait metrics. These metrics were compared to those of healthy controls and correlated with the CMT-FOM score.

Results:
Fifteen participants and five age/sex matched controls (ages 18-64) completed assessments. Compared with controls, participants with CMT demonstrated decreased stride counts and increased stride duration during the 6MWT. Stride duration was moderately correlated with the CMT-FOM score. Preliminary results of data derived from wearable sensors will be presented.

Conclusions:
Conclusion: Stride count and duration during the 6MWT in participants with CMT were significantly different from health age-matched controls and stride duration showed correlation with the CMT-FOM. These gait parameters may serve as biomarkers for functional measures. Further examination of feasibility and reliability of repeated assessment or translation to remote assessments in a larger population is necessary to determine utility in clinical trials.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support: Charcot-Marie-Tooth Association

Keywords: CMT, body worn sensors, clinical trial readiness, functional biomarkers, gait assessment
Cryptic Limb weakness

Poster No:
20a

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Introduction:
Peripheral neuropathy is a well-known manifestation of anti-Hu syndrome. We report a case of a 70yr female who presented with subacute onset of progressive asymmetric lower limb weakness that was initially diagnosed as motor variant of GBS suggested by Neurophysiology. She showed poor response to Rx with IVIG, Steroids and Plasmapheresis. Further investigations shows Positive Anti-Hu Ab and extensive search including a PETCT revealed an FDG intense avid lesion at left lung hilum highly suggestive of SCLCA

Methods:
70-year-old woman presented with a 3-week history of right leg weakness that progressed on to involve left leg. Positive examination findings include: hypotonia of legs with power of 0/5 in all muscle groups of lower limbs. DTR were absent in both knee and ankle. Plantar responses were mute. Sensory examination was normal for all modalities. CTCAP and MRI Spine performed due to antecedent weight loss and back pain. MRI showed no evidence of cord lesion or high-grade cervical stenosis.

Results:
CSF shows Albumin cytological dissociation. She was initially managed as GBS. IVIG Commenced – bronchoconstriction with low SPO2 and Maculopapular rash on legs/back during 2nd day. NCS-EMG represented 'AMAN form of GBS' but It is worth considering a paraneoplastic process affecting the motor nerves or possibly an atypical presentation of a diffuse anterior horn cell process. CSF AntiHU+ve and Patient managed with IVMP X 5days and PLEX. Repeat MRI-mild enhancement of several cauda equina nerve roots. PET: lesion with intense FDG uptake at the superior aspect of the left hilum suspicious of malignancy particularly small cell CA. Clinical Oncology discussed Radical RT-55Gy in 20 Fractions X 4weeks.

Conclusions:
In conclusion we present a case of progressive asymmetric lower limb weakness that was initially diagnosed as AMAN(GBS) however extensive evaluation revealed a predominant 'paraneoplastic motor neuropathy' attributed to ANNA-1(Anti-Hu) which is commonly associated with small cell lung CA.

References:
Yes

References 1:
Denny Brown (1947) Primary Sensory Neuropathy with Muscular changes associated with carcinoma.

References 2:
References 3:

References 4:

Grant Support:

Keywords: CRYPTIC LIMB WEAKNESS
PRODUCTIVITY LOSS IN PATIENTS WITH CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY: A NATIONWIDE POPULATION-BASED STUDY IN SWEDEN

Poster No:
21a

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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare autoimmune inflammatory disorder of the peripheral nervous system (PNS). Population-level real-world evidence are limited; this study aimed to evaluate the employment status and sickness absence among patients with CIDP in Sweden.

Methods:
Data were obtained from four nationwide registers provided by the National Board of Health and Welfare in Sweden and linked through the unique personal identity number. Patients with ≥ 1 diagnosis of CIDP (ICD-10 G61.8) from 01/01/2001 to 12/30/2017 were selected. Date of the first CIDP diagnosis was designated as index date with baseline as 1-year period prior to index date. All individuals were followed until death, lost to follow up or end of study. Employment status and sickness absence were evaluated for patients aged 18-65 years within 1-year post-index follow-up up to a maximum of 16 years.

Results:
At index, mean (±SD) age of 1,444 patients with CIDP was 58.7 (±17.0) years; 37% were female. The median follow-up time was 5.58 years (Q1-Q3: 2.06-10.2). From 2007 to 2017, the annual incidence of CIDP slightly increased from 0.8 per 100,000 person-years to 1.0 per 100,000 person-years. The prevalence of patients seeking healthcare increased from 2.0 per 100,000 person-years to 3.3 per 100,000 person-years during the same period. Unemployment rates remained constant over time with 40.9% (n=291/711) employed at 1-year, 39.0% (n=171/439) at 5-year, 40.7% (n=83/204) at 10-year. Among patients who were employed in 1-year post-index period (n=417), 50.8% (n=212/417) reported ≥ 1 sickness absences, of which 48.6% (n=103/212) reported having absence for >6 months.

Conclusions:
CIDP continues to impose a substantial work productivity loss to patients and healthcare systems. Future research should fully characterize the burden of this rare disease and aim to understand how appropriate treatment can mitigate disability and associated symptoms for this population.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Chronic Inflammatory Demyelinating Polyneuropathy, Outcomes Research, Burden of Illness, Quality of life, Work productivity
**Jumpy Stump Syndrome: A Case Study**

**Poster No:**
22a

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**Introduction:**
Since the early accounts of jumpy stump syndrome on amputees in the mid-19th century, research behind the topic has been relatively stagnant. Scientists have agreed that the potential mechanism behind this condition is peripheral nerve damage, with further evidence showcasing neuromas as another cause. 'Jumpy stump' is not fully comprehended but there are multiple treatments that have shown to subsidize its debilitating effects. We report a case of a left above knee amputee patient who developed jumpy stump with the goal of better characterizing its mechanisms and treatments.

**Methods:**
A 34-year-old male underwent a left above knee amputation after developing chronic regional pain syndrome and flexion contracture following an arthroscopic medial meniscus repair. 5-6 years later, the patient developed stump pain and underwent two revision amputations. 6 months following the last revision he developed severe and uncontrollable stump spasms. The patient tried Mirapex, Baclofen, Sinemet, and a sympathetic block, all of which failed to relieve his symptoms. He underwent a targeted muscle reinnervation (TMR) procedure in which a 1 cm neuroma on the sciatic nerve was resected and three nerve branches were found to create the TMR, one of which penetrated the adductor compartment, one the vastus lateralis, and one the hamstring. 3 weeks post-operatively the patient reported overall improvement but he continued to have spastic movements of the sartorius and lateral hip flexors. 7 weeks post-operatively his sartorius was injected with 30 mL of 70% isopropyl.

**Results:**
The muscle stopped spasming almost immediately after the injection and 2 weeks later, the patient noted a tiny wiggle of the muscle but overall, he felt his symptoms were almost entirely resolved. 3 months after the injection the patient's symptoms were stable. Physical activity with lateral movement triggers some wiggling of the muscles, however, he reports no problems with daily office work.

**Conclusions:**
With its origins not clearly identified, jumpy stump syndrome still does not have standardized treatment methods. Our case demonstrates that isopropyl injection and TMR may be an effective treatment modalities to diminish the debilitating effects of jumpy stump.

**References:**
Yes

**References 1:**

References 3:

References 4:

Grant Support:

Keywords: Jumpy stump syndrome, Amputation, Dystonia, Myoclonic
Evaluation of the use of Objective Outcome Measures for Inflammatory Neuropathies in Clinical Practice

Poster No:
23a

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Introduction:
Chronic Inflammatory Neuropathies (CINs) are rare disorders characterized by autoimmune attack on peripheral nerves. Since immunomodulatory therapies have significant potential risks and high costs, they should be used only when indicated and effective. While a set of objective outcome measures (OOMs) are recommended for trials in CINs, the measures have not been widely used in routine clinical care. The goal of this project is to evaluate the feasibility of using OOMs in the clinical setting and evaluate which measures best reflect patients' abilities, deficits, and response to treatments.

Methods:
Prospective data was collected from 26 participants with a diagnosis of CIDP or MMN. Participants completed validated patient-reported outcome measures including activity and participation scores (I-RODS/MMN-RODS), quality of life (EQ-5D-5L), pain and fatigue, as well as grip strength, 9-hole peg test, 10 meter walk, muscle strength (MRCss) and sensation (mISS). Participants provided feedback on ease of use, length of time, relevancy, and suggested alternative measures to capture their limitations. Focus groups were conducted to collect qualitative data on using the measures.

Results:
Of the nine measures, nearly all participants reported the measures were easy to complete and took an appropriate amount of time. Over 60\% of participants reported all measures were relevant to them, with variability in which were most relevant to each patient. The top three ranked measures according to relevance were muscle strength testing, quality of life questionnaire and daily activities questionnaire. The most commonly suggested alternative measures included assessments of balance, dexterity, and detailed gait assessment.

Conclusions:
OOMs allow for appropriate monitoring of patients over time and optimization of immunotherapy treatment. By tracking longitudinal results of outcomes that matter to patients, patients can better participate in shared-decision making. Clinicians should adopt OOMs as a tool to monitor patients with CINs going forward. Additional measures that were reported as relevant to patients should be further investigated.

References:
Yes

References 1: 

References 2: 
References 3:

References 4:

Grant Support:

**Keywords:** CIDP, Outcome Measures, Value Based Healthcare
A recurrent missense variant in ITPR3 is associated with demyelinating CMT

Poster No:
24a

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Introduction:
The diagnostic yield in demyelinating Charcot-Marie-Tooth disease (CMT1) is typically ~80-95%, of which at least 60% is due to the PMP22 gene duplication. The remainder of CMT1 is more genetically heterogeneous.

Methods:
We used whole exome sequencing (WES) and whole genome sequencing (WGS) data to investigate novel causal genes and mutations in a cohort of ~2,000 individuals with CMT disease submitted to the Genesis project.

Results:
We identified a recurrent missense variant in ITPR3, a recently described CMT gene, in more than 16 individuals from seven different families. All families presented with slow nerve conduction velocities and an autosomal dominant or de novo inheritance, matching the diagnostic category of CMT1. Sanger sequencing confirmed the co-segregation of the CMT phenotype with the presence of the variant, including a four-generation family with multiple affected second-degree cousins, and a de novo inheritance in an isolated patient. ITPR3 encodes IP3R3 (inositol 1,4,5-trisphosphate receptor 3), which, like its paralogs ITPR1 and ITPR2, is highly expressed in the nervous system. Based on protein modelling, this residue is located in the dimerization interface and could interfere with the dimerization process. We are currently testing this hypothesis using in vitro modelling.

Conclusions:
Here we show that a recurrent ITPR3 missense mutation is associated specifically with a demyelinating phenotype and could account for a relatively large proportion of unsolved CMT1 patients.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: demyelinating CMT, inherited peripheral neuropathy, inositol receptor 3, ITRP3
Activation of Keratinocyte Gq-linked G-Protein Coupled Receptors Remodels Dorsal Root Ganglion Neurons Single-Cell Transcriptomic Profile.

Poster No:
25a

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Introduction:
Keratinocytes are closely juxtaposed to cutaneous nerve terminals, enabling communication between keratinocytes and cutaneous nerves. We investigated potential mechanisms that mediate this communication. We genetically expressed stimulatory DREADDs (hM3Dq) into K14 basal keratinocytes (K14) in mice as a tool for mimicking the activation of Gq-linked G protein-coupled receptors (GPCRs) in K14 expressing cells. We have shown that activation of these DREADDs reduced innervation of the epidermis indicating that activation of K14 Gq-linked GPCRs can regulate nerve fiber degeneration in the epidermis.

Methods:
We used bulk and single-cell RNA (scRNA-seq) sequencing from the skin and Dorsal Root Ganglion (DRG) taken from mice expressing hM3Dq into K14 keratinocytes and compared control mice receiving saline and mice receiving CNO to activate K14 keratinocytes expressing hM3Dq. We used RNAscope on frozen sections of the DRG and skin to validate the scRNA-seq results.

Results:
Bulk RNA sequencing of the epidermis revealed changes in a set of genes associated with neurite outgrowth, including class III semaphorins, potentially impacting cutaneous nerve degeneration. Using RNAscope we found dramatic changes in the expression of semaphorins and their receptors in distinct DRG neurons subtypes. Using single-cell RNA-seq from lumbar DRG we profiled the transcriptome of 10,000 individual DRG cells and found that hM3Dq mediated stimulation of keratinocytes induced changes in DRG single-cell gene expression profile resulting in the identification of a novel DRG neuronal subtype among the nonpeptidergic nociceptors (NP1.2).

Conclusions:
Our findings indicate that activation of basal keratinocytes Gq-linked GPCRs can result in profound changes in DRG neuronal transcriptomic profile resulting in a phenotypical switch (plasticity) of DRG neurons. Furthermore, our results suggest possible therapeutic effects of activating or blocking specific keratinocyte Gq-linked GPCRs for promoting axon regeneration in small fiber neuropathy.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: neuropathic pain, DRG, Single-Cell Transcriptomic Profile, keratinocytes, G-Protein Coupled Receptors
Modelling Charcot-Marie-Tooth disease with hiPSCs-derived motor neurons model

Poster No:
26a

Authors:
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Introduction:
Charcot-Marie-Tooth disease (CMT) is the most common hereditary neuropathy. Currently, more than 90 genes have been identified as responsible for CMT, including the GDAP1 gene. Under physiological conditions, this gene leads to the production of a protein mainly expressed on the mitochondria external membrane of peripheral nerves. In order to investigate the physiopathological effects of GDAP1 mutations, we generated different cell-types including human induced-pluripotent stem cells (hiPSCs) derived motor-neurons (MNs) starting from patient and controls dermal biopsies. Then, we compared GDAP1 RNA expression level in these various cell-types in order to choose the more appropriate one for our next studies.

Methods:
Starting from dermal biopsies of healthy individuals and of a CMT2H patient carrying a non-sense mutation (PTC, Premature-Termination-Codon) in homozygous state in GDAP1 (c.581C>G, p.Ser194*), we generated Fibroblasts (FB); we reprogrammed them into hiPSCs, following Pr. Yamanaka protocol and we differentiated them into Neural Progenitors (NP) and into Motor-Neurons (MN), following Dr Faye protocol. In these four cell-types, we realized RNA extraction, reverse-transcription and quantitative RT-PCR analyses.

Results:
We obtained rapidly the human FBs, and after several months of culture, we obtained hiPSc, NPs and MNs. In control cells (derived from healthy individuals), the RNA expression level studies showed that FBs and hiPSc expressed weakly GDAP1, while NPs, and even more significantly MNs expressed strongly this gene. Interestingly, in MNs derived from the CMT2H patient, harboring a homozygous PTC, the GDAP1 mRNA level was drastically reduced, probably degraded by the NMD system (non-Sens mediated Decay).

Conclusions:
These results highlight the importance of generating MNs to study GDAP1, and probably other CMT genes. The comparison of control and patient hiPSC-derived motor neurons will be very useful to better understand molecular mechanisms associated to GDAP1-mutations in CMT disease. These models could also be employed in the evaluation of new therapeutic strategies.

References:
No
References 1:
References 2:
References 3:
References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth, motor neuron, GDAP1, mitochondria, iPSCs
Depression In Patients With Charcot-Marie-Tooth Disease Type 1A (CMT1A): Findings From A Real-World Digital Study

Poster No:
27a

Authors:
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Introduction:
This analysis aimed to examine patient-reported diagnosis of, and consequences associated with, depression among Charcot-Marie-Tooth disease type 1A (CMT1A) patients in European and US real-world practice.

Methods:
Adults with CMT1A were recruited to an ongoing international observational study exploring the real-world impact of CMT. Data were collected via CMT&Me, a bespoke digital app developed for this study, through which participants were asked questions on demographic and employment variables. This interim analysis examined participants (n=937) from France, Germany, Italy, Spain, the UK and the US.

Results:
Thirty-eight percent of participants (n=238/628 who reported other medical conditions) reported having been diagnosed with depression in addition to CMT1A; higher than in the general population. Of these, 54% (n=112/208 who also reported symptom severity) and 35% (n=72/208) reported moderate or severe CMT1A symptom severity respectively. Forty-three percent of participants diagnosed with depression (n=102/238) reported that they used, or had previously used, antidepressants. Reported diagnosis of depression varied considerably by country. Highest rates were among participants in the US and UK (48% and 40% respectively – of which 17% (n=17/103) and 38% (n=25/66) reported severe symptom severity respectively), while lowest rates were among participants in France and Italy (29% and 18% respectively – of which 53% (n=9/17) and 31% (n=5/16) reported severe symptom severity respectively). Of participants who responded to the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) instrument (n=685), 62% reported concerns with anxiety/depression.

Conclusions:
Over a third of participants reported diagnosis of depression in addition to CMT1A. This is not surprising for a disease with this symptom burden; however, depression itself as a comorbid condition represents significant disease burden and can affect treatment and outcomes for CMT1A – this warrants further analysis and exploration.

References:
No
References 1:

References 2:

References 3:

References 4:

Grant Support:

**Keywords:** Charcot-Marie-Tooth disease, Depression
Work Impacts In Patients With Charcot-Marie-Tooth Disease Type 1A (CMT1A): Findings From A Real-World Digital Study

Poster No: 28a

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Introduction:
This analysis aimed to examine patient-reported impacts to working life for Charcot-Marie-Tooth disease type 1A (CMT1A) in European and US real-world practice.

Methods:
Adults with CMT1A were recruited to an ongoing international observational study exploring the real-world impact of CMT. Data were collected via CMT&Me, a bespoke digital app developed for this study, through which participants were asked questions on demographic and employment variables. This interim analysis examined participants (n=937) from France, Germany, Italy, Spain, the UK and the US.

Results:
Of participants who responded to this question (n=607, mean age: 45), 54% (n=328/607) reported working for pay; this was similar across countries with the lowest being France (46%, n=33/72). Twenty percent (n=122/607) reported not working due to disability; this was highest in the US (27%, n=46/172) and lowest in Italy (10%, n=9/91). Of those working for pay, 74% (n=241/328) reported their work life was affected by CMT1A. Highest rates were in Spain (96%, n=23/24), while lowest were in Italy (65%, n=35/54). Frequently reported ways that CMT1A affected work life were type of job (54%, n=131/241 who specified ways in which work life was affected), number of sick days (30%, n=73/241) and working part-time (30%, n=73/241). Participants reported missing a mean 1.4 workdays in the past two weeks due to CMT1A, equivalent to approximately 36 days per year. Of those unemployed (7%, n=42/607), 71% (n=30/42) reported that CMT1A was a contributing factor. Highest rates were in Italy (91%, n=10/11), while lowest were in Germany (0%).

Conclusions:
CMT1A has a substantial impact on patients' ability to work, which is comparable across European countries and the US. Patients are absent from work approximately 36 days per year due to CMT1A. Further research is needed to explore indirect costs associated with these losses, and to better manage impact on patients' work lives.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease, Productivity loss
Netazepide is neuroprotective in a mouse model of vincristine-induced sensory neuropathy

Poster No:
29a

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Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) is a side effect of several antineoplastic agents. Regardless of their mechanisms of actions, signaling induced by chemotherapeutic agents result in an enhanced nociceptive input. Our recent findings in a mouse model of VCR-induced peripheral neuropathy (VIPN) showed an up-regulation of cck2r gene, coding for the cholecystokinin type 2 receptor (CCK2R). Over the past decades, the established role of CCK2R activation in directly facilitating nociception, has led to the development of several CCK2R antagonists. In the present study, we examined whether CCK2R blockade by Netazepide (NTZ) can prevent from VIPN.

Methods:
VIPN was induced by intraperitoneal (i.p.) injections of VCR at 100 µg/kg/d during 7 days (D0 to D7). NTZ (2 mg/kg/d or 5 mg/kg/d, per os) was administered one day before VCR treatment until D7. The onset of tactile allodynia induced by VCR was assessed with von Frey monofilaments. Immunohistochemistry and morphological analyses were performed on DRG, skin and sciatic nerve.

Results:
VCR induced tactile allodynia from D1 to D7 in mice, which was correlated to DRG neuron and intraepidermal nerve fiber (IENF) loss, and by enlargement and loss of myelinated axon in sciatic nerve. NTZ administration was able to completely prevent the occurrence of allodynia. Similarly, NTZ treatment prevented the decrease of IENF density and swelling of myelinated axons, as well as DRG neuron loss and myelinated nerve fiber loss in sciatic nerve. We found that CCK2R co-localized with S100, a cytoplasmic marker of schwann cells.

Conclusions:
The finding that blockade of CCK2R by NTZ protects against VCR-induced sensory neuropathy strongly supports further exploration of its therapeutic potential in patients receiving such chemotherapy.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Chemotherapy-induced peripheral neuropathy, vincristine, tactile allodynia, netazepide, CCK2R
The Charcot-Marie-Tooth Disease Gene Curation Expert Panel (ClinGen)

Poster No:
30a

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Introduction:
ClinGen has created the CMT Gene Curation Expert Panel to evaluate and define the clinical validity of genes and variants. The ClinGen curation process is uniquely recognized by the FDA and thus will contribute to regulatory considerations of gene-based diagnosis and therapies.

Methods:
The curation process includes reviewing genetic and experimental evidence from the literature and assigning a clinical validity classification for a gene-disease relationship. Many genes are implicated in more than one phenotype, therefore a standardized pre-curation process (lumping or splitting criteria) is necessary to define the disease entity according to MonDO (Monarch Initiative). In the gene curation process, biocurators evaluate the strength of evidence to support or refute a claim that variations in reported genes cause CMT. Evidence supporting the gene-disease relationship includes case-level data, co-segregation analyses, and functional experiments. For each category, a suggested number of points is given for genetic and experimental evidence, leading to the final classification of the gene, ranging from definitive to refuted. The final classification is reviewed, discussed, and approved by the gene curation expert panel.

Results:
We have already completed the curation for 30 CMT genes: 22 genes have been classified as definitive (TRPV4, SBF2, HINT1, EGR2, HSPB8, NTRK1, FIG4, INF2, BSCL2, DST, DNM2, FGD4, GDAP1, GJB1, MPZ, MTMR2, NEFH, TTR, INF2, SLC25A46, and YARS1), 4 genes as moderate (SBF1, ATL3, GNB4 and LITAF), 3 genes as limited (ARHGF10, PMP2 and MARS1), 1 gene as disputed (MED25), and 1 gene as 'no known disease relationship' (KIF1B). The final classification is published at the ClinGen website.

Conclusions:
In summary, the CMT Gene Curation Expert Panel is a collaborative effort to analyze and define the clinical relevance of known CMT genes, improving our knowledge of genomic variations, and providing valuable resources for precision medicine and research.
References: No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, gene curation, ClinGen
Downregulation of leukocyte LKB1/AMPK signaling is associated with the severity of Guillain-Barre syndrome independently of autophagy

Poster No:
31a

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Introduction:
The intracellular energy sensor AMP-activated protein kinase (AMPK) regulates cell metabolism and function mainly through suppression of mechanistic target of rapamycin complex 1 (mTORC1) and subsequent increase in autophagic degradation of cellular components.

Methods:
The status of AMPK/mTORC1 pathway and autophagy was analyzed in peripheral blood mononuclear cells (PBMC) of 23 patients with acute demyelinating GBS, an immune-mediated peripheral polyneuropathy, and 20 age/sex-matched healthy control subjects.

Results:
The activation of liver kinase B1 (LKB1)/AMPK/RAPTOR signaling axis, assessed by immunoblotting, was significantly reduced in GBS compared to control subjects. On the other hand, the phosphorylation of mTORC1 activator AKT and mTORC1 substrate 4EBP1, as well as protein levels of autophagy markers LC3, ATG5, beclin-1, and p62 were not affected in GBS PBMC despite a minor transcriptional downregulation of autophagy genes. The suppression of AMPK signaling in GBS leukocytes correlated with the increased phosphorylation of extracellular signal-regulated kinase (ERK) and protein kinase C (PKC) substrate glycogen synthase kinase-3β, while no association with p38 mitogen-activated protein kinase (MAPK) was observed. Moreover, the in vitro experiments in HL-60 myeloblastic leukemia cell line indicated that PKC activation could be an upstream signal leading to both AMPK inhibition and ERK stimulation. The downregulation of LKB1/AMPK signaling, but not the activation status of autophagy, mTORC1, AKT, ERK, PKC, or p38 MAPK, correlated with overall disability and/or muscle strength loss in GBS patients. Finally, the retrospective study in a diabetic cohort of GBS patients demonstrated that the treatment with AMPK activator metformin was associated with milder GBS symptoms compared to insulin/sulphonylurea therapy.

Conclusions:
Collectively, these data indicate that the impairment of LKB1/AMPK pathway might contribute independently of autophagy and mTORC1 to the development and/or progression of GBS, thus representing a potential therapeutic target in this autoimmune disease.

References:
No
Grant Support: The study was supported by unrestricted grant from Kedrion, by Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant No. 41025) and by Serbian Society for the Peripheral Nervous System.

Keywords: Guillain-Barre syndrome, autophagy, LKB1/AMPK signaling, peripheral blood mononuclear cells
Single Nucleotide Polymorphisms in Cytokine Genes in Patients with Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Poster No:
32a

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Introduction:
Precise pathways of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) pathogenesis are still insufficiently understood, but CIDP is considered to be an autoimmune disease. Single nucleotide polymorphism (SNP) may alter cytokine gene expression, with potential influence in pathogenesis of the autoimmune diseases. The aim of this study was to analyze SNPs in cytokine and cytokine receptor genes in a large cohort of CIDP patients.

Methods:
We assessed SNPs in IL-10 gene: rs1800871, rs1800896, and rs3024505; IL-6 gene: rs1800795; TNF gene: rs1800629 and rs361525; IL-12B gene: rs3212227 and rs6887695; p40 gene: 10045130; and IL-23R gene: rs11209026 and rs2201841. Analyses was performed in 89 CIDP patients and 486 healthy control subjects (HCs).

Results:
We found statistically significant difference in both allele and genotype frequencies between CIDP patients and HCs for rs1800896 (p<0.001). G>T polymorphism (rs3212227) in IL-12B gene was more common in males vs. females with CIDP (97% vs. 85%, p<0.05). GG homozygosity in rs6887695 in IL-12B gene was more common in early-onset vs. late-onset CIDP (62.2% vs. 36.6%, p<0.05). C>G polymorphism (rs1800795) in IL-6 gene was more frequent in CIDP patients with diabetes mellitus (96% vs. 76%, p<0.05).

Conclusions:
Difference in IL-10 SNP was found in our cohort of CIDP patients which was also seen in other autoimmune diseases. Differences in SNPs between genders, between patients with early vs. late onset CIDP, and between patients with vs. without diabetes, may potentially suggest different pathogenesis in these subgroups of CIDP patients.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: Chronic Inflammatory Demyelinating Polyradiculoneuropathy, Single Nucleotide Polymorphisms, Cytokine, Genes, cytokine receptor
Pharmacological inhibition of GCN2 is efficacious in mouse models of CMT2D

Poster No:
33a

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Introduction:
Dominant mutations in tRNA synthetase genes in mice activate the integrated stress response (ISR) through the sensor kinase GCN2. Inhibiting GCN2 at or before disease-onset prevented ISR activation and greatly mitigated the neuropathy. Here we provide additional preclinical data on GCN2 inhibition in mouse models of Gars/CMT2D.

Methods:
We performed two studies using an experimental GCN2 inhibitor (GCN2iB) in Gars-ETAQ mice modeling CMT2D. First, mice were treated with GCN2iB starting after disease onset, at 5-weeks-of-age. Second, mice were treated at disease-onset, but treatment stopped after 4 weeks to test necessity of life-long treatment.

Results:
When treatment with GCN2iB was started post-onset (P35) and continued for 5 weeks, Gars mice showed improvement over the course of the study, gaining body weight, improving motor performance and showing better neurophysiological outcomes. The basis for this post-onset improvement is under investigation, but the ability of the drug to improve function and not just prevent disease is important. In a second cohort, treatment was started at disease onset (P14) and continued for 4 weeks, then treatment stopped and mice were followed for an additional 4 weeks. These mice showed an improvement in motor performance during the treatment phase, but performance declined when treatment stopped. Neurophysiology data is still being analyzed, but preliminary findings indicate some benefit persisted even four weeks after treatment was ended. However, continued treatment is likely required to maintain benefit.

Conclusions:
Inhibiting GCN2 is beneficial in mouse models of CMT2D even when treatment is started after the onset of disease, improving the potential relevance of this approach for patients. When treatment was stopped, some of the improvements were lost, suggesting that continued treatment will be needed for maximal benefit.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support: NIH R37 NS054154

Keywords: tRNA synthetase, integrated stress response, preclinical study, CMT2D, drug target
Searching for potential biomarkers in Guillain-Barré syndrome: calprotectin and peripheral myelin protein 2

Poster No:
34a

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Introduction:
Discovery of peripheral nerve myelin damage and inflammation biomarkers in Guillain-Barré syndrome (GBS) could help in the differential diagnosis, predicting prognosis, and monitoring treatment response. Calprotectin is a protein mainly involved in inflammatory processes and correlates with disease activity in systemic autoimmune and disorders chronic inflammatory demyelinating polyneuropathy1. Peripheral myelin protein 2 (PMP2) is an important protein for lipid dynamics and myelin membrane stability in peripheral nerve. The aim of this pilot study is to assess the role of serum calprotectin as an inflammatory biomarker and serum PMP2 as a myelin damage in GBS.

Methods:
Aleatory selection from all GBS patients included in the International GBS Outcome study (IGOS) from Spain was done (25 for calprotectin and 30 for PMP2). Serum was obtained at disease onset. Calprotectin was test by a chemiluminescence assay and PMP2 by ELISA in both GBS patients and healthy controls (HC).

Results:
Serum calprotectin levels were significantly higher in GBS (n=23) compared to HC (n=48), with a mean of 4.3±5.9µg/ml vs 1.2±0.9µg/ml (p<0.05). Patients with higher levels of calprotectin (>2µg/ml, n=13) showed no differences with patients with lower levels in terms of GBS variant and severity measured by maximum GBS disability score (GDS). Two patients had calprotectin levels >20µg/ml. Both were classified as acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and maximum GDS was not significantly higher. Mean serum PMP2 levels were 3.2±7.5ng/ml in GBS patients (n=30) and 0.7±2.1ng/ml in HC (n=48), with no significant differences observed (p=0.28).
**Conclusions:**

Calprotectin is elevated in a subset of GBS patients but no correlation with disease activity or phenotype was found in this pilot study. Whether this elevation relates to disease-specific mechanisms or other confounding factors needs further assessment. Serum PMP2 levels tested by ELISA do not help to distinguish myelin damage in GBS patients.

**References:**

No

**References 1:**

**References 2:**

**References 3:**

**References 4:**

**Grant Support:**

**Keywords:** Guillain-Barré Syndrome, Biomarkers, Calprotectin, Peripheral myelin protein 2, Inflammation
Zebrafish in vivo imaging of innate immune cell interactions with cutaneous axons in a paclitaxel neurotoxicity model

Poster No:
35a

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Introduction:
The mechanisms underlying paclitaxel-induced neurotoxicity are poorly understood. We demonstrated that paclitaxel induces the expression of Matrix-Metalloproteinase 13 (MMP-13) in epidermal keratinocytes and this promotes the degeneration of unmyelinated cutaneous sensory axons. Since MMPs play an important role in immune cell function, and inflammation has been linked to paclitaxel neurotoxicity, we sought to capture interactions between innate immune cells and cutaneous axons in live animals and determine the role of MMP-13 in this process.

Methods:
Here we characterized leukocyte behavior with time-lapse imaging of two transgenic lines Tg(mpo:GFP/casper) and Tg(mfap4:tdTomato_CAAAX).

Results:
Paclitaxel treatment for 24h resulted in neutropenia, similar to chemotherapy patients, indicating that zebrafish are useful to study the effects of chemotherapy on innate immune cells. We further uncovered that paclitaxel treatment caused significant changes in the migratory velocity of leukocytes. For instance, at low (1µM), but not high, paclitaxel concentrations, macrophages accumulated near the caudal vein plexus where leukocytes extravasate from the circulation, suggesting that paclitaxel dosage impacts leukocyte migration behavior. We also generated 3D reconstructions of axons interacting with leukocytes. Although we expected that macrophage co-localization with axons is increased in the presence of paclitaxel if involved in axon degeneration, we observed decreased co-localization. In contrast, neutrophil binding to axons was significantly increased. Thus, although leukocyte numbers are reduced overall upon paclitaxel treatment, their interactions with axons vary depending on the type of leukocyte. Further research is currently being conducted to better characterize axon-leukocyte interactions over time and the role MMP-13 in this process. The most recent findings will be presented at the meeting.

Conclusions:
In summary, our unique zebrafish in vivo model is useful in determining the impact of chemotherapeutic drugs on immune cells in living animals and defining immune cell interactions with cutaneous axons and their involvement in paclitaxel neurotoxicity.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

**Keywords:** paclitaxel, innate immune cells, zebrafish, sensory axons, inflammation
Predictive Modeling to Investigate the Mechanism(s) Underlying Dominant Peripheral Neuropathy Caused by Aminoacyl-tRNA Synthetase Variants

Poster No:
36a

Authors:
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Institutions:
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Introduction:
Aminoacyl-tRNA synthetases (ARSs) are ubiquitously expressed, essential enzymes that ligate amino acids to cognate tRNAs in the cytoplasm and mitochondria. Mutations in five ARSs cause autosomal dominant, axonal peripheral neuropathy, presenting the question: how do mutations in ARSs, which are essential in all tissues, lead to tissue-specific effects? While protein translation and the integrated stress response have been implicated downstream of neuropathy-associated ARS variants, a unifying pathological mechanism that explains the locus and allelic heterogeneity has not been identified.

Methods:
All five neuropathy-associated ARSs function as cytoplasmic dimers, which is consistent with a dominant-negative effect. If this is the primary disease mechanism, it would be expected that certain variants in any cytoplasmic dimeric ARS could exert a dominant-negative effect and lead to dominant neuropathy. To test this, we are employing a predictive modeling strategy in which we introduced missense mutations into threonyl-tRNA synthetase (TARS1), a cytoplasmic dimeric ARS not yet implicated in neuropathy. We are testing three missense mutations reported to be both loss-of-function and dominantly lethal when overexpressed in bacteria.

Results:
We tested these variants in a humanized yeast complementation assay, which revealed that one variant is hypomorphic and that two are loss-of-function alleles, similar to other neuropathy-associated ARS variants. We next tested these variants in a humanized yeast dominant toxicity assay, where we co-express mutant TARS1 in conjunction with wild-type TARS1. Our preliminary data suggest that the two loss-of-function variants are dominantly toxic in the presence of wild-type TARS1, consistent with a dominant-negative effect.

Conclusions:
Moving forward, we will develop a heterozygous C. elegans model and assess for dominant motor behavior deficits. Successful completion of this study will provide insight into the mechanism(s) underlying ARS-associated neuropathy and will inform clinicians to screen all genes encoding a cytoplasmic dimeric ARS for pathogenic variants in patients with peripheral neuropathy.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support: A. A. is supported by a grant from the National Institute of General Medical Sciences (GM136441).

Keywords: Neuropathy, aminoacyl-tRNA synthetase, Yeast, Mendelian Disease
Complement inhibition prevents paranodal loop injury in an anti-GM1 antibody-mediated paranodal demyelinating mouse model

Poster No:
37a

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Institutions:
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Introduction:
The involvement of the complement pathway in Guillain-Barré syndrome (GBS) pathogenesis has been demonstrated in both patient biopsies and animal models. It has been established through animal modelling that anti-ganglioside antibodies (AGAbs) mediate injury through the activation of complement and the formation of membrane attack complex pores in neural membranes, allowing the uncontrolled influx of ions and water into the cell. The influx of calcium ions activates the calcium-dependent protease, calpain, leading to cleavage of cytoskeletal structural proteins such as neurofilament, actin and ankyrin.

Methods:
Complement inhibition has been demonstrated to provide effective protection from injury in in vivo AGAb-mediated mouse models representative of Miller Fisher syndrome and acute motor axonal neuropathy (AMAN). Due to the limited availability of animal models representative of the demyelinating variant of GBS, it is unknown whether complement inhibition would be an effective therapy for patients with acute inflammatory demyelinating polyneuropathy (AIDP). Herein, we used a recently developed anti-GM1 antibody-mediated paranodal demyelinating mouse model, representative of AIDP, to determine the relevance of complement inhibition as a therapeutic for AIDP.

Results:
Anti-GM1 antibody-mediated injury to the paranode results in significant disruption to the axo-glial junction, leading to detachment of the paranodal loops and conduction block. Here, we demonstrate that C2 inhibition significantly attenuates injury to the axo-glial adhesion molecules and improves respiratory function in an in vivo paranodal demyelinating mouse model.

Conclusions:
These data establish that complement inhibition mitigates injury in a paranodal demyelinating model, representative of demyelinating syndromes associated with anti-GM1 antibodies like GBS and multifocal motor neuropathy. This outcome suggests that both AMAN and AIDP patients could be included in future complement inhibition clinical trials.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support: Study funded by Argenx

Keywords: GBS, complement inhibition, paranode, demyelinating polyneuropathy
Microtubule acetylation rescues capsaicin-induced neurite degeneration and may predict fiber regeneration

Poster No:
38a

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Institutions:
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Introduction:
Sensory nerve endings degenerate as the consequence of different insults, like immune-mediated or metabolic diseases and chemotherapy, but they also show unique regenerative capability. The mechanisms behind these processes might differ in the various disorders, and the reason why some patients show higher spontaneous nerve fiber regeneration is unknown.

Methods:
To better understand the mechanisms underlying sensory neurons degeneration and regrowth, we used the experimental capsaicin treatment, a model that can be easily applied to cell cultures and transferred to human beings. Capsaicin, an agonist of transient receptor potential vanilloid type 1 channel, induces a fast degeneration of peripheral sensory nerves, with dynamic reorganization of microtubules and formation of axonal swellings reminiscent of intracellular trafficking block. We selected 10 small fiber neuropathy patients whose follow-up (range 3-6 months) distal leg skin biopsy showed either recovery or worsening of intraepidermal nerve fiber density (IENFD) compared to baseline biopsy. Moreover, we challenged differentiated F11 cells with capsaicin and performed a broader investigation of cell morphology and 3D architecture of microtubule network. F11 cells were also exposed to ricolinostat (ACY-1215), a first-in-line inhibitor of HDAC6 known to increase microtubule acetylation.

Results:
Baseline biopsies of patients showing improved follow-up IENFD revealed a 2-fold increase of acetylated-positive/PGP9.5-negative fibers compared to those with worsened IENFD. In F11 cells, capsaicin treatment caused reorganization of the microtubule system, shortening of neurites and axonal swellings, whereas ricolinostat-induced microtubule acetylation reduced axon varicosities and promoted neurites elongation.

Conclusions:
Our findings suggest that modulation of microtubule acetylation can be neuroprotective and acetylated-positive/PGP9.5-negative rate is a valuable proxy of nerve ending regeneration in small fiber neuropathy patients. These data are under validation in murine sensory neurons and capsaicin-treated healthy volunteers.
References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Axon regeneration, Micotubule acetylation, Capsaicin, Small fiber neuropathy, HDAC6-inhibitor
Target Therapies: Towards a Tailored Therapy in Anti-MAG Antibody Neuropathy with Ibrutinib, Venetoclax and Obinutuzumab.

Poster No:
39a

Authors:
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Introduction:
Anti-myelin-associated glycoprotein (MAG) antibody neuropathy is associated with IgM monoclonal gammapathy of undetermined significance (MGUS) or lymphoproliferative disorders. Rituximab is currently used in anti-MAG neuropathy, despite efficacious in less than 50% of patients. Ibrutinib, an oral inhibitor of Bruton's tyrosine kinase, has been shown to be effective in Waldenstrom's Macroglobulinemia (WM), especially with MYD88-L265P mutated and CXCR4-S338X wild-type.

Methods:
We assessed the mutational profile of MYD88 and CXCR4 genes in 60 patients (39 men, mean age 71.2±9.8 years) with anti-MAG neuropathy. Of them, 29 (48.3%) had IgM-MGUS, 27 (45%) WM, 4 (6.6%) marginal zone lymphoma or chronic lymphocytic leukemia (CLL/MZL). Molecular analysis was performed using allele specific–PCR, from bone marrow mononuclear cells in 45/60 patients and from circulating mononuclear cells in 15/60. All the patients were assessed with INCAT (Inflammatory Neuropathy Cause and Treatment) Disability Score, INCAT Sensory Sum Score, MRC sum score.

Results:
42 patients (70%) carried the MYD88-L265P mutation: 25/27 (92.6%) WM patients, 16/29 (55.2%) MGUS and 1/4 (25%) CLL/MZL. All the patients were CXCR4-S338X wild-type. As expected, the mutation was significantly more frequent in WM patients (p=0.001). 39 patients were treated with rituximab with benefit in 23 (58.9%). There was no significant difference in neuropathy severity and treatment response between mutated and unmutated patients. Five WM MYD88-L265P mutated patients were treated with ibrutinib; 2 LLC patients (1 MYD88-L265P mutated) were treated with obinutuzumab and 1 LLC MYD88 wild-type was treated with venetoclax. All 8 patients were unresponsive to rituximab, and reported early and progressive improvement, as shown by clinical scales.

Conclusions:
In conclusion, we confirm in anti-MAG antibody neuropathy the high prevalence of the MYD88-L265P mutation, a potential effective mutational target for ibrutinib, despite it does not seem to be a prognostic factor of neuropathy severity or response to rituximab. In non-responders patients, new effective target-therapies should be considered.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: anti-MAG neuropathy, MYD88 mutation, ibrutinib, venetoclax, obinutuzumab
Prevention of neuropathic pain development via a plasma fraction

Poster No:
40a

Authors:
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Introduction:
Chronic neuropathic pain (NP) is highly prevalent among older adults where it is associated with significant suffering, disability, social isolation, and greater costs and burden to health care systems. Pharmaceutical treatment of chronic pain in this aged population is usually only partially effective and is often limited by side effects, and therefore the development of novel non-opioid therapies for NP has become paramount. In the present study, we focused on the impact of a plasma fraction (PF) in a peripheral nerve injury model in aged mice. We previously demonstrated that PF reverses signs of aging within CNS by decreasing neuroinflammation and increasing neurogenesis.

Methods:
In this study, NP was induced by Chronic Constriction Injury (CCI) of the sciatic nerve of 22 month-old C57/BL6 mice, measuring endpoints of mechanical allodynia, thermal hyperalgesia, pain score and static weight bearing.

Results:
Animals subjected to nerve injury showed a significant decrease in mechanical and thermal pain thresholds that were persistent for at least 5 weeks. Administration of PF significantly ameliorated these behavioral metrics measured starting 2 weeks after surgery with efficacy maintained for the duration of the study. Stronger and long-term effects of PF on pain threshold were observed when compared to Gabapentin, the standard drug for treating NP. On the other hand, recombinant human albumin had no effect on pain behaviors, suggesting that PF contains proteins responsible for this positive effect. In order to understand better the nociceptive properties of PF, a reversal dosing paradigm was designed where PF was dosed 14 days after CCI, when NP was already established.

Conclusions:
A delayed reversal of nociception deficits was observed with PF treatment suggesting regenerative mechanisms rather than analgesic properties. Our findings will provide a new rationale for the development of this novel PF as therapy for NP.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: Neuropathic Pain Treatment, Plasma fraction therapy, Schwann cell/glial
Ice-Induced Epidermal Denervation: A New Model To Study Degeneration And Regeneration Of Skin Nerves

Poster No:
41a

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Introduction:
Experimental models of nerve degeneration/regeneration can explore the mechanisms of re-innervation in physiological and pathological conditions. By serendipity, we discovered that ice-spray could affect the integrity of intraepidermal nerve fibers (IENF). We designed a study to investigate the effect of skin cooling and its usefulness as fast and safe in vivo model of nerve degeneration and regeneration.

Methods:
We collected two baseline skin biopsies at distal lateral leg from 10 subjects. The first after standard anesthesia with lidocaine, the second after local freezing with ice-spray. We performed follow-up skin biopsies one day and one week after the baseline sampling in two subjects. Intraepidermal nerve fiber density (IENFD) was evaluated in each sample, at baseline and follow up. We also performed morphological studies using cytoskeletal markers such as tubulins (TuJ1) and neurofilaments (NF-L) to evaluate the extent of the occurred damage.

Results:
All subjects showed marked epidermal denervation after ice-spray treatment, compared to sampling after lidocaine injection (mean IENFD 2.63±2.4; 6.7±4.53, p=0.001). Follow-up IENFD after one day was unchanged, whereas it returned similar to baseline after one week. Morphological studies suggest diffuse cytoskeletal damage.

Conclusions:
Our findings demonstrate for the first time a transient epidermal denervation induced by ice-spray anesthesia, followed by complete reinnervation within one week, providing a new model for studying experimental degeneration and regeneration that could be used in different pathological conditions affecting small peripheral nerves.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: skin biopsy, small nerve fibre, denervation, regeneration, ice-spray
Sirtuin1 Mediated Deacetylation of E3 Ubiquitin Ligase NEDD4-1 Regulates Axonal Growth and Treats Diabetic Peripheral Neuropathy

Poster No:
42a

Authors:
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Institutions:
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Introduction:
Neuronal over expression of Sirtuin 1 (SIRT1) protein, a NAD+-dependent deacetylase, prevented and reversed high fat diet (HFD)-induced diabetic peripheral neuropathy (DPN) [Brain. 2019;142(12): 3737-3752]. NeuroSIRT1 deacetylated NEDD4-1 protein, which is a modulator of axonal and dendritic growth. The purpose of this study was to determine, if knockout of SIRT1 protein in neurons exacerbates DPN, prevents NEDD4-1 deacetylation and decreases neurite length in cultured DRG neurons.

Methods:
Neuron-specific CamK2a-CRE/ERT2 mice was mated with floxed SIRT1 mice to generate an inducible nSIRT1 fl/fl mouse. Adult nSIRT1KO phenotype was induced with tamoxifen administration. nSIRT1 fl/fl and nSIRT1KO mice were fed with HFD for 4 months. A second group of mice were fed with HFD for 2 months and then an allosteric activator of SIRT1, SRT2104 (1.33 mg/kg), was added to the HFD for additional 2 months. Neuropathy end points (Sciatic Motor Nerve Conduction Velocity (SMNCV), Tail Sensory Conduction Velocity (TSNCV), Tail Motor Latency (TML) and Mechanical Allodynia (MA-Von Frey) were measured at 2 month and 4 months. Intraepidermal nerve fiber density (IENFD) was measured in hind-paw.

Results:
There was a progressive decrease in SIRT1 protein in DRG neurons in nSIRT1KO mice. MA, NCV and IENFD were abnormal in HFD-fed mice compared to CD-fed in both nSIRT1fl/fl and nSIRT1 KO mice at 4 months. Addition of SRT2104 to the HFD after 2 months on HFD reversed changes in MA, NCV and IENFD at 4 months only in nSIRT1 fl/fl mice but not in nSIRT1 KO mice. Dorsal root ganglion (DRG) protein extracts showed increased acetylation of NEDD4-1 protein in HFD mice and addition of SRT2104 prevented NEDD4-1 acetylation only in nSIRT1 fl/fl mice but not in nSIRT1 KO mice. NEDD4-1 siRNA decreased neurite growth in DRG cultures.

Conclusions:
SIRT1 mediated ubiquitination is important in prevention of DPN and failure of SIRT1 activation increases the severity of DPN.

References:
Yes

References 1:
References 2:

References 3:

References 4:

**Grant Support:** Supported in part by NIH NIDDK- R01DK107007 to JR

**Keywords:** SIRT1, Transgenic mice, NEDD4-1, Ubiquitination, Nerve Conduction
Administration of AICAR, an AMPK Activator, Prevents and Reverses Diabetic Polyneuropathy (DPN) by Regulating Mitophagy

Poster No:
43a

Authors:
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Institutions:
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Introduction:
Exercise interventions have been shown to slow progression of diabetic neuropathy (DN). AICAR (5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside or Acadesine), which importantly mimics the effect of exercise, is an Adenosine Mono Phosphate Kinase (AMPK) activator. AMPK is a master activator of the SIRT1-PGC1a mitochondrial (Mt) biogenesis pathway. This study determined if administration of AICAR rescued mice from DPN induced by a high fat diet (HFD) or by Streptozotocin (STZ) administration.

Methods:
WT C57BL6 mice were fed with Control Diet (CD) or HFD for 4 months. Neuropathy was determined by mechanical allodynia (MA), nerve conduction velocity (NCV) at 0, 2 and 4 months and Intraepidermal nerve fiber density (IENFD) at 4 months. AICAR was administered at 2 months (reversal) and at the start of HFD administration (prevention). AICAR was administered subcutaneously (500 mg/kg). In further experiments, AICAR was administered to STZ treated mice with early neuropathy after 2 months. Presence of neuropathy was measured 4 months post STZ.

Results:
Administration of AICAR prevented and reversed the development of neuropathy in HFD-fed mice and reversed neuropathy in STZ mice. AICAR levels in blood and neurons were increased in treated mice. Western blot of neuronal protein extracts showed decreased levels of phosphorylated AMPK in HFD and STZ mice. AICAR treatment increased phosphorylation of AMPK, increased the mitochondrial fission factor (Mff), and recruit dynamin-related protein 1 (DRP1) to promote mitochondrial fission. AMPK also phosphorylated autophagy activating kinase 1 (ULK1) at Serine-555 to mitochondria to promote mitophagy.

Conclusions:
AICAR mediated AMPK phosphorylation prevented and reversed DPN, and is associated with increased mitochondrial turnover that is critical for axonal regeneration. AICAR, unlike metformin, is a direct activator of AMPK, and may be more effective in preventing diabetic complications.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

**Keywords:** Exercise mimetic, Diabetes, Mitochondria, Mitophagy, Ubiquitination
Clinical and Genetic Characterization of NEFL-related neuropathy in Taiwan

Poster No:
44a

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Introduction:
Mutations in the neurofilament light polypeptide gene (NEFL) are an uncommon cause of Charcot-Marie-Tooth disease (CMT). The aim of this study is to elucidate the clinical characteristics and genetic spectrum of NEFL-related neuropathy in a Taiwanese CMT cohort.

Methods:
Mutational analysis of the coding regions of NEFL was performed by Sanger sequencing or targeted resequencing. Twenty-one patients from nine CMT pedigrees, identified from a cohort of 508 unrelated CMT patients, were found to have a NEFL mutation. Their genetic, clinical and electrophysiological features were analyzed.

Results:
The mean age of disease onset was 13.5 ± 9.6 (1-40) years. Family history was present in 81.0% of patients. Intermediate CMT with ulnar nerve motor nerve conduction velocities between 25 and 45 m/s was the most common clinical presentation. Six patients (28.6%) had additional features apart from typical neuropathic phenotypes, including motor developmental delay, spasticity, cerebellar signs, sensory ataxia, neuropathic pain and scoliosis. Six NEFL mutations were identified, including two novel variants (p.P8S, p.N98Y) and four pathogenic mutations (p.P8R, p.P22S, p.N98S, and p.E396K). NEFL p.E396K was the most common mutation, accounting for 33.3% of the patients with NEFL-related neuropathy in our cohort.

Conclusions:
NEFL mutations account for 1.8% (9/508) of the CMT patients in Taiwan. The present study delineates the clinical and genetic features of NEFL-related neuropathy in Taiwan, and provides useful information for diagnosis and management of NEFL-related neuropathy, especially in patients of Chinese descent.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:
Keywords: Charcot-Marie-Tooth disease (CMT), neurofilament light polypeptide gene (NEFL), NEFL-related neuropathy
Assessing Nerve Pathology with Quantitative MRI in a HNPP Mouse Model

Poster No:
45a

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Introduction:
Hereditary neuropathy with liability to pressure palsies (HNPP) is caused by a heterozygous deletion of the human PMP22 gene. Haploinsufficiency of PMP22 results in disruption of myelin junctions leading to excessive myelin permeability in HNPP nerves. Using quantitative MRI (qMRI), we have shown an increased nerve proton density (PD) strongly correlated with fatigue severity in persons with HNPP. We hypothesize that PD changes relate to the increased myelin permeability, thereby contributing to fatigue in HNPP. In this study, we utilize a HNPP mouse model (Pmp22+/-) to determine molecular substrates for the PD changes and test the hypothesis.

Methods:
Pmp22+/- (n=4) and Pmp22+/+ (n=4) mice were imaged on 7T MRI in vivo. Each animal was imaged twice at 3- and 6-month old, then repeated 5 days after the 6-month scan for test-retest reliability. qMRI indices were measured using manually delineated regions on bilateral sciatic nerves.

Results:
Compared with Pmp22+/+ mice, Pmp22+/- mice had a lower PD, T1, T2; and a higher magnetization transfer ratio (MTR) at 6-month old, but these differences were not seen at 3-month old. While there was a longitudinal increase of MTR, and a decrease of PD and T1 for Pmp22+/- mice over the 3-month interval, but the T2 value was unchanged.

Conclusions:
HNPP is characterized by focal myelin thickenings known as 'tomacula' in peripheral nerves. The qMRI results indicate an increase of myelin contents and a decrease of water content in Pmp22+/- nerves from young adult mice which may reflect a gradual increase of tomacula. However, these qMRI changes are expected to move in opposite direction as demyelination and tomacular degeneration take place in aged mice. Taken together, this pilot study demonstrated the feasibility of the qMRI methods to monitor the progression of peripheral nerve pathologies in a HNPP mouse model in vivo.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: NIH/NINDS R01NS115748 and NIH/NCATS R21TR003312
Keywords: HNPP, Quantitative Magnetic Resonance Imaging, Pmp22, Myelin, Monitoring Biomarker
Fibroblasts are superior options to whole blood and other peripheral tissues for CMT and HSP diagnosis through RNA-seq

Poster No:
46a

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Introduction:
Genetic diagnosis of patients with rare Mendelian diseases remains challenging. RNA sequencing (RNA-seq) data from patient cells is often additionally leveraged to aid identification of causal variants. RNA-seq data from the affected neural tissue would be most informative for such analyses, however collecting such samples from living patients is typically not possible. It is imperative to balance ease of collection of patient tissues with their clinical utility.

Methods:
Therefore, we evaluated whole blood, patient-derived fibroblasts and lymphocytes as candidate tissues because they are non-invasive and easy to collect from patients. To identify whether these tissues express genes related to three rare neurological Mendelian diseases (Charcot-Marie-Tooth (CMT), hereditary spastic paraplegia (HSP)) in healthy conditions, we analyzed RNA-seq data from three neural tissues (cortex and tibial nerve) and three peripheral tissues (whole blood, fibroblast, and lymphocyte).

Results:
Unsurprisingly, cortex and tibial nerve were found to reliably express a greater percentage of disease-related genes than the peripheral tissues at 80.4% and 85.3%. Encouragingly, fibroblasts still expressed over 74.7% of these disease-related genes. Whole blood and lymphocytes only had 50.4% and 65.8% of CMT disease related genes expressed. To reveal whether fibroblast tissues can be used to diagnose HSP in a clinical setting, induced pluripotent stem cells (iPSCs), iPSC-derived cortical neurons, fibroblasts were collected from HSP patients and processed for RNA-seq in addition to genomic sequencing. Gene quantification, splicing detection and differentially expressed gene (DEG) analysis were performed.

Conclusions:
Based on the splicing and DEG analysis results between four different groups, we identified a list of HSP causal genes that can be reliably detected in fibroblasts. We also evaluated the potential benefits of using iPSC-derived neurons over fibroblasts for diagnosis using sets of samples collected from the same patients. Taken together our results indicate that fibroblast tissues have potential to be non-invasive yet accurate ways to diagnose HSP and CMT.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: CMT, Genetic diagnose, RNA-seq, HSP, Fibroblast
Open Label Study to Assess the Safety of VM202 in Patients with Charcot-Marie-Tooth Disease Type 1A

Poster No:
47a

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Introduction:
We performed this study to assess safety and define efficacy measures of hepatocyte growth factor (HGF) DNA plasmid, VM202, administered by intramuscular injections in patients with Charcot-Marie-Tooth disease type 1A.

Methods:
Twelve participants were treated with VM202 in both tibialis anterior, peroneus longus, and gastrocnemius muscles on day 0, 14, 90, and 104. Participants were followed for nine months to evaluated possible adverse events. Disease severity was assessed using Charcot-Marie-Tooth Neuropathy Score version 2 (CMTNS-v2) and functional outcome was evaluated using functional disability scale (FDS), overall neuropathy limitation score (ONLS) leg scale, 10-meter walk test (10MWT). In addition, changes in fatty infiltration level of lower limb muscles and electrophysiologic parameters such as compound motor action potential (CMAP), sensory nerve action potential (SNAP), and nerve conduction velocity (NCV) were assessed.

Results:
Eleven of 12 participant completed the study. VM202 was well tolerated and only two mild possibly drug related adverse effects, ankle edema and injection side pruritus were reported and they disappeared without any sequelae. VM202 showed possible effects in severity of disease parameters when we assess the patients by CMTNS-v2 and FDS. In addition, VM202 might have effects for sensory function when we analyzed the sensory sub-items of CMTNS-v2.

Conclusions:
VM202 was well tolerated with minor treatment emergent adverse effects such as ankle edema and injection site pruritus. In addition, VM202 might have potential therapeutic effects in lowering disease severity and improving sensory functions.

References:
No

References 1:

References 2:
Grant Support: This study was sponsored by Helixmith. Co., Ltd.

Keywords: Charcot-Marie-Tooth Disease, Safety
DRG satellite glial cells: involvement in chemotherapy-induced peripheral neurotoxicity

Poster No:
48a

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Introduction:
Chemotherapy-induced peripheral neurotoxicity (CIPN) is one of the major dose-limiting side effects of paclitaxel (PTX) and cisplatin (CDDP) chemotherapy. In dorsal root ganglia (DRG), their preferential peripheral targets, sensory neurons are in intimate relationship with satellite glial cells (SGCs) which have a crucial role in maintaining the perineuronal homeostasis. SGCs activation associated with glial fibrillary acidic protein (GFAP) upregulation and morphological abnormalities as well as an increment in the crosstalk between adjacent SGCs were detected after neuronal injury. Gap junctions composed of Connexin (Cx) proteins are supposed to regulate SGCs coupling, essential for neuronal function.

Methods:
Here, we investigated whether SGCs can undergo modifications after chronic administration of PTX or CDDP in rats. Twelve rats were injected i.v. with PTX 10 mg/Kg once a week for 4 weeks, 12 with CDDP 2 mg/Kg, i.p., twice a week for 4 weeks and 24 with the respective vehicles. Neurophysiological analysis and behavioural tests were performed at baseline and at the end of treatments. DRG were collected for microscopy observations, GFAP and Cxs protein expression and localization and finally for ex vivo electrophysiological and coupling studies with fluorescent dye Lucifer yellow.

Results:
At the end of treatment, PTX and CDDP-treated rats developed a painful sensory axonopathy and a painless mild sensory neuropathy, respectively. At microscopy level, an evident reduction of interstitial space between neuron–SGC units were observed in DRG of PTX-treated animals. IHC-qualitative and quantitative analysis showed an increased GFAP-positivity following PTX treatment, supporting SGCs activation. In addition, perineuronal spot distribution of Cxs was evident at IF analysis in PTX-treated rats with a higher Cx43 staining signal, supported by WB. Similar preliminary analyses were conducted on CDDP-treated animals showing some differences.

Conclusions:
Therefore, the investigation of the interactions SGC-SGC and SGCs-neurons could be important in the identification of new molecular mechanisms underlying CIPN.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: neuroxicity, chemotherapy, glial cells
Do IVIG treatment related fluctuations predict long-term CIDP disease activity status or clinical outcomes?

Poster No:
49a

Authors:
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Introduction:
The GRIPPER study quantified IVIG treatment-related fluctuations (TRF) by recording daily grip strength for 6 months in patients with CIDP. Frequent-TRF and no-TRF groups were identified by defining TRF as a change in 3-day averaged grip strength by ≥10% on ≥2 consecutive days. We subsequently sought to explore the long-term impact of TRFs, particularly if TRFs predict successful IVIG tapering, long-term IVIG usage, or strength and disability deterioration.

Methods:
In this retrospective study of GRIPPER participants data collected during routine clinical care after GRIPPER completion was reviewed and compared between TRF status groups.

Results:
Data was available on 18 of 25 original GRIPPER patients. Nine were classified as frequent-TRF and 9 as no-TRF. Mean follow-up was 42 (range 12-68) months. Drug-free remission was achieved in 3/9 frequent-TRF vs 2/9 no-TRF (p=1.00). Although the proportion of patients receiving less IVIG at last clinical follow-up compared to GRIPPER conclusion was similar (66% in both groups), another immunotherapy (all rituximab) was used in 3 frequent-TRF patients vs 0 in the no-TRF group. Long-term grip strength deterioration was more common in frequent-TRF patients (right=38%/left=40%) than no-TRF (right=20%/left=0%), although not statistically significant. I-RODS deterioration followed a similar trend (worsening 25% frequent-TRF vs 0% no-TRF).

Conclusions:
The presence or absence of TRFs poorly predicted long-term disease activity status or IVIG usage, but may provide meaningful information on patients in need of treatment escalation with non-immunoglobulin immunotherapy. The small number of patients precludes determination of the long-term clinical impact of short-term TRFs. However, the observation that grip strength and disability deterioration were more common in frequent-TRF patients is notable and requires further investigation. The failure of this study to find predictive value in future disease activity status highlights the importance of identifying disease activity biomarkers to augment clinical data and guide treatment decision making.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, grip strength, CDAS, outcome measures, IVIG
**Vagal Afferent Free Fatty Acid Receptor 3 (FFAR3) Regulates Feeding Behavior**

**Poster No:**
50a

**Authors:**
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**Introduction:**
The vagus nerve mediates communication between the gastrointestinal (GI) tract and the central nervous system (CNS) for proper regulation of energy balance and glucose homeostasis. Vagal neurons are mostly sensory (afferent), transmitting meal-related mechanical, hormonal, and nutrient information from the gut to the brain. Vagal afferent neurons relay signals from the gut microbiota to the CNS, but the molecular mechanisms of this interaction are poorly understood. For instance, gut bacteria ferment dietary fiber producing short-chain fatty acids (SCFAs) that regulate host metabolism and feeding behavior dependent on the vagus nerve, although the precise mechanisms are unclear. SCFAs can activate several GPCRs including free fatty acid receptor 3 (FFAR3).

**Methods:**
We assessed the expression patterns of SCFA-binding receptors in vagal neurons and confirmed that Ffar3 is indeed expressed in vagal neurons innervating the GI tract. We generated a Ffar3 'floxed' mouse model for Cre-recombinase driven deletion of Ffar3. By crossing phox2b-cre and Ffar3 flox mice, we generated vagal-FFAR3 knockout (KO) mice and comprehensively characterized their feeding behavior and energy balance in response to various dietary conditions including fasting/refeeding, western diet (WD), and propionate supplementation in the drinking water.

**Results:**
Both male and female vagal-FFAR3KO mice consumed larger meals, and ate more calories after fasting/refeeding and western diet (WD) challenges. In addition, the anorectic effect of propionate supplementation was abolished in obese vagal-FFAR3KO mice. Sequencing approaches combining ex vivo and in vivo experiments demonstrated that FFAR3 activation by propionate likely cross-talks with intracellular calcium, cholecystokinin (CCK) and leptin receptor pathways to regulate ingestive behaviors.

**Conclusions:**
Collectively, our data show that FFAR3 in vagal afferent neurons regulates feeding behavior and mediates propionate-induced decrease in food intake.

**References:**
No

References 1:

References 2:

References 3:
References 4:

Grant Support: National Institutes of Health Grants F31 DK126441 (T.M.C.), R01 DK117404 (to V.M.-A.), P01 DK119130-03 5827 (L.G.) and Department of Veterans' Affairs Merit Grant No. 2I01BX003382-01 (B.T.L.).

Keywords: gut-brain, vagus, microbiota, satiety
The clinical phenotype of a novel TTR variant (Glu89Val) in patients with hereditary transthyretin amyloidosis

Poster No:
51a

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Introduction:
Hereditary transthyretin amyloidosis (ATTRh) is a rare disease characterized by the deposition amyloid in tissues. There are over 120 TTR mutations and the most prevalent is Val30Met. In Romania, the most common mutation is Glu54Gln, characterized by a mixed phenotype. There are 4 other mutations identified in Romanian patients: Val30Met, Glu89Lys, Ile107Val and Glu89Val. There are no published data on the phenotype of this new Glu89Val mutation so far. The aim of this work is to present the clinical characteristics of the first patients identified with Glu89Val variant.

Methods:
We evaluated two patients diagnosed with ATTRh Glu89Val. They were both investigated for the presence of ATTRh (TTRgene sequencing, salivary gland biopsy, Congo red stain and immunohistochemistry) and AL was excluded. Investigations were performed to assess the organ involvement (neurological involvement: EMG, Sudoscan; cardiac involvement: ECG, NT-proBNP, echocardiography, CMR and 99mTc-HDP Scintigraphy).

Results:
The first patient was diagnosed at 66 years-old, presenting with sicca syndrome, paresthesia and fatigue. The second patient was diagnosed at 63 years-old with complaints of carpal tunnel syndrome, gastrointestinal dysfunction, fatigue, weight loss, hypotension and erectile dysfunction. Both patients had the Glu89Val mutation in the transthyretin gene. There was no family history in either case, and the cases were not related. The 35 years-old daughter of the second patient had the same mutation. Both patients had neurological (manifested by sensory peripheral neuropathy and autonomic neuropathy) as well as cardiac involvement at diagnosis (cardiac hypertrophy of 18-20 mm, diffuse concentric late gadolinium enhancement at CMR and high NT-proBNP).

Conclusions:
These cases, with this novel TTR variant, have mixed phenotype, late onset, no family history of the disease and no apparent common origin. The neurological involvement is mild and cardiac involvement presents with high IVS diameter. Autonomic neuropathy is present and carpal tunnel syndrome precedes the diagnosis by several years in one case.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: amyloidosis, TTR, hereditary, transthyretin
Evaluation of sex-related differences in oxaliplatin-induced changes in the expression of endocannabinoid receptors and enzymes in lumbar ganglia

Poster No:
52a

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Introduction:
Oxaliplatin-induced neuropathic pain is a frequent and debilitating side effect of cancer therapy. The endocannabinoid system (ECS), integrated by endogenous ligands, enzymes and receptors, plays a crucial role in regulating pain neurotransmission. Sex differences have been observed in clinical and experimental pain, including pain induced by some chemotherapeutic agents. The aim of this study was to evaluate whether oxaliplatin administration induced changes in the expression of different components of the ECS, and if those changes, as well as the development of allodynia, differed between male and female rats.

Methods:
Von Frey and Choi Tests were used to evaluate the development of mechanical and cold allodynia in animals receiving oxaliplatin. By using real time RT-PCR, the expression levels of cannabinoid canonical (CB1, CB2) and non-canonical receptors (GPR55, 5HT1A), and the main enzymes involved in the synthesis (DAGLa, DAGLb, NAPE-PLD) and degradation (MGL, FAAH) of endocannabinoids were evaluated in lumbar dorsal root ganglia from male and female rats.

Results:
Oxaliplatin administration induced the development of mechanical and cold hypersensitivity and allodynia. No significant sex-related differences were observed in these pain-related behaviors. The antineoplastic agent also induced robust changes in the expression of the different components of the ECS in lumbar ganglia. A marked upregulation of CB1, CB2 and 5HT1A was detected in both sexes. While DAGLb mRNA levels remained unchanged, DAGLa was downregulated in male and upregulated in female rats. Finally, MGL and NAPE-PLD showed increased levels only in male animals, while FAAH resulted upregulated in both sexes.

Conclusions:
Our results reveal previously undescribed sex-related changes in cannabinoid receptors and enzymes that may contribute to the physiopathology of oxaliplatin-induced neuropathic pain in male and female rats.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: endocannabinoid system, chemotherapy-induced pain, allodynia, dorsal root ganglia, sex-related differences
NATURAL HISTORY STUDY OF SORD NEUROPATHY

Poster No:
53a

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Introduction:
We have recently established biallelic mutations in the sorbitol dehydrogenase (SORD) gene as a common and potentially treatable cause of axonal neuropathy. This global observational study aims at reporting the full genotype-phenotype spectrum of SORD neuropathy and at defining valid outcome parameters for future clinical trials.

Methods:
Through an international network of collaborators, we have identified 149 individuals with biallelic mutations in SORD. Clinical data were collected according to a standardised protocol. Genetic and clinical data from 101 patients are available and are presented.

Results:
Seventy-three cases carried the common c.753delG;(p.Ala253GlnfsTer27) variant in a homozygous state. In 27 cases, the c.753delG variant was found in compound-heterozygosity with a second missense or
nonsense variant, including c.458C>A;(p.Ala153Asp) which appeared to be the second most common mutation (n=18). Fasting serum sorbitol level was elevated (14.2±2.7 gr/L, n.v.<0.25), without significant differences across different genotypes. Patients were diagnosed with CMT2 (64%), dHMM (31%), and CMT intermediate (5%). The mean age of symptom onset, including difficulty walking and running, was 17±10 years (range 3-51 years). Foot dorsal and plantar flexion were weak (MRC<5) in 96% and 79% of patients, respectively, while sensation was preserved in over 60% of the cases. The neuropathy was mild in two thirds of cases, who did not require walking aids., MRC scores of foot dorsiflexion correlated inversely with the age of the subjects and declined significantly over 1 year, while CMTES did not (n=23),

Conclusions:
SORD neuropathy appears to be a frequent recessive form of axonal, motor predominant CMT, with prominent foot dorsal and plantar flexion involvement. Fasting serum sorbitol is a reliable biomarker of the condition and can provide functional validation of variants within the expanding genotype spectrum of the disease. Foot dorsiflexion strength represents a promising outcome measure which should be considered in future therapeutic trials on this condition.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, SORD
Sensory quantification suggests partially conserved neural substrates for hind limb pain associated with distinct etiologies

Poster No:
54a

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Introduction:
Despite what we have learned about the heterogeneity of the sensory system, there remains a significant gap in our understanding of the role subtypes of sensory neurons play in neuropathies and pain conditions. Our overarching hypothesis is that there are distinct roles for sensory neuron subtypes in distinct types of pain.

Methods:
To begin to test our hypothesis, we used a battery of in vivo, modality-specific assays of sensation to determine if distinct subsets of sensory neurons are implicated in pain produced by distinct etiologies. We compared phenotypes of two distinct mouse models that consistently produce hind limb pain: the spared nerve injury model of traumatic neuropathic pain and the intravesicular acrolein model of cystitis, which produces bladder pain as well as 'referred pain' in the feet.

Results:
As expected, spared nerve injury models exhibited pan-modality hypersensitivity in a spatially restricted dermatome affecting the sural region of the lateral foot. The phenotype included static (punctate) mechanical hypersensitivity of the glabrous skin in addition to dynamic mechanical hypersensitivity of the glabrous and hairy skin as well as thermal hyperalgesia of the glabrous skin. Interestingly, in the cystitis model, we identified a spatially restricted dermatome of the foot that exhibited modality-specific hypersensitivity. The sural region of the lateral glabrous foot exhibited static mechanical hypersensitivity, while other regions of the foot and other modalities of sensation exhibited no change.

Conclusions:
These data suggests that while the cellular mediators of dynamic touch contribute to pain after traumatic nerve injury, they play a minimal role in 'referred pain' secondary to cystitis. However, the neural mediators of static allodynia appear conserved across the two types of pain, along with a spatial distribution that suggest common anatomic substrates. This functional evidence for distinct role of sensory neuron subtypes underscore the importance of the cell-type specific strategies for investigating pain mechanisms.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support: NIDDK K12DK100022 UW-Madison K12 Urologic Research (KURe) Career Development Grant

Keywords: Neuropathic pain, Allodynia, Visceral pain, Bladder pain, Nerve injury
REAL-WORLD EXPERIENCE WITH INOTERSEN AT CEPARM UNIVERSITY HOSPITAL.

Poster No:
55a

Authors:
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Introduction:
Introduction: Hereditary transthyretin amyloidosis (hATTR) is a progressive lethal disease. Inotersen is a subcutaneous antisense oligonucleotide (ASO) that is approved to treat hATTR with polyneuropathy (PN). Objective: To evaluate disease progression in patients treated with inotersen in the post-approval trial real world practice.

Methods:
Methods: (PND) polyneuropathy disability scale, (NIS) total neuropathy impairment score, ECG, (IVS) intraventricular septum thickness, (CM) cardiomyopathy, (NYHA) New York Heart Association classification for heart failure, (BMI) body mass index, and (KPS) Karnofsky performance status, were evaluated at day one (D1) and at 67 months (55-76, SD 7.6).

Results:
Results: 10 ATTRV30M subjects were included (6 men); mean disease duration at D1 of 3 years (1.5-6, SD1.4); mean age at D1 of 45.4 years (31-68, SD 13.9). At D1 3 patients were at PND I, 5 at II, 2 at IIIA. At last evaluation (LE): 4 patients were at PND I, 3 at II, 1 at IIIA, and 2 at IV. Both at D1 and at LE, 3 patients had CM with 2 at NYHA 1 and 2. ECG at D1 was abnormal for 8 patients, mostly due to conduction abnormalities. At LE, abnormalities persisted in 6 patients; in 2 of those pacemakers were implanted. IVS thickness > 12mm was present in 4 patients at D1 and in 2 at last visit. At D1 mean NIS was 48.2 (12-129.75, SD39.8); KPS was 77 (50-90, SD 12.5); BMI was 22.6 (14-30.5, SD 8.2). At last visit (October 2021), mean NIS was 52.6 (16-141, SD42.4); KPS was 77.7 (50-90, SD12); BMI was 24.8 (18.9-31.4, SD 4.9). NIS progression of >10 was identified in 4/9 patients. There was no case of glomerulonephritis and no platelet decrease grade 4.

Conclusions:
Conclusion: Based on these limited data, we conclude that inotersen was well tolerated and effective to treat patients.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support: NA

Keywords: Amyloidosis, Inotersen, Polyneuropathy, ATTR
Imaging calcium changes in ex vivo mouse models of axonal Guillain-Barré syndrome

Poster No:
56a

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Introduction:
The acute motor axonal neuropathy (AMAN) variant of Guillain-Barré syndrome (GBS) is caused by targeted attack of the motor axon plasma membrane by autoantibodies against gangliosides. In animal models, these antibodies activate the complement cascade causing calpain-mediated damage. Calpain is activated when calcium enters the nerve via the terminal complement pore. Herein we developed a method to detect and quantitate changes in intra-axonal calcium in a mouse model of AMAN, with the aims of determining whether calcium influences axonal injury/survival and establishing whether calpain inhibition influences axonal outcome.

Methods:
Triangularis sterni nerve-muscle explants from Thy1-TNXXL mice (expressing a genetically encoded FRET-based calcium indicator in axons) were incubated with anti-ganglioside antibody, alone or followed by normal human serum as a source of complement. Explants were then imaged live for 1-hour post injury.

Results:
Calcium rose significantly in injured explants, firstly at the motor nerve terminal (MNT) and moving retrogradely to the large bundles at diminishing levels. Antibody and complement were only detectable at the MNT and first node of Ranvier, though disruption of axonal proteins occurred more proximally. Morphological changes were seen at distal and proximal sites. Distal sites (where complement was deposited) showed acute axonal breakdown, whereas proximally, axons developed vacuoles reminiscent of early signs of degeneration. Inhibition of calpain did not affect the wave of calcium but did protect axons from all morphological changes.

Conclusions:
Our study represents the first investigation of axonal calcium in GBS mouse models. We show the surprisingly high linear extent of calcium influx in an injury which appears limited to the distal axon, suggesting this calcium flood may be responsible for disruption to areas not directly targeted by complement. Calpain inhibition remains a promising candidate for not only acute complement-pore driven injury but also proximally, where axons show early signs of degeneration.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support: Wellcome Trust [grant number 202789].

Keywords: Calcium, Axon, Guillain-Barré syndrome, Complement, Live imaging
Repeat expansion size predicts age of onset in RFC1 CANVAS and disease spectrum

Poster No: 57a

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Introduction:
Biallelic repeat expansions in RFC1 have been identified as the cause of cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS). Based on the first descriptions, RFC1 disease has variable phenotype, onset and progression, however the factors underlying this heterogeneity are still largely unknown.

Methods:
In this study, we investigated the effect of the repeat expansion size on age at onset, clinical phenotype and disease course in a multicenter cohort of 316 patients with biallelic AAGGG RFC1 repeat expansions confirmed by Southern Blotting. Furthermore, we assessed the stability of the repeat during intergenerational transmission in 19 families.

Results:
Median age at onset of imbalance was 55 years (range 30-80) and median disease duration at last follow up was 10 years. At last examination, 45% of patients showed a full-blown CANVAS, 16% an isolated sensory neuropathy and 39% neuropathy with cerebellar or vestibular involvement. RFC1 expansion ranged from 249 to 3885 repeats. An inverse correlation, which was stronger for the smaller allele, was observed between the repeat size and age at neurological onset. A larger expansion was also predictive of a more complex phenotype and a faster progression to disabling manifestations, including cerebellar involvement and loss of independent walking. RFC1 expansion appeared stable during parental transmission, with no or minimal variation (<10% size) in most cases.

Conclusions:
RFC1 disorder shows heterogeneous clinical presentation and disease course. A smaller expansion has a favorable prognostic role and is associated with later disease onset, later appearance of cerebellar symptoms and delayed need for walking aids. Albeit time consuming and limited by strict qualitative and quantitative requirements of DNA, Southern blotting is recommended after PCR screening in all RFC1 positive cases to better inform patients on their prognosis.

References:
Yes

References 1:

References 2:

References 3:

References 4:

**Grant Support:** EAN Research Fellowship 2021

**Keywords:** Repeat expansion disorders, RFC1, CANVAS, meiotic instability, Southern Blot
Anxiety and depression in small fiber neuropathy

Poster No:
58a

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Introduction:
Psychiatric comorbidity is common in patients with chronic pain. In peripheral neuropathic pain patients, particularly anxiety and mood disorders are frequently present and associated with a high level of catastrophizing. Small fiber neuropathy (SFN) is a peripheral neuropathy characterized by chronic neuropathic pain. In 47% of SFN patients, an underlying somatic condition is present. The quality of life of SFN patients is severely reduced in comparison with healthy individuals, and can be attributed to both physical and mental factors. However, studies about the specific mental health status of SFN patients are scarce.

Methods:
The Maastricht University Medical Center+ is a tertiary referral center in the Netherlands for patients suspected of SFN. Since 2009 all patients are evaluated in a standardized day case setting. This has led to a large cohort of SFN patients, with data on demographics, medical history, diagnostic tests (e.g. intraepidermal nerve fiber density, quantitative sensory testing and laboratory tests) and the results of various validated questionnaires about pain (visual analogue pain scale, neuropathic pain scale), SFN-specific symptoms, daily functioning and mental health. The Hospital Anxiety and Depression Scale (HADS) is used to identify signs of anxiety and depression and the Pain Catastrophizing Scale (PCS) is taken to measure the degree of catastrophizing in the patients diagnosed with SFN.

Results:
The aim of this study is to describe the prevalence of anxiety and depression in a large cohort of SFN patients and to search for associated factors, including demographics, pain intensity and duration, other SFN-related symptoms, the presence of underlying somatic and psychiatric conditions and the level of catastrophizing

Conclusions:
The results will be presented.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: Small fiber neuropathy, Pain, Depression, Anxiety
Comparison of Amyloid Detection in the Skin and Tenosynovium of Transthyretin Amyloidosis Patients

Poster No:
59a

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Introduction:
Transthyretin mediated amyloidosis (ATTR) is a progressive, fatal multi organ disease that can occur with variant or wildtype transthyretin. Carpal tunnel syndrome (CTS) is recognized as an early manifestation of ATTR. Skin biopsies from the distal limb are a diagnostic tool to detect amyloid in ATTRv-peripheral neuropathy (ATTRv+PN) and serve as a biomarker for disease severity and progression.

Methods:
We examined 3mm distal leg skin biopsies and transverse carpal ligament tissue obtained from CTS release surgery for amyloid deposits from 11 subjects (9 ATTRv, 2 ATTRwt), mean age 64.5 ± 8.3 years who presented with peripheral neuropathy and were found to have CTS. Surgery was performed 3 mo - 6 years after PN diagnosis. 50µm thick sections from 3mm d.leg skin biopsies and carpal tunnel synovial tissue were stained for Congo red and anti-TTR immunohistochemistry. Skin was assessed for IENFD (PGP9.5).

Results:
D.leg IENFD was significantly reduced (% mean±SD, 3.1±4.1) compared to age/gender matched controls. Amyloid was detected in d.leg skin in 36% by Congo red staining and 82% by IHC. 82% had amyloid detected in synovium by Congo red. Amyloid burden (% tissue volume involved with amyloid) was higher in synovium than d.leg skin (mean±SD,% synovium:36.5±21.4 vs Skin 9.3±21.4), though the overall sensitivity to detect amyloid in both tissues was 82%.

Conclusions:
Skin tissue has a high diagnostic yield, similar to tenosynovium, in detecting variant and wildtype TTR amyloid, though tenosynovium has a larger amyloid burden. Immunohistochemistry against TTR is more sensitive than Congo red. Our findings suggest a ATTR/v+PN diagnosis can precede CTS diagnosis, and that CTS is often underrecognized in this population.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Transthyretin amyloidosis, familial polyneuropathy, hereditary amyloidosis, peripheral neuropathy, carpal tunnel syndrome
Neuroprotective effect of hIg in mouse models of chemotherapy-induced neuropathy

Poster No:
60a

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Introduction:
The occurrence of neuropathic pain is a major dose-limiting effect of common anticancer agents, justifying dose reduction or discontinuation and possibly affecting cancer prognosis. Neuroinflammation has been described to be associated with chemotherapeutic compounds, such as vincristine (VCR), paclitaxel (PTX) or oxaliplatine (OXP). Interestingly, human immunoglobulins (hIg) have been found to exert anti-inflammatory effects. This project aims at investigating the effect of hIg on mouse models of VCR-, PTX- and OXP-induced neuropathy.

Methods:
Each model of chemotherapy-induced peripheral neuropathy has been characterized as valid, mimicking the clinical features of the disease. HIgs (0.5 g/kg/3d, i.p.) were administered 24h before the first chemotherapy injection. The onset of neuropathic pain was assessed by functional tests to measure mechanical sensitivity in VCR, PTX and OXP-induced neuropathy models, and cold nociception for OXP-model. Concomitantly, an in vitro study was executed to evaluate the effect of hIg on the anticancer properties of chemotherapies in human cancer cell lines. For that, we performed viability assays using hIg alone (from 0 to 12 mg/mL) or in combination with anticancer agents.

Results:
Preventive treatment with hIg alleviated mechanical allodynia, induced by VCR and OXP. In addition, hIg accelerated recovery of normal mechanical sensitivity in our PTX-induced neuropathy model. Moreover, hIg treatment completely abolished the occurrence of cold hyperalgesia induced by OXP. On human cancer cell lines, hIg alone decreased cell viability in a dose-dependent manner. Furthermore, hIg treatment in combination with VCR or PTX potentiated cancer cell death, and did not affect anticancer properties of OXP.

Conclusions:
In conclusion, our work demonstrates that hIg could be a promising therapy for preventing the onset of chemotherapy-induced neuropathy. Moreover, hIg did not affect anticancer properties of chemotherapies, but rather exacerbated cancer cell death in combination with VCR or PTX. Thus, our results pave the way for a potential utilization in a clinical context.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: chemotherapy-induced neuropathy, neuropathic pain, human immunoglobulins, mouse model, cancer cell line
Activation of the UPR transcription factors XBP1 and ATF6 modulates disease severity in CMT1B mice

Poster No:
61a

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Introduction:
Myelin protein zero (P0), encoded by the MPZ gene, is the most abundant protein in myelin of peripheral nerves. In humans, MPZS63del and MPZR98C mutations cause mild and severe Charcot-Marie-Tooth (CMT) type 1B, respectively. Similar demyelinating neuropathies occur in transgenic mice carrying these mutations. Both P0S63del and P0R98C mutant proteins are retained in the endoplasmic reticulum (ER) where they activate an unfolded protein response (UPR). The UPR is characterized by the activation of the PERK/eIF2alpha, ATF6 and IRE1/Xbp1 pathways.

Methods:
We have previously reported that the induction of CHOP and GADD34, two downstream mediators of PERK, is pathogenetic in MpzS63del mice (Pennuto, 2008; D’Antonio, 2013) and that prolonging eIF2alpha phosphorylation is instead highly beneficial (Das, 2015), but the role of the other UPR branches remained largely unknown. To investigate the IRE1 pathway in CMT1B, we generated new models of CMT1B in which the XBP1 gene, a key transcription factor downstream of IRE1, is deleted or overexpressed in Schwann cells specifically.

Results:
We observed that the absence of XBP1 dramatically worsened dysmyelination as well as electrophysiological and locomotor parameters in young and adult MpzS63del and MpzR98C neuropathic animals. This suggests that the activation of XBP1 targets, that RNAseq analysis identified as mostly ER-associated degradation genes, plays a critical role in limiting mutant P0 toxicity, which cannot be compensated by other stress responses. Remarkably, in both MpzS63del and MpzR98C mice overexpressing XBP1, we observed an improvement of disease parameters, such as myelin thickness and nerve conduction velocities. Similarly, also the ablation of ATF6 largely worsened the CMT1B neuropathic phenotype in both models.

Conclusions:
Altogether, these data demonstrate that the IRE1/Xbp1 and ATF6 pathways have a critical adaptive role in CMT1B neuropathy characterized by protein misfolding and suggest that activating them may prove beneficial for CMT1B and perhaps for other neuropathies characterized by UPR activation.
References:
Yes

References 1:

References 2:

References 3:
Pennuto M., Tinelli E., Malaguti M.C., Del Carro U., D’Antonio M., Ron D., Quattrini A., Feltri M.L., and Wrabetz L. 'Ablation of the UPR-mediator CHOP restores motor function and reduces demyelination in Charcot Marie Tooth 1B mice' Neuron 57(3):393-405

References 4:

Grant Support:

Keywords: Schwann cell, neuropathy, myelin, Unfolded protein response, CMT
Persistence of intact sensory afferents and myelin thinning correlates with long-term hypersensitivity after partial crush of the peripheral nerve

Poster No:
62a

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Institutions:
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Introduction:
Preclinical models of traumatic neuropathic pain typically involve permanent denervation of part of a peripheral nerve. However, clinically-relevant injuries often consist of a mixture of neuropraxia and axonotmesis in which axon regeneration and functional recovery may occur.

Methods:
We compared the neuropathology of full and partial (i.e. incomplete) acute sciatic nerve crush injury in adult mice of both sexes. Nerve injury was performed using a custom-modified hemostat. Assays of thermal and mechanically-evoked pain-like behavior were paralleled by transmission electron microscopy, immunohistochemistry and anatomical tracing of Aβ, Aδ and C-fibre afferents at acute (2-7 days) and chronic (>30 days) time-points.

Results:
In both crush models, gross sensitivity (pin-prick) and motor control (Rotarod; toe spreading) recovered approximately 14 days after injury; in contrast, partial crush of the nerve resulted in a transient thermal and chronic tactile hypersensitivity that was not observed after a full crush injury. The partially crushed nerve was characterized by survival of greater numbers of small diameter myelinated axons in the distal nerve, as well as intraepidermal nerve fibres in the hind paw skin at day 7 after injury. Tracing experiments revealed intact afferents in the partially crushed nerve surviving beyond the window of Wallerian degeneration, and fewer sensory neurons were positive for the axotomy marker ATF3, the presence of which was inversely proportional to neuronal size as defined by histochemical markers. Axon morphology at day 30 revealed a larger average G-ratio after partial crush (0.72±0.013) compared to full crush (0.67±0.010) and control (0.65±0.018) nerves (p=0.0005, one-way ANOVA).

Conclusions:
Acute partial crush nerve injury is characterized by the escape of small diameter axons from Wallerian degeneration resulting in chronic hypersensitivity that coincides with an apparent thinning of myelination. Comparing two similarly traumatic nerve injuries with differing sensory outcomes may yield insights into the pathophysiology of neuropathic pain.

References:
No

References 1:
Grant Support: National Research Foundation of Korea grants (NRF-2018R1A5A2024418 and NRF-2021R1A2C3003334) funded by the Korean government MSIT (Ministry of Science and ICT). UKRI Future Leaders Fellowship programme (grant number MR/V02552X/1). Medical Research Council

Keywords: Neuropathic pain, Peripheral nerve injury, Nerve crush, Mouse model, Axon morphology
Myelinated human sensory neurons provide a platform for the reproducible screening of peripheral nerve-reactive autoantibodies in patient sera

Poster No:
63a

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Institutions:
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Introduction:
Autoantibodies reactive against nodal/paranodal cell-adhesion molecules (CNTN1, Caspr1, NF155 and NF186) are increasingly detected in the serum of patients with inflammatory neuropathies. Here, we report on the development and validation of myelinated, human stem cell-derived sensory neurons for use as an unbiased cell-based screening assay for peripheral nerve autoantibodies in neuropathy patients.

Methods:
Sensory neurons derived from human induced pluripotent stem cells were seeded onto either coverslips or 96 well glass-bottom microplates, and myelinated using rat Schwann cells. Specific labeling of serum IgG in co-cultures targeting axons, nodes of Ranvier, myelinated internodes and non-myelinating Schwann cells was assessed in a cohort of suspected immune-mediated neuropathy patients and controls. All samples were previously confirmed as nodal/paranodal antibody positive or negative on ELISA or transfected cell-based assays. Reproducibility was assessed by two independent observers blinded to the clinical phenotype and previous serological results in a sample cohort of 56 patients and controls. Agreement of IgG positivity/negativity was compared across two different stem cell lines over duplicate experiments performed by each observer.

Results:
253 patient samples were tested. Overall, 58% (35/60) of nodal/paranodal seropositive samples demonstrated IgG reactivity (10/21 NF155; 8/10 CNTN1/Caspr1; 9/11 CNTN1; 8/18 pan NF) in the co-culture system, whereas only 1/31 healthy controls was positive. 13% (21/162) of nodal/paranodal seronegative samples from suspected neuropathy patients were also positive in the co-cultures, suggesting the presence of autoantibodies against currently unidentified targets. Inter-experiment and inter-observer validation of blinded immunoreactivity scores showed strong agreement (Fleiss' Kappa statistic = 0.737; n = 56 subjects, 8 raters).

Conclusions:
The use of live cell cultures that mimic the native molecular composition of peripheral nerves permits the reproducible detection of peripheral nerve reactive antibodies in neuropathy and other patients. Positive samples that are otherwise seronegative on routine diagnostic tests hold the potential for novel autoantibody discovery via an immunoprecipitation and mass spectrometry analysis pipeline.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support: Medical Research Council (grant number MR/P008399/1), GBS/CIDP Foundation International Benson Fellowship, University of Oxford COVID-19 Research Response Fund.

Keywords: Autoantibodies, High-throughput screening, Autoimmune neuropathies, Induced pluripotent stem cells, In vitro assays
MAVERICK: Variant prioritization for Mendelian diseases using deep learning

Poster No:
64a

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Institutions:
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Introduction:
In only about 50% of patients with suspected monogenic diseases a causal genetic variant can be identified. Identifying and correctly classifying novel variants or entirely novel disease genes and resolving them from the several hundred-fold excess of rare benign variation poses a serious challenge. To alleviate this problem, here we introduce MAVERICK: a Mendelian Approach to Variant Effect Prediction built in Keras.

Methods:
MAVERICK is an ensemble of transformer-based neural networks that can classify a wide range of protein-altering SNVs and indels and assesses whether a variant would be pathogenic in the context of dominant or recessive inheritance.

Results:
In our tests, MAVERICK outperforms all other tested programs that assess pathogenicity in a Mendelian context. In patient whole exome or whole genome sequencing data, we find that MAVERICK ranks novel causative pathogenic variants on top in 70% of cases when the gene is a known disease and within the first five candidate variants in 90% of cases; without any knowledge of the phenotype or mode of inheritance. MAVERICK particularly excels at identifying pathogenic variants on novel disease genes: it ranks the true causal variant in novel disease genes on top in 40% of cases and within the first five candidate variants in 70% of cases. Since MAVERICK is a genotype-only classifier, we additionally show that it can be combined with popular phenotypic prioritization tools such as GADO, HiPhive, and Phenix to further improve performance. We applied MAVERICK to a large cohort of 173 patients with CMT and dHMN and successfully solved 66% of cases on the first prediction and 93% of cases within five predictions. Further, MAVERICK has already aided discovery of two novel Mendelian disease genes.

Conclusions:
MAVERICK represents a significant step towards 'computer aided genomics' and automated identification of causal variants in patients with known and with novel Mendelian diseases.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Deep Learning, Variant Prioritization, CMT, Genetic Diagnosis, Mendelian Inheritance
**Peripherally Administered EphrinB2-FC Induces Thermal Hyperalgesia and Mechanical Allodynia in Mice**

**Poster No:**
65a

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**Introduction:**
Synaptic adhesion molecules like ephrins, and their receptors, play important roles in synaptic development and plasticity in the Central Nervous System (CNS). These genes are also highly expressed in the PNS where their functions are less well understood. Interestingly, we have observed increased expression of EphB2, a key neuronal ephrin receptor, in neuropathic pain patient dorsal root ganglion (DRG) samples. Our prior work has shown that intrathecal (IT) administration of ephrinB2-FC is sufficient to induce mechanical hypersensitivity and grimacing in mice, and this effect is completely dependent on NMDA receptors. Here we sought to assess whether injection of ephrinB2 injection into the hindpaw of mice can cause pain hypersensitivity. A second objective is to understand if the peripheral action of ephrinB2 shares the same mechanism with central administration.

**Methods:**
We used naïve C57blk6 male mice to assess pain behaviors. Animals were injected with either 100ng of ephrinB2-FC or Vehicle into the hind paw. Mechanical withdrawal threshold was determined by the up-down method. Thermal hyperalgesia was determined using the Hargreaves test. Assessment of affective pain responses was assessed using the mouse grimace scale.

**Results:**
A single dose of ephrinB2-FC injected intraplantarly was sufficient to induce thermal hyperalgesia and mechanical hypersensitivity in the ipsilateral hind paw of male mice.

**Conclusions:**
While ephrinB2-FC delivered both intraplantarly and intrathecally can induce mechanical hypersensitivity, only ephrinB2-FC administered to the hind paw is able to induce thermal hyperalgesia. We are currently exploring if this behavioral effect is seen in both sexes and if this signaling is NMDA receptor dependent in the periphery.

**References:**
No

**References 1:**

**References 2:**

**References 3:**

**References 4:**

**Grant Support:** NIH R01 NS111976-01
Keywords: EphrinB2, Chronic Pain, DRG, Inflammation
Is This An Acute Autonomic Neuropathy Related To Covid Vaccine?

Poster No:
66a

Authors:
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Introduction:
Acute autonomic neuropathy is an extremely rare syndrome and may clinically manifest with abnormalities in cardiovascular, gastrointestinal and urogenital systems, and also visual impairment due to disturbance of pupils constriction.

Methods:
We describe a young and previously healthy woman presenting an acute episode of pandysautonomia with clinical and electrophysiological evidence of autonomic dysfunction and spared somatic motor and sensory function.

Results:
A 26-years old healthy woman presented with a four-days history of recurrent postprandial vomiting, diarrhea, headache and fainting, one day after her second dose of the COVID-19 vaccine AstraZeneca/Oxford. Manifestations were mild in the first day, including headache, lightheadedness, and vomiting. On the day after she had a syncope while taking a shower. She was admitted at the ER for further investigation. Then, her symptoms got worse and she started experiencing recurrent episodes of palpitation, nausea, dizziness, and fainting. She noted tingling on her hands and feet, worse on her left side. On neurological examination, an anisocoria and light-near-dissociation reflex were noted. She had reduction of tactile, thermal and evoked pain bilaterally, but worse on the left. Strength and deep tendon reflexes were normal though. At the third minute of orthostasis on tilt test heart rate was 180 bpm, she had palpitation, dizziness, and no significant blood pressure variation. CSF was normal, at the 10th day of symptoms. Brain MRI was normal. NCS performed at day's 10 and 20 were within normal limits. Small-fibre evaluation was carried out revealing decreased RR variability. QST and QSART were abnormal. She was treated with high dose of IV methylprednisolone and IgIV with recovery.

Conclusions:
Its etiology remains unknown, but the good response to treatment with IvIG and steroids support an immunological component. The correlation between COVID19 vaccine and her episode remains uncertain but is possible.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: pandysautonomia, COVID-19 vaccine, autonomic neuropathy
Charcot-Marie-Tooth type 1A and POEMS Syndrome: An Unusual Association of Two Demyelinating Neuropathies

Poster No:
67a

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Introduction:
CMT1A is the commonest type of hereditary neuropathy, presenting as a slowly progressive length-dependent sensory and motor neuropathy, areflexia, pes cavus and uniform reduction of NCV. POEMS is a paraneoplastic disorder of plasma cells frequently associated to a sensory and motor demyelinating neuropathy. Distinction of both diseases is important, as early treatment significantly changes POEMS prognosis.

Methods:
Describe a woman with CMT1A and atypical progression due overlap to POEMS syndrome.

Results:
The proband was diagnosed at age 40 with CMT1A. Her symptoms were mild and slowly progressive, as expected for most CMT1A. At age of 56, her walk deteriorated fast, she started with difficulty to climb stairs and frequent falls, associated with positive sensory symptoms. Additionally, she lost about 17 kg in 8 months. On examination, first came to our attention the changes in her skin color. She also had hepatosplenomegaly, lymphadenomegaly, papilledema, and generalized edema. NCS revealed a marked worsening in the velocities. A monoclonal IgA lambda peak was detected. Lytic lesions were found, and bone marrow biopsy revealed 25% monoclonal plasma cells. Based on clinical and laboratory findings, a diagnosis of POEMS syndrome was made. Systemic chemotherapy followed by autologous bone marrow transplantation was performed. She evolved with dramatic improvement in motor and sensory symptoms.

Conclusions:
In the setting of an inherited neuropathy of slow progression, a sudden clinical decline and a rapid progression, should raise attention for an associated condition. In the case we present, the systemic manifestations and the laboratory investigations permitted a fast diagnosis and treatment of POEMS syndrome. Significant changes in the natural history of an inherited neuropathy should be considered a red flag for an associated condition.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, POEMS syndrome, Demyelinating, Genetics, Paraneoplastic
Lack Of Segregation Contributes To The Diagnostic Gap In Hereditary Peripheral Neuropathies

Poster No:
68a

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Introduction:
Next-generation sequencing (NGS) is an unmistakable part of the diagnostic toolset in rare hereditary peripheral neuropathies. Despite novel research strategies and international collaborations, a wide scientific gap remains in solving these rare disorders. Here we present the results of two years of diagnostic NGS analysis for peripheral neuropathy cases and emphasize that a lack of possibility to perform segregation analysis in daily practice contributes to the clinical diagnostic gap.

Methods:
Descriptive analysis of a two-years collection of diagnostic targeted gene panel (114 genes) and application of Moon software (Diploid), a platform that uses artificial intelligence to autonomously diagnose rare Mendelian diseases. ACMG guidelines were applied and ad interim multidisciplinary discussion provided a critical review of phenotype-genotype associations.

Results:
In total 64 cases with a presumable hereditary peripheral neuropathy were discussed multidisciplinary after NGS analysis. 47 patients were contributed by our neuromuscular department, the remaining 17 patients by secondary care neurologists. Reported phenotypes were highly heterogenous: sensory-motor peripheral neuropathies (n=42), HMN (n=9), HSAN (n=1), one small fibre neuropathy and 1 case of plexopathy. 10 cases showed atypical presentations of peripheral neuropathy. In total 9 cases were genetically solved (HARS1, MYH7, POLG2, POLG, PRNP, REEP1, SH3TC2, SLC12A6, SORD). 55 cases remained unsolved; 10 of those were later shown to have an acquired etiology (10/60 = 17%). Additionally 16 class 3 variants are awaiting segregation analysis rendering a possible genetic diagnosis in 15 cases (15/45 = 33%).

Conclusions:
The scientific gap in solving the genetic etiology in rare inherited peripheral neuropathies remains significant to date. Additionally, our cohort puts forward an evenly important clinical diagnostic gap in hereditary neuropathies. Factors that significantly enlarge this gap are difficulties in distinguishing acquired versus inherited etiologies and the lack of possibility of segregation analysis in clinical practice.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease, Clinical genetics, Diagnostic gap, Next-generation sequencing
Lack of Skin Cell-secreted Neurotrophic Factors results in a Small Fiber Neuropathy

Poster No:
69a

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Introduction:
Small fiber neuropathy (SFN) is a disorder in which the small unmyelinated sensory fibers are affected. In skin conditions such as Epidermolysis Bullosa (RDEB), there is degeneration of the distal part of these fibres secondary to chronic skin injury, followed by a failure of these fibers to regenerate, even when the skin injury has receded. In the skin, keratinocytes and fibroblasts are known to express these neurotrophic factors to guide axonal re growth after injury.

Methods:
Patients with SFN secondary to RDEB and controls. Small skin injury and collected biopsies from the sites of injury 2 or 10 days after. RT-PCR to evaluate the increase in mRNA expression of neurotrophic factors and its receptors. ELISA NGF and GDNF protein level. Primary keratinocytes from patients and controls and produced an invtro scratch injury to induce secretion of growth factors that were measured using ELISA. We used rat sensory neurons to test the functionality of these growth factors secreted by human keratinocytes in vitro

Results:
We observed that NGF and GDNF transcripts and protein were increased following skin injury control, which was not seen in SFN RDEB patients. Primary human keratinocytes from control subjects produce NGF and GDNF following in vitro scratch, while keratinocytes from SFN secondary to RDEB patients have a very diminished production of these factors. Rat sensory neurons grown with CM from control human keratinocytes showed increased neurite outgrowth compared to neurons grown with medium from SFN secondary to RDEB patient's keratinocytes. Also, test the ability of topically applied exogenous neurotrophic factors to produce regeneration of fibers into the skin of SFN animals.

Conclusions:
Patients with SFN secondary to RDEB do not respond secreting growth factors following skin injury as control subjects do. However, keratinocytes from our patients fail to secrete neurotrophic factors.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support: MILLENNIUM NUCLEUS FOR THE STUDY OF PAIN Doctoral Scholarship funded by the National Agency for Research and Development (ANID)

Keywords: small fiber neuropathy, sensory, neurotrophic factors
MRI measured Dixon fat fraction is a responsive outcome measure in CMT1X, CMT1B and CMT2A.

Poster No:
70a

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Introduction:
We have previously shown that muscle fat fraction (FF) is a responsive biomarker over 12 months in CMT1A and HSN1. (1),(2) This study investigated FF responsiveness at thigh and calf in patients with CMT due to mutations in GJB1, MFN2 or MPZ.

Methods:
Sixty patients, twenty with each CMT subtype and thirty age and sex matched controls were recruited in London and Iowa. All participants with CMT1X are male. Baseline and 12-month follow-up assessments included MRC scoring, ONLS, CMTESv2, CMT-HI and quantitative MRI muscle FF of thighs and calves. Following blinded manual segmentation, Dixon FF was calculated at baseline and follow up and analysed using a paired t test.

Results:
Despite the pandemic, 55 of 60 participants with CMT returned for follow up visits (363-978 days) and preliminary analysis of calf data corrected to 365 day intervals showed that baseline mean fat fraction (presented as mean±s.d.) for controls is 2.1±1.0% with no significant annual change 0.1±0.4%. In patients with CMT2A mean baseline FF was 46.4±21.6% with annual increase 1.8±2.5%, p=0.009, standardised response mean (SRM) 0.72. In patients with CMT due to mutations in MPZ mean baseline FF was 26.0±24.2% with annual increase 1.8±2.2%, p=0.005, SRM=0.80. In patients with CMT1X mean baseline FF was 31.7±25.0% with annual increase 2.0±2.1%, p=0.0002, SRM=0.94.

Conclusions:
Statistically significant increases in FF at mid-calf were seen in all groups but not in controls and responsiveness of MRI was high in all groups, most notably in those with CMT1X, perhaps as this is the
most homogenous group. Detailed analysis of the whole cohort data is ongoing including at thigh level which will be particularly interesting in the more severe CMT2A cohort.

References:
Yes

References 1:

References 2:
Morrow JM, Evans MRB, Grider T, Sinclair CDJ, et al. Validation of MRC Centre MRI calf muscle fat fraction protocol as an outcome measure in CMT1A. 2018 Neurology, 91 (12) e1125-e1129

References 3:

References 4:

Grant Support: Muscular Dystrophy Association of the US.

Keywords: MRI, Charcot Marie Tooth, fat fraction, outcome measure, biomarker
Severe or not severe, that is the question - leveraging whole genome sequencing for comprehensive genetic modifier evaluation in CMT1A

Poster No:
71a

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Introduction:
Heterozygous duplications of PMP22 are the most common cause of Charcot-Marie-Tooth disease. Why some patients are more severely affected than others is still not fully understood. In this study, we aim at identifying new genetic disease modifiers using whole genome sequencing and genotype-phenotype correlations.

Methods:
The study design encompasses four steps: 1. statistical analyses to define mild vs. severe phenotypes and conduct sample size estimations; 2. phenotype-based patient selection; 3. whole genome sequencing; and 4. bioinformatic analysis of genetic variant clusters in defined phenotype subsets. For the first step, we have analyzed previously collected CMT1A clinical datasets retrieved from the RDCRN-INC database. Phenotype information was available from 2,190 patients out of 1,317 families. Including follow-up, we assessed 12,441 visits in total. To understand not only disease severity at baseline, but phenotype dynamics, we compared the 5-year follow-up data for foot dorsiflexion strength and CMT examination score version 2 (CMTES-2), the two most complete data sets overall.

Results:
Our results confirmed that foot dorsiflexion strength and CMTES-2 correlate with age and disease duration, reflecting on the natural disease course. As a limitation, foot dorsiflexion was normal in 27% of the patients, which makes it difficult to define statistical outliers. CMTES, on the other hand, only reached a significant increase after a follow-up time span of seven years, therefore being less representative for disease dynamics in this cohort. We decided to combine those two parameters in a curated minimal data set specific for this CMT1A modifier study, together with information on age at onset, ancestry, and sex.

Conclusions:
Based on power analyses, we aim at sequencing whole genome data from 500 mildly and 500 severely affected patients, ideally. Interested colleagues are being invited to contact us.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support: NIH funding, German Research Foundation

Keywords: Charcot-Marie-Tooth disease, PMP22, Genetic modifiers, whole genome sequencing, genotype-phenotype correlations
Neuropathies amidst the pandemic: remote assessment of patient needs and phenotype validation

Poster No:
72a

Authors:
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Institutions:
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Introduction:
The past two years have been overshadowed by Covid-19 limiting direct patient contacts. In this study, we developed a new questionnaire to assess patient needs, concerns, and symptoms confronting the global pandemic.

Methods:
We included individuals with hereditary neuropathies (n=15), autoimmune-inflammatory neuropathies (n=26), or idiopathic small fiber neuropathies (n=45). For validation, we used previous clinical examination reports. Forty-six percent of the included patients were female, 52% male, and one patient 'diverse'. The mean age at examination was 52.67±13.37 years (range: 19-79 years).

Results:
Most of the patients (59%) reported mild to moderate limitations in their daily life activities due to Covid-19. A severe impairment was reported in 28%. Due to the pandemic, 54% of the patients were more concerned about their own and 76% about their relatives' health. Patients with a positive family history were 2.4x more likely to be seriously worried about their relatives' health. We observed that patients with more wide-spread sensory loss reported higher impairment levels than those with distal sensory loss only. Overall, 37% of the patients said that contracting Covid-19 was their main concern, including the presumed risk of a severe course. Further 34% were worried that their neuropathy might worsen if they ever contracted Covid-19. Thirty-three percent of the patients experienced limitations in their treatment options, e.g. by not being able to continue their physical therapy. Seven percent were concerned about social distancing, as daily care required direct interactions with others. Patients with hereditary, autoimmune, or small fiber neuropathies did not show any differences in their Covid-related daily-life impairment. Previous clinical results correlated with patient-reported sensory levels; and gait unsteadiness was reported significantly more often in patients with afferent ataxia.

Conclusions:
We conclude that Covid-19 imposes a relevant daily-life burden on neuropathy patients. Patient-reported outcome measures are a valid remote strategy if in-person visits are not possible.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support: IZKF TN1-9/IA 532009, German Research Foundation (DFG, DO 2386/1-1)

Keywords: Charcot-Marie-Tooth disease, Chronic Inflammatory Demyelinating Polyradiculoneuropathy, Small Fiber Neuropathies, Virtual Visits, Covid-19
Comparison of the diagnostic accuracy of the EAN/PNS and EFNS/PNS diagnostic criteria for Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Poster No:
73a

Authors:
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Introduction:
To compare the sensitivity and specificity of the newly published EAN/PNS criteria for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with those of the EFNS/PNS.

Methods:
Sensitivity and specificity of the two above-mentioned criteria were evaluated in 492 CIDP patients and 156 controls with axonal or immune-mediated neuropathy. Comparison of the utility of nerve conduction studies of varying extensiveness and of the sensitivity of the two sets of criteria in typical CIDP and variants were also assessed.

Results:
EFNS/PNS criteria had a sensitivity of 91% for possible CIDP and 78% for probable/definite CIDP, while the EAN/PNS criteria had a sensitivity of 81% for possible CIDP and 67% for CIDP. Using supportive criteria, the sensitivity of the EAN/PNS criteria for possible CIDP increased slightly to 83%, thus remaining lower than that of the EFNS/PNS criteria. The EAN/PNS criteria were less sensitive for the diagnosis of distal CIDP than for the diagnosis of typical CIDP, whereas no difference in the sensitivity of the EFNS/PNS criteria among the different CIDP variants was observed. Specificity of the
EFNS/PNS criteria was 55% for possible CIDP and 74% for probable/definite CIDP, while the EAN/PNS criteria had a specificity of 70% for possible CIDP and 83% for CIDP. More extensive studies increased the diagnostic sensitivity of both the sets of criteria but reduced the specificity.

**Conclusions:**
In our patient populations, the EAN/PNS criteria were more specific but less sensitive than the EFNS/PNS criteria. More extensive nerve-conduction studies improved diagnostic yield but resulted in loss of specificity.

**References:**
No

**References 1:**

**References 2:**

**References 3:**

**References 4:**

**Grant Support:** The study was supported by a Grant from Ministero della Salute, Ricerca Finalizzata (Progetto RF-2016-02361887). The study derives from a project initially supported by Regione Lombardia, Italy, (Rare Disease Project 2013 'A Database from Lombardia on CI

**Keywords:** chronic inflammatory demyelinating polyradiculoneuropathy, diagnostic criteria, CIDP, guidelines, diagnosis
A diagnostic score for the diagnosis of anti-MAG neuropathy or CIDP in patients with high titers of anti-MAG antibodies

Poster No:
74a

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Introduction:
We developed a diagnostic score to discriminate anti-MAG neuropathy from CIDP and applied it to patients with atypical anti-MAG neuropathy.

Methods:
We compared the clinical and electrophysiological features of patients with a diagnosis of typical anti-MAG neuropathy with those of patients with a diagnosis of CIDP. The association of each feature with the diagnosis was assessed in the two groups. Features showing a significant association with the diagnosis were included in a multivariable logistic regression model and adjusted odds ratios were estimated for each feature. A score ranging from 1 to 3 was applied to each feature based on the magnitude of the estimated odds ratios. The score was then applied to patients with a clinical diagnosis of CIDP who were discovered to have high anti-MAG antibody titers (CIDP-MAG).

Results:
We included 31 anti-MAG neuropathy patients, 45 typical CIDP patients, and 16 CIDP-MAG patients. Scores in anti-MAG antibody patients ranged from 1 to 5, while in CIDP patients ranged from -7 to -1. Using our score, 4/16 CIDP-MAG patients were diagnosed to have anti-MAG neuropathy and 12/16 patients to have CIDP. Response to intravenous immunoglobulin in the CIDP-MAG patients classified as CIDP was similar to that of definite CIDP patients and higher than that of anti-MAG neuropathy patients.

Conclusions:
Our score permitted to accurately discriminate, among patients with anti-MAG antibodies, patients with CIDP from patients with anti-MAG neuropathy. This score may help in the treatment of patients with anti-MAG antibodies with a CIDP-like presentation.

References:
No

References 1:
Grant Support: The study was supported by a Grant from Ministero della Salute, Ricerca Finalizzata (Progetto RF-2016-02361887). The study derives from a project initially supported by Regione Lombardia, Italy, (Rare Disease Project 2013 ’A Database from Lombardia on CID

Keywords: chronic inflammatory demyelinating polyradiculoneuropathy, antibody, diagnostic criteria, MAG, neuropathy
Diagnostic value of standardized nerve ultrasound of the plexus brachialis in chronic inflammatory neuropathies.

Poster No:
75a

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Introduction:
Nerve ultrasound (US) is a practical and widely available, innocuous technique with low costs that is now increasingly used as an important complementary diagnostic tool in immune mediated neuropathies. Although brachial plexus was often included in the published sonographic studies, there is still considerable variability with regards to which elements of the brachial plexus should be evaluated. We therefore aimed to evaluate the diagnostic accuracy of an extensive US protocol of the brachial plexus in chronic inflammatory neuropathy (CIN).

Methods:
All consecutive patients with suspected CIN, seen at our neuromuscular outpatient between March 2018 to March 2020 were eligible for inclusion. All patients underwent a standardized set of extensive electrodiagnostic testing and US protocol, including (nerve roots, trunks and supraclavicular part of plexus), and appropriate laboratory testing. We used logistic regression and ROC analysis to determine the most optimal plexus US protocol and compared the test characteristics with that of most recent diagnostic consensus criteria.

Results:
We included 132 patients (77 CIDP, 27 atypical CIDP, 28 MMN) and 169 disease controls (97 axonal neuropathies, 72 lower motor neuron syndromes) We found that combination of cross-sectional measurements (CSA) of the plexus trunks and C5 to C7 nerve roots had the highest diagnostic yield. In contrast, longitudinal and supraclavicular measurements appear to have no added diagnostic value. In addition, our shortened protocol with improved cut-off values yielded a sensitivity of 90.2% and an enhanced specificity of 92.3%. Importantly, our US protocol identified 22% of patients with a CIN diagnosis that responded to treatment who were otherwise missed with routine electrodiagnostic studies and other supportive criteria.

Conclusions:
Our study shows that plexus US assessment for CIN can be limited to a practical protocol, improving detection with minimal burden. This shortened US protocol is relatively easy to implement in routine practice, but still warrants consideration of relevant imaging mimics.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

**Keywords:** Nerve ultrasound, CIDP, chronic inflammatory neuropathy, plexus brachialis, imaging
An exploratory study of cognitive involvement in hereditary ATTRv

Poster No:
76a

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Introduction:
Transthyretin (TTR) is a transport protein of the thyroid hormone thyroxine and the retinol-binding protein bound to retinol. The main source of TTR is the liver, but TTR is also found in the epithelial cells of the choroid plexus in the brain. ATTRv amyloidosis is a rare autosomal dominant disorder caused by mutations of the TTR gene. Cognitive consequences of lack of normal TTR and the mutant TTR in human still remain to be elucidated. Only a few neuropsychological assessment of these patients were published previously. The hereditary ATTRv amyloidosis is a very rare disorders, especially in non-endemic areas, therefore despite the small size of the cohort and exploratory nature of our study, the findings may provide some clues for a better understating of the cognitive involvement in the ATTRv amyloidosis.

Methods:
Ten patients with genetically proven ATTRv were included in the study. Detailed neuropsychological tests and cranial MRIs were performed. Biomarkers including amyloid beta 1-42, total tau and phosphorylated tau were investigated in the cerebrospinal fluid samples by an enzyme-linked immunosorbent assay using INNOTEST Aβ1–42, hTau-Ag and phospho-Tau(181P) in vitro diagnostic (IVD) assays.

Results:
Median age of the cohort was 52 years (ranges 34-72). Neuropsychological assessment results were compatible with impaired executive functions in all patients expect one, long term visual and long term verbal memory (severe in 4, moderate in 1). Visuospatial judgment and perception were impaired in six. Mean CSF Aβ1-42 (pg/ml) was 878.0 ±249.5 in patients with cortical atrophy on MRI whereas 1210.0 ±45.9 in patients without any cortical atrophy. Cranial MRI showed cortical atrophy in six patients.

Conclusions:
Our data suggested the significance of the TTR protein in cognitive functions and highlighted the importance of close follow-up of cognitive functions in ATTRv amyloidosis patients. This study also highlights the need for drugs which can cross the blood brain barrier.

References:
Yes

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: Cognitive Involvement, Hereditary ATTRv Amyloidosis, TTR
Evaluating the Multi-Site Feasibility, Reliability and Validity of a Remote Functional Assessment (CMT-rFOM) for CMT1A

Poster No:
77a

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Institutions:
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Introduction:
Remote research assessments may reduce burden on study participants and facilitate participation in clinical trials for those distant from research centers. The COVID-19 pandemic has created urgency in gaining knowledge of safety and feasibility of performing measures remotely. The CMT-Functional Outcome Measure (CMT-FOM) is a face-to-face functional assessment tool. We wished to explore whether elements of the CMT-FOM could be assessed remotely. In this study, we assess the feasibility, reliability and validity of this remotely administered CMT-FOM (CMT-rFOM).

Methods:
An expert panel selected items of the CMT-FOM (9-hole peg test (9HPT), timed up and go (TUG), standing tandem with eyes open, and 30-second chair stand test) and added turning cards to create the CMT-rFOM. As part of the Accelerate Clinical Trials (ACT-CMT) study, a multi-site, international study, participants were invited to participate. After an in-person visit, participants were sent home with required equipment. Within 7-21 days of the in-person visit, a remote assessment was performed by the clinical evaluator via video conferencing. A subset of individuals completed a second remote visit for reliability analysis. Demographic data, availability and access to technology, and specific coding for missing data was also collected to help inform feasibility of remote assessments. Validity was ascertained by correlating with face-to-face measures and participants were asked their opinion on participating in the remote visit.

Results:
54 individuals were invited to participate in the remote study. 48 participants have enrolled and 43 have completed remote visits. Most frequently, safety concerns limited the feasibility of balance assessments performed remotely. Results regarding the multi-site feasibility, reliability, and validity of remote assessments will be presented.

Conclusions:
These remote assessments of function, if feasible and reliable, may reduce participant burden, increase participation of those living further from research centers, and provide more frequent monitoring during clinical trials.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Funding: Supported by NIH grant # NIH 1 U01 NS109403-03 to DNH.

Keywords: Remote Assessments, CMT, Outcome measures, clinical trials
Feasibility of Capturing Digital Biomarkers using Wearable Sensors to Assess Balance, Gait and Physical Activity in Individuals with CMT

Poster No:
78a

Authors:
Kayla Cornett¹, Katy Eichinger², Gita Ramdhar², Timothy Estilow⁴, Brooke McAdam², Paige Howard⁶, Gabrielle Donlevy¹, Magdalena Dudziec⁶, Elizabeth Wojciechowski¹, Valeria Prada⁷, Chiara Pisciotta⁸, Gyula Acsadi⁹, Mary Reilly¹⁰, Steven Scherer¹¹, Davide Pareyson⁸, David Herrmann², Michael Shy¹², Joshua Burns¹

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Introduction:
Clinical trials are on the horizon for Charcot-Marie-Tooth (CMT) and therefore, reliable, valid, and sensitive measures are necessary. Established clinical outcome assessments, such as the validated CMT Pediatric Scale and CMT Exam score are important for efficacy trials as they assess function. However, these measures have demonstrated limited sensitivity to disease progression over periods of time of typical clinical trials. Advances in technology provide the opportunity to use wearable sensors to assess balance, gait, and physical activity quantitatively, which may be more sensitive for early phase studies.

Methods:
500 participants with CMT 1A, 1B, 2A and 1X are being recruited across 7 international sites. Participants complete assessments of gait and balance using Mobility Lab (APDM, Inc) every 6 months and physical activity using ActiGraph devices every 12 months. Feasibility of using these digital biomarkers in children and adults with CMT was assessed through adverse events, participation and preliminary data available to date.

Results:
150 participants have been recruited to date. Assessing balance, gait and physical activity in individuals with CMT using Mobility Lab and ActiGraph devices is feasible. No adverse events have been reported to date and participants are interested in participating in the study. Mobility Lab measures balance impairments in greater detail than we can observe in functional measures and measures gait impairments similar to those reported previously by 3D gait analysis in a more resource effective manner. ActiGraph measures community physical activity with an average step count to date of 4,500 steps per day over 7 days. Mobility Lab and ActiGraph data will be presented.

Conclusions:
Discussion: Reliable, valid and sensitive outcome measures are necessary for clinical trials in CMT. Gait and balance parameters, derived from wearable sensors are feasible to use in individuals with CMT and may serve as novel digital biomarkers of function for clinical trials.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: U54NS0657-12

Keywords: digital biomarkers, physical activity, gait, wearable sensors, CMT
DIETARY INTERVENTIONS IN DB/DB MICE IMPROVE METABOLIC AND KIDNEY PROFILES, BUT NOT PERIPHERAL NEUROPATHY

Poster No:
79a

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Institutions:
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Introduction:
Diabetic kidney disease (DKD) and diabetic peripheral neuropathy (DPN) are common complications of type 2 diabetes (T2D), with unclear pathogenesis and limited treatment options. Dietary interventions improve T2D complications, yet the mechanisms underlying these improvements in DPN and DKD are incompletely characterized. The aim of the current study was to evaluate the impact of different dietary regimens on DPN and DKD in the BKS db/db mouse model of T2D.

Methods:
Three dietary regimens were compared over 12 weeks: dietary restriction (DR) mice received 25% of normal food intake. Caloric restriction (CR) mice were fed a low-carbohydrate diet. Alternate day feeding (ADF) mice were fed the standard control diet and CR diet on alternating days. BKS Db/+ and db/db mice fed ad libitum, served as non-diabetic and diabetic controls, respectively. At 22 weeks, terminal metabolic, DKD, and DPN phenotyping were performed.

Results:
At the end of the study, we found that all three interventions ameliorated body weight and glycemic status compared to db/db mice. However, body composition analysis revealed that these interventions did not change the percentage of body fat when compared to db/db mice fed ad libitum. All three dietary interventions improved renal function (polyuria and elevated urinary albumin/creatinine ratio [ACR]) and structure (mesangial index and glomerular expansion). However, they had no effect on sensory and motor nerve conduction velocity recordings.

Conclusions:
Collectively, these findings highlight that dietary interventions aimed at improving body weight and glycemic status are critical to alleviate DKD risk. However, they are not sufficient to rescue large fiber deficits, which are more closely associated with percent body fat composition. Accordingly, these results suggest that dietary interventions aimed at providing healthy unsaturated fats and improving fat profiles may be a promising non-pharmacological approach to improve nerve function in T2D.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support: Funding was provided by the National Institutes of Health (NIH) (1R24082841 to ELF), Novo Nordisk Foundation (NNF14OC0011633 to ELF), the Nathan and Rose Milstein Research Fund (to SAE), NeuroNetwork for Emerging Therapies at the University of Michigan (t

Keywords: Dietary interventions, peripheral neuropathy, fat profile, type 2 diabetes, db/db mouse
Determining the prevalence of distal symmetric polyneuropathy in a low-income U.S. patient population

Poster No:
80a

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Introduction:
Distal symmetric polyneuropathy (DSP) is a disabling, painful condition associated with falls and reduced quality of life. Black people and people with low-income are underrepresented in existing DSP studies. Therefore, the Flint Neuropathy Study is an ongoing study assessing DSP prevalence and associated risk factors in a predominantly Black, low-income setting.

Methods:
Patients >40 years of age presenting to the Hurley Medical Center Outpatient Internal Medicine Residency Clinic in Flint, Michigan were enrolled. Demographics, clinical characteristics including medication use, anthropomorphic measurements, fasting lipids, fasting glucose, and Hemoglobin A1C, were collected. Glucose intolerance was defined using the 2021 ADA diagnosis and classification of diabetes mellitus criteria, whereas metabolic syndrome was defined using the harmonized criteria from the IDF, NHLBI, AHA, WHF, IAS, and IASO societies. DSP was defined using the Michigan Neuropathy Screening Instrument Questionnaire Index (MNSIQI). Means and frequencies were performed, as appropriate, and analysis of variance was used to examine the association between DSP and metabolic syndrome and glycemic status.

Results:
81 participants (62% female, 57.5 years (SD 8.7), 67% Black, 53% Medicaid, 22% less than high school education) have enrolled to date. At enrollment, 28 (35%) reported a history of T2DM whereas 9 (11%) were prediabetic. 39 (48%) met criteria for metabolic syndrome. 7 (9%) were newly diagnosed with glucose intolerance during the study. Mean MNSIQI score was 2.65 (SD 1.56) with 48/81 (56%) meeting criteria for DSP. DSP was associated with a history of glucose intolerance (prediabetes: MNSIQI score 2.74, T2DM: 3.21 vs no history: 2.03, p<0.01) as well as metabolic syndrome (2.95 vs 2.11 p=0.028).

Conclusions:
DSP is extremely common and underrecognized in this patient population with low incomes. Characterizing the DSP burden and risk factors in these individuals is essential to improve our understanding of DSP and to ensure equal representation in implementation efforts to address DSP symptoms and associated outcomes.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support: NINDS 5R25NS089450, NCATS UL1TR002240, NIDDK P30-DK-02926, NIDDK P30-DK089503

Keywords: distal symmetric polyneuropathy, low-income population, underrepresented patient population, diabetes, metabolic syndrome
Pharmacokinetics and Safety of Topical versus Oral Administration of Amitriptyline Hydrochloride – Implications for Neuropathic Pain

Poster No:
81a

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Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) is a common and challenging complication of antineoplastic agents. Dose reduction or premature cessation of chemotherapy due to severe pain may impact treatment efficacy and patient survival. Prevalent chemotherapeutics interfere with voltage-gated sodium channels (VGSC) in primary sensory neurons causing peripheral sensitization. Amitriptyline hydrochloride (AMT) is a potent inhibitor of VGSC affecting transduction in nociceptors. The efficacy of oral AMT (25-150 mg/d) in CIPN is generally considered as modest and accompanied by a significant risk of adverse events. Topical administration of AMT to painful sites may augment effects at nociceptors and reduce adverse events.

Methods:
The phase I, randomized, open-label, parallel arm study compared safety and pharmacokinetics of the topical hydrogel ATX01, containing AMT 10 or 15%, to oral AMT in 45 healthy volunteers. During the treatment period of 14 days, two cohorts applied topical ATX01 10% or 15% twice daily to both hands and feet, and one cohort took oral AMT 25 mg/d. At days 1 and 14 blood samples were taken at pre-dose, and at a further 11 timepoints. Pharmacokinetic parameters were calculated.

Results:
After two weeks of topical ATX01 10% or 15%, plasma concentrations of AMT and the active metabolite nortriptyline did not exceed corresponding plasma levels under oral AMT. Volunteers did not report on any drug-related local or systemic adverse events.

Conclusions:
Topical AMT turned out to be well tolerated in healthy volunteers over a period of 2 weeks with limited plasma exposure as compared to oral AMT 25 mg, the lowest dosage applied in neuropathic pain. The positive outcomes of the study together with the local administration of the topical drug directly on the painful extremities allowing to target nociceptors warrant further clinical development to establish the efficacy of ATX01 in CIPN.

References:
Yes

References 1:
Chief Medical Officer of AlgoTherapeutix

References 2:
References 3:

References 4:

Grant Support:

Keywords: chemotherapy-induced peripheral neuropathy, amitriptyline, voltage-gated sodium channel, nociceptor, pain
LXR synthetic agonist GW3965 modifies neuronal lipid homeostasis and decreases prostaglandin production in the dorsal root ganglia of obese mice

Poster No:
82a

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Introduction:
The prevalence of peripheral neuropathy is owed to the increasing diabetic and overweight population. Chronic neuropathic pain as a result of peripheral neuropathy is a major disabling symptom in obese individuals. Neuropathic pain management is limited and ineffective, as glucose management for diabetic and prediabetic individuals fails to reduce or improve pain symptoms. It is necessary to understand the mechanisms behind neuropathic pain and associated neuronal dysfunction to identify potential therapeutic options. Recent studies focus on lipid dysfunction associated with excess fat intake and obesity as a target for neuropathic pain management. We assessed the role of Liver X Receptors (LXRs), which are nuclear transcription factors that regulate lipid homeostasis, phospholipid remodeling, and inflammation. We have previously observed that the activation of LXRs using the synthetic agonist GW3965, protects mice from Western diet (WD)-induced mechanical allodynia.

Methods:
To further understand the mechanisms of LXR-activation on obesity-induced pain, we used translating ribosome affinity purification (TRAP) to evaluate the WD-induced translatomic and lipidomic changes in sensory neurons of WD-fed mice treated with the LXR agonist GW3965.

Results:
We observed that GW3965 treatment may regulate and maintain lipid homeostasis in sensory neurons of the dorsal root ganglia. Interestingly, treatment with GW3965 decreased prostaglandin D2 levels in the dorsal root ganglia of obese mice, which suggests downstream mechanisms to attenuate obesity-induced neuronal dysfunction and inflammation. We observed a decrease in neuronal free fatty acid content, accompanied by an increase in lysophosphatidylcholine, phosphatidylcholine, and cholesterol ester species, which may have interplaying mechanisms upon LXR activation.

Conclusions:
Given our observations, LXR activation may protect neurons from metabolic insults that contribute to neuropathic pain. Future studies are required to understand these interplaying mechanisms behind LXR activation and lipid homeostasis in the peripheral nervous system to downstream inflammatory pain pathways, which may help identify effective therapeutic options.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Liver X Receptors, GW3965, Peripheral Neuropathy, Lipids, Inflammation
Ketone Metabolism in the Peripheral Nerve Contributes to the Analgesic Effect of a Ketogenic Diet.

Poster No:
83a

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Introduction:
Therapeutic use of a ketogenic diet (KD) to alleviate painful neuropathies, including diabetic peripheral neuropathy (DPN), is gaining traction in preclinical and clinical settings. These diets replace glucose as the primary fuel source with ketone bodies, which are metabolized in peripheral tissues by a 3-oxoacid CoA-Transferase 1 (OXCT1)-dependent pathway. Here, we report that a KD is less effective in alleviating nociceptive responses following injection of methylglyoxal in sensory neuron-specific, Advillin-Cre driven knockout of OXCT1 (SNACKO mice).

Methods:
We bred OXCT1(lox/lox)Advillin-Cre(+/−) mice to OXCT1(lox/lox) mice to generate mice lacking peripheral neuron OXCT1 expression. Mice were fed either KD or standard chow diet (n=6-8/group) for one week and metabolic data were collected. Mice then received an intraplantar injection of either vehicle or 30μg methylglyoxal. Both the number of nociceptive behaviors (lifting, biting, shaking) and time engaged in those behaviors were quantified by a blinded observer for 5 minutes following the paw injection.

Results:
Wildtype mice exhibit strong staining of OXCT1 in all cells within the dorsal root ganglia, whereas SNACKO mice only display OXCT1 staining in satellite glia and immune cells. Chow-fed mice injected with methylglyoxal displayed nocifensive behaviors, and SNACKO mice displayed increased nociception compared to wildtypes (number: p = 0.091; time: p < 0.042). Consumption of a KD reduced MGO-evoked nociception in both wildtype and SNACKO mice, though the reduction of nociception was attenuated in SNACKO mice (number: p < 0.042; time: p = 0.057). Moreover, SNACKO mice displayed significant but small reductions in blood glucose (p < 0.01) and elevated ketones (p = 0.082) after 1 week of a KD.

Conclusions:
These studies demonstrate metabolic changes resulting from KD administration contribute in part to the analgesic effects of KD in mice. The metabolic changes in SNACKO mice (glucose and ketone concentrations) suggest OXCT1 expression in peripheral neurons plays some role metabolic regulation.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support: This work was supported by NIH grants RO1 NS043314 (DEW), the Kansas Institutional Development Award (IDeA) P20 GM103418, Kansas University Training Program in Neurological and Rehabilitation Sciences (NIH T32 award) supported by NIH Award Number T32HD057

Keywords: Ketogenic Diet, Methylglyoxal, Pain, Neuropathy, Diabetes
Predictors of Mobility, Balance, and Lower Extremity Function in Adult Charcot-Marie-Tooth Disease Type IA

Poster No:
84a

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Institutions:
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Introduction:
Impaired mobility impacts quality of life (QOL) in adults with CMT1A. The Charcot-Marie-Tooth disease Functional Outcome Measure (CMTFOM) is a clinical outcome measure that assesses lower extremity (LE) flexibility, sensation, strength, function, balance, and mobility. Components of these domains have demonstrated to be modifiable impairments in patients with CMT. The aim of this study was to establish impairment-based characteristics associated with mobility in a large cohort of adults with CMT1A.

Methods:
As part of the prospective Accelerate Clinical Trial Readiness in CMT (ACT-CMT) study, the CMTFOM was administered to 214 adults (58% women) mean age 44.5 (+ 15 y/o) with CMT1A. A forward stepwise regression analysis was performed to identify impairment-based predictors of function, including: the Six Minute Walk Test (6MWT), Timed Up and Go (TUG), timed 4 stair climb, 10 meter walk/run (10MWR). An additional stepwise regression analysis was performed to determine the predictors of performance on the balance items of the CMT-FOM (stance with feet apart on line eyes open, stance with feet apart eyes closed, and single leg stance with eyes closed). Individual item z scores were summed and averaged for a total balance score.

Results:
Balance and proximal strength were significant (p<0.001) predictors of 6MWT (R2=.39), TUG (R2=0.35), Stair Climb (R2=0.32), and 10MWR (R2=0.47). Proximal strength, distal strength (plantar/dorsiflexion), and pinprick sensation were significant (p<0.001) predictors of balance (R2=0.34).
Conclusions:
Balance and proximal strength appear to be the strongest predictors of function for adults with CMT1A. Because balance and proximal strength have been shown to be amendable to rehabilitative interventions in previous work, our results motivate assessing interventions involving resistive strengthening and balance training protocols as targets for improving physical functioning for adults with CMT1A.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: NIH grant # NIH 1 U01 NS109403-03

Keywords: Charcot-Marie-Tooth(CMT), Rehabilitation
Plasma Neurofilament Light Chain Concentration Correlates with the Disease Severity of IgM Paraproteinemic Neuropathies

Poster No:
85a

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Institutions:
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Introduction:
IgM paraproteinemic neuropathies (IgM-PN) encompass a group of rare and various chronic axonodemyelinating neuropathies of heterogeneous long-term prognosis. Recently, the plasma concentration of the neurofilament light chain (pNfL) appears to be a promising biomarker for quantifying axonal damage in neuropathies. We aimed to determine prospectively whether the pNfL is increased in IgM-PN and whether it correlates with the disease severity.

Methods:
From May 2020 to July 2021, we included consecutive patients with IgM-PN with or without anti-MAG activity. We assessed the disease severity using clinical [Sensory Modality Sum Score (SMS), Neuropathy Impairment Scale (NIS)] and functional scores [Overall Neuropathy Limitations Scale (ONLS), 10-Meter Walk Test (10MWT)]. Patients underwent nerve conduction studies. We classified neuropathies as demyelinating according to the EFNS/PNS 2010 criteria. We collected plasma samples the same day of the clinical assessment and measured the pNfL by an ultrasensitive technique (SiMoA). We also obtained plasma samples from 14 healthy controls.

Results:
We enrolled 35 patients with IgM-PN: 18 anti-MAG neuropathies and 17 without anti-MAG activity (respectively 94% and 12% with a primary demyelinating pattern), mean age 76±4 years, 62% males, mean disease duration of 10±8 years, and a mean ONLS score of 3±2. The pNfL was increased in patients (median 23.6 pg/ml) compared to controls (median 9.9 pg/ml, p<0.0001) and correlated with all disease severity scores (SMS: r=-0.40, p=0.0165; NIS: r=0.56, p=0.0005; ONLS: r=0.59, p=0.0002; 10MWT: r=0.70, p<0.0001). In the regression models, NIS and ONLS scores were significant predictors of the pNfL while age was not.

Conclusions:
We showed an increase in the pNfL in patients with IgM-PN. The pNfL correlated with the clinical and functional severity of the neuropathy. A longitudinal follow-up is necessary to study the variation of the pNfL during the disease course and assert if it would be a useful surrogate marker for future clinical trials.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Neurofilament light chain, Anti-MAG neuropathy, IgM monoclonal gammopathy, Biomarker, Prognosis
“Chronic Idiopathic Axonal Polyneuropathy” of adulthood with MME variants.

Poster No:
86a

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Introduction:
Fully penetrant bi-allelic loss-of-function (LoF) variants of the Membrane MetalloEndopeptidase (MME) gene, encoding the metalloprotease nephrilysin, cause autosomal recessive axonal Charcot-Marie-Tooth disease (CMT2T) with adult onset; heterozygous LoF or missense MME variants may represent incompletely penetrant, dominantly-inherited susceptibility factors for axonal neuropathies in an aging population (Senderek J et al., Neurology 2020). We aimed at investigating the contribution of MME to a pathologically series of probands with chronic idiopathic axonal polyneuropathy (CIAP).

Methods:
After exclusion of the biallelic RFC1 AAGGG repeat expansion associated with CANVAS (Tagliapietra M et al., J Neurol 2021), 200 probands with chronic axonal neuropathy which had remained ‘idiopathic’ after a sural nerve biopsy, were analysed by Next Generation Sequencing on an Ion Torrent PGM Dx platform using a custom-designed panel covering 24 associated with CMT-related neuropathies.

Results:
Focusing on MME, 4 probands, including 3 apparently sporadic patients and a patient from an autosomal recessive pedigree, were homozygous for the common p.Pro156LeufsX14 pathogenic mutation. In those probands onset was referred between the fifth and sixth decades (range: 43-54 years) although two of them had pes cavus since infancy; evolution at biopsy was mild to severe (CMTNS 9-30); 2 patients were previously treated with intravenous IVIG. Three sporadic probands, affected with a mild to moderate motor sensory polyneuropathy with onset between the sixth and eighth decades carried the heterozygous pathogenic p.Tyr347Cys mutation. Eight sporadic probands harbored 6 heterozygous missense variants of uncertain significance; two of those variants had been previously reported as pathogenic when homozygous or compound heterozygous. In all 15 patients nerve biopsies were consistent with a chronic axonal neuropathy with variable loss of large-myelinated fibers and clusters of regenerating fibers.

Conclusions:
The report emphasizes the pathogenic relevance of MME mutations which can masquerade as CIAP.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** Chronic Idiopathic Axonal Polineuropathies, Neprilysin, MME
Neuropathy Progression In ATTRv Patients After Orthotopic Liver Transplant

Poster No:
87a

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Introduction:
Orthotopic liver transplant (OLT) was the first approved treatment in ATTRv patients by stopping the production of the amyloidogenic TTR, ameliorating disease progression. However, some patients still have neuropathy progression despite OLT. Treatment options are limited for these patients but new therapies may emerge in the near future. Our aim is to characterize ATTRv patients with neuropathy progression post-OLT and identify potential predisposing factors.

Methods:
Patients with ATTRv treated with OLT were included. Neuropathy progression was defined as worsening of Polyneuropathy Disability Score (PNDs) after OLT. Patients with neuropathy progression were compared to patients with no progression. A Cox regression model analysis was performed to identify predisposing factors for progression.

Results:
We included 69 patients with ATTRv (68 Val30Met; 1 Ser52Pro) treated with OLT with a mean age of 51+-9.4 years; 52% were male. Mean follow-up was 9+-5 years. The mean age at OLT was 39+-9.3 years with a mean disease duration of 3+-2.5 years. Most patients had baseline PNDs=1 (68%). Thirteen patients (22%) were previously treated with TTR stabilizers. We identified 12 patients (17%) with neuropathy progression (11 Val30Met; 1 Ser52Pro). Three patients died during follow-up. Comparing to patients with no neuropathy progression, patients were older at the time of OLT (44+-11.7 vs 38+-8.5; p=0.03) and had more severe neuropathy at OLT (PNDs=1: 42% vs 74%; PNDs>1: 58% vs 26%; p=0.04). No differences regarding duration of disease until OLT and duration of follow-up was found. In the Cox regression model analysis, increasing age at OLT was associated with a 10% risk of neuropathy progression per year (HR 1.1; 95%CI: 1.0-1.1; p=0.01). Additionally, patients with PNDs=2 had an increased risk of neuropathy progression (HR 3.7; 95%CI: 1.1-12.2; p=0.03).

Conclusions:
Despite the effectiveness of OLT, a subset of patients develops disease progression. Older age at OLT was the main predisposing factor for neuropathy progression. These findings may help in patient selection for emerging therapies.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: ATTRv, Amyloidosis, Liver transplantation, Neuropathy
Co-occurrence of Canvas and Sjögren syndrome: two common causes of sensory ganglionopathy

Poster No:
88a

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Introduction:
RFC1 biallelic expansions causing CANVAS syndrome and Sjögren syndrome are among the most frequent causes of sensory ganglionopathy. Thus, the occurrence of both diseases in a given patient presenting with a ganglionopathy might be possible. However, little is known about the specific clinical and electrophysiologic phenotype of these patients.

Methods:
Patients with a genetically confirmed CANVAS syndrome followed in our center were ascertained and their personal history of Sjögren syndrome (based on clinical symptoms and a positive SSA/SSB antibody analysis and/or positive salivary gland biopsy findings) was collected.

Results:
Among the 71 patients with a genetically confirmed CANVAS syndrome, six patients (all females) had also a diagnosis of Sjögren syndrome, as defined above. Mean age at onset of the ganglionopathy was 61 years, four patients had gait instability and positive sensory symptoms such as pins and needles, one had only gait instability and one had only positive sensory symptoms at onset. All but one patient had a previous history of chronic cough and all but one patient had additional signs at presentation including pes cavus (n=3), a cerebellar syndrome (n=2), associated vestibulopathy (n=1) and dysautonomia (n=1). Dry eyes or mouth was present in all six patients. One patient has lost ambulation at the age of 78 years, after 15 years of progression of the disease. The sensory ganglionopathy was slowly progressive in all six patients. Two patients had adverse effects from corticosteroid and immunosuppressor therapy (recurrent infections and osteoporotic fractures).

Conclusions:
The diagnosis of a Sjogren syndrome in a patient with a sensory ganglionopathy should not exclude RFC1 expansion sequencing and vice versa given that this may have important therapeutic implications.

References:
Yes

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: CANVAS, Sjögren syndrome, ganglionopathy
GM2 gangliosidosis can present as an isolated SMA-like hereditary motor neuropathy

Poster No:
89a

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Introduction:
The current diagnosis yield of spinal muscular atrophy (SMA) negative for the SMN1 deletion is low. GM2 gangliosidosis caused by biallelic mutations in the HEXA (Tay-Sachs) and HEXB genes (Sandhoff disease), with subsequent low hexosaminidase(s) activity, can mimic SMA-like hereditary motor neuropathy.

Methods:
Case report of a patient with a pure SMA-like hereditary motor neuropathy in which Sandhoff disease was diagnosed. We then searched retrospectively for other patients with a pure motor onset of the disease from our late-onset (>10 years) GM2 gangliosidosis database.

Results:
A 45 year-old female presented with slowly progressive proximal lower limb weakness since the age of 11 years. Although psychomotor development was normal, she had a personal history of scoliosis and used orthopedic insoles. Upon clinical examination, weakness predominated in psoas (MRC 0/5) and quadriceps (MRC 1/5) muscles, been milder in proximal upper limbs. Reflexes were present in the lower limbs and were brisk in the upper limbs. ENMG was neurogenic. SMN1 gene analysis was normal. A DYNC1H1 VUS was found on a large CMT gene panel but lower limb muscle MRI was not compatible with this diagnosis. Hexosaminidases A + B and Hexosaminidase B levels were markedly reduced enabling the diagnosis of Sandhoff disease. Among our cohort of 13 patients with late-onset GM2 gangliosidosis, four had a pure motor onset (median 14, range 10-26), two showing brisk reflexes. Cerebellar atrophy on MRI was present in three patients. Two patients developed later-on mild cognitive symptoms and two a mild cerebellar ataxia.

Conclusions:
Hexosaminidase activity essay should be considered in all patients presenting with a SMA-like hereditary motor neuropathy. We suggest including HEXA and HEXB in hereditary neuropathy gene panels.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Hereditary motor neuropathies, Hexosaminidase, Neurometabolic diseases, Next generation sequencing, Enzyme essay
Using machine learning to prioritize rare repeat expansions for pathogenicity

Poster No:
90a

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Introduction:
Repeat expansions are an area of growing interest for inherited peripheral neuropathies because of the recent discovery of a microsatellite in RFC1 as a cause of cerebellar ataxia with neuropathy and bilateral vestibular areflexia (CANVAS). We hypothesize that additional pathogenic repeat expansions exist causing Charcot-Marie-Tooth (CMT) and related disorders, but the discoveries have been hindered by technological challenges. Here, we spotlight a novel machine learning algorithm to classify the pathogenicity of rare repeat expansions in whole genomes datasets.

Methods:
We previously described a pipeline to identify rare, expanded tandem repeats (TRs) in whole genomes using ExpansionHunter Denovo. We processed ~3,000 rare disease whole genomes from the Undiagnosed Diseases Network and the GENESIS database (including ~150 CMT and hereditary spastic paraplegia phenotypes) through this pipeline. This resulted in 476 rare TRs that are candidates for pathogenicity. Since not all rare variants are disease-causing, we developed a machine learning algorithm, which incorporates mechanistic and functional properties of TRs to distinguish between benign and pathogenic rare repeat expansions.

Results:
Our algorithm has a precision of 1.0 and a recall of 0.70. Precision is the more important metric to optimize here since we want to minimize the selection of benign TRs for further investigation as this will deviate resources from exploring the pathogenicity of truly disease-causing variants. The extremely low false positive rate signifies the value of this method for selecting strong candidates to push forward into functional studies.

Conclusions:
Currently, we are validating our method, after which we will apply this machine learning algorithm to the candidate TRs from previous analyses to prioritize them for pathogenicity.

References:
Yes

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Bioinformatics, Short tandem repeats, Genetics, Machine learning
Slowly progressive ALS observed over 27 years confirms the phenotypic spectrum of first transmembrane domain variants in SPTLC1

Poster No:
91a

Authors:
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Introduction:
Serine palmitoyltransferase, long-chain base subunit 1 (SPTLC1) variants were described to cause Hereditary Sensory and Autonomic Neuropathy type 1 (HSAN1) (1). Recently, variants in SPTLC1 were identified in patients with juvenile onset Amyotrophic lateral Sclerosis (ALS) (2). We describe the phenotype for a patient with early onset ALS who had a SPTLC1 variant, confirming the expansion of this phenotypic spectrum.

Methods:
Neurological evaluations including exam and testing were performed in a large Neuromuscular Clinic. Patients enrolled into the Inherited Neuropathies Consortium (INC). Phenotype-driven genetic testing was performed. Patients with negative testing had whole genome sequencing (WGS) on a research basis. Data was reviewed through the Genesis platform.

Results:
Patient presented at 23 years with progressive weakness in arms. EMGs showed evidence of chronic anterior horn cell disease with denervation/reinnervation. NCS normal. MRIs of the cervical spine normal. Muscle biopsy showed marked type 1 muscle fiber. Progression of weakness later caused difficulty climbing steps and lifting objects by 30. Hospitalization required in her 40s for hypoxemic hypercapnic respiratory failure. Ambulation ability was lost, requiring a wheelchair. Trilogy ventilation was required with mask use and cough assist also required. Exam at 50 showed significant weakness in upper and lower extremities including neck flexion/extension weakness. Sensory exam normal. Reflexes at knees and ankles brisk(3+), biceps brisk, triceps absent. No known family history. Genetic workup included SMA, C9orf72, and Hereditary Motor Neuropathy, negative. A de novo c.115_117del (p.Leu39del) variant was identified in SPTLC1 on WGS and was clinically confirmed.

Conclusions:
This patient is another example of early onset, slowly progressive ALS caused by a variant in SPTLC1. The L39del variant was identified in other patients with this presentation and frequently de novo(2). This provides continued evidence that variants in the first transmembrane domain results in ALS and testing for this gene should be considered for this phenotype.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: ALS, genetic, phenotype
Comparison of high-resolution nerve ultrasound in late-onset hereditary transthyretin amyloidosis with polyneuropathy and CIDP patients

Poster No:
92a

Authors:
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Introduction:
Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) remains a diagnostic challenge due to variety of clinical and electrophysiological presentations, including occasional findings of demyelinating features on nerve conduction studies and albumin-cytological dissociation on cerebrospinal fluid examination, inducing misdiagnosis with chronic inflammatory demyelinating polyneuropathy (CIDP). High-resolution nerve ultrasound (HRUS) is a non-invasive, fast and economic tool in distinguish different types of nerve alterations in neuropathies, and has been recently included in EAN/PNS guidelines on diagnosis of CIDP. The aim of this cross-sectional, prospective study is to investigate the utility of HRUS of peripheral nerves in differentiating ATTRv-PN from CIDP patients.

Methods:
Fifteen patients with genetically confirmed late-onset ATTRv-PN and 25 patients with CIDP were included. For each patient, we collected clinical, electrodiagnostic, and HRUS data of the peripheral nerves. All patients underwent an extensive electrodiagnostic study of median, ulnar, sural, peroneal, and tibial nerves. Nerve cross sectional area (CSA) was detected in 26 nerve sites, including the brachial plexus, median, ulnar, and peroneal nerves.

Results:
HRUS showed that the CSA of the brachial plexus, median nerve at the axilla, arm, and forearm, ulnar nerve at the forearm, and peroneal nerve at the popliteal fossa were significantly larger in CIDP than in ATTRv-PN patients. However, ATTRv-PN patients showed quantitative HRUS abnormalities in several segments, especially at proximal and entrapment sites, and ATTRv-PN nerve CSA of median and ulnar nerves at the axilla and arm was significantly larger in patients than in healthy controls. Although electrodiagnostic study showed isolated or multiple abnormalities compatible with demyelination in ATTRv-PN patients, only two fulfilled EAN/PNS criteria for CIDP diagnosis, in which HRUS data were comparable to CIDP patients.

Conclusions:
High-resolution ultrasonography of peripheral nerves provides reliable information in patients with ATTRv-PN. Its usefulness as a diagnostic tool to differentiate ATTRv-PN from CIDP might be limited.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support:

**Keywords:** High-resolution ultrasonography, hereditary transthyretin amyloidosis with polyneuropathy, ATTRv-PN, CIDP, Electrophysiology
Submicron topographic cues enhance directionality of peripheral nerve regenerating fibers

Poster No:
93a

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Institutions:
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Introduction:
Peripheral nerve injury is a debilitating disease characterized by loss of sensation and/or motor function at the affected site. Although fibers in the peripheral nervous system spontaneously regenerate after injury, in many cases, full functional restoration is not achieved. One likely explanation is that regenerating fibers do not reach the peripheral target because of their propensity to grow in undesired directions in the absence of proper biochemical and biophysical cues. Therefore, the aim of this study is to optimize directional axon outgrowth using surfaces with nano- to micro-scale anisotropic topographic patterns as a biophysical guide. Our hypothesis is that the topographic patterns will confer directionality of growth and enhance the fiber's ability to reach peripheral targets in a timely manner.

Methods:
For this study we explanted DRG from adult mice ex vivo on chemically identical surfaces, with a repetitive groove width of 700nm as compared to a flat control. Axon growth was observed in time-lapse 72-96 hours after initial plating in phase contrast microscopy. Angles of growth relative to the grooves and axon growth speeds were analyzed using ImageJ. Additionally, DRG were similarly cultured in 5 mm diameter 3D half-tube structures with 700 nm grooves, 2000 nm grooves, and flat controls on the inner wall. DRG were immuno-labelled and imaged after 6 days in ImageJ.

Results:
DRG grown on both 2D and 3D topographic surfaces exhibit significantly more directional axon growth parallel to the grooves compared to the flat control, as well as a marginally faster axon growth speed. Moreover, fibers grown on 3D-half-tubes with inner-wall topography exhibited longer axon outgrowth than control.

Conclusions:
Our results may be used to better understand the various mechanisms of peripheral nerve regeneration and be applied towards the fabrication of implantable, fully enclosed tubes with specialized topography to ultimately restore nerve function.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support: MWU Intramural Interdisciplinary grant award

Keywords: Axonal growth, topography, directionality, DRG, mouse model
Development of ORT247, a Monoclonal Antibody Antagonist of EphA4, for the treatment of CMT and ALS

Poster No:
94a

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Institutions:
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Introduction:
ORT247, a human IgG4 kappa monoclonal antibody, exhibits high affinity and selectivity for EphA4 receptor. The EphA4 receptor is a member of the erythropoietin-producing hepatocellular (Eph) family of receptor tyrosine kinases. EphA4 signaling increases following axonal injury and reduces neural repair processes. Inhibition of EphA4 signaling promotes axon outgrowth following injury and improves outcomes in preclinical models of axonal degeneration such as ALS. Thus, EphA4 inhibition is a proposed therapeutic intervention to slow progression and restore function in neurodegenerative diseases. An extensive nonclinical program was conducted to evaluate the safety and efficacy of ORT247 in preparation for possible human clinical trials in CMT and ALS.

Methods:
The affinity and selectivity of ORT247 for EphA4 were evaluated by SPR and ELISA assays. Functional activity was demonstrated in cultured neurons. In vivo efficacy studies were conducted in mouse models of ALS and of CMT1a and CMT2e. Safety studies were conducted in mouse and non-human primate.

Results:
ORT247 binds with high affinity to the ligand-binding domain of EphA4 and exhibits 10–100-fold selectivity for EphA4 compared with other EphA/EphB receptors. ORT247 blocks ligand-induced EphA4 clustering, downstream signaling, and axon growth cone collapse in cultured cortical neurons. In vivo studies show that ORT247 treatment enhances NMJ innervation, promotes nerve conduction, decreases serum neurofilament levels, and improves functional outcomes, such as muscle strength and locomotor deficits, in the transgenic mouse models of Charcot–Marie–Tooth type 1a and 2e. Additionally, ORT247 improves NMJ function as measured electrophysiologically in SOD1 G93A mice. The safety of ORT247 is supported by toxicology studies conducted in CD-1 mice and cynomolgus monkeys administered ORT247 via intraperitoneal injection and intravenous infusion, respectively.

Conclusions:
Nonclinical efficacy and safety data support the clinical development of ORT247 in patients with CMT and ALS.

References:
No

References 1:

References 2:
Keywords: EphA4 receptor, Ephrin, Neuromuscular junction, CMT1a, CMT2e
Hickam’s dictum on a case of progressive weakness and hypermobility: a double genetic hit disorder.

Poster No:
95a

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Introduction:
The implementation of the next-generation sequencing (NGS) technics in clinical practice changed the molecular approach and improved patient/families' care. However, the massive information obtained with these tests are still not fully manageable. In some cases, it may be tempting to close the diagnostic investigation with a single positive result, even if necessary to expand the known clinical manifestations, asserting Occam’s razor, a medical principle that says that a single explanation is the most likely. However, the clinical evaluation remains sovereign to the point of directing the reasoning and defining whether the eventual finding is sufficient for the diagnosis or if we need to look for a second explanation, approaching to Hickam’s dictum, another diagnostic principle which in turn says that there can be more than one explanation for a patient's various symptoms.

Methods:
Clinical description, WES analysis and their correlation.

Results:
A 14-year-old male patient, son of consanguineous parents, presented a slowly progressive, symmetrical, distal predominant neurogenic weakness since the age of 1 year, associated to striking joint hypermobility and spinal deformities. His WES revealed a homozygous class 4 variant at the IGHMBP2 gene (c.2796delC, p.Cys932TrpfsTer46) related to distal hereditary motor neuropathy (dHMN) type VI and CMT2S. As this gene did not explain the hypermobility, a further search at the WES, using a virtual panel for hypermobility genes, revealed a second class 4 homozygous variant at the ALDH18A1 gene (c.121 C>T, p.Arg41Cys), related to cutis laxa, explaining the remaining of the clinical picture.

Conclusions:
We suggest that Occam’s razor is not always superior to Hickam's dictum. In genetic cases, when a strong pathogenic variant does not explain the full clinical picture, the possibility of a double hit genetic disorder should be considered. In such cases, a judicious clinical analysis is essential to shape the genetic data search.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: Neurogenetics, Inherited neuropathies
Plasma Neurofilament Light Chain Concentrations are Elevated in Youth-onset T2D and Associate with Diabetic Neuropathy

Poster No:
96a

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Introduction:
The lack of easily measurable, clinically meaningful biomarkers remains a challenge in executing clinical trials for diabetic neuropathy (DN). Plasma Neurofilament light (NFL) chain concentration has emerged as a promising biomarker in immune-mediated neuropathies.

Methods:
A nested case-control study was performed in participants with youth-onset type 2 diabetes (T2D) enrolled in the prospective Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study. Plasma NFL levels were measured at 4-year intervals from 2008-2020 in 50 participants who developed DN (score >2 on MNSI-E in 2020) and 50 participants with T2D and no DN.

Results:
In 2020, NFL levels from DN and non-DN TODAY participants (mean age 27 years) were elevated when compared to 40 control subjects without T2D (mean age 22 years) (mean NFL concentration 12.5 and 8.44 pg/ml versus 4.1 pg/ml, p<0.0001). Among participants with T2D, NFL concentrations were similar in the DN and no DN groups at first assessment, however, levels were higher in DN participants at all subsequent assessments (p=0.027), including the last one in 2020 (p=0.009). NFL levels increased over time in both groups, with higher degrees of change in DN participants (interaction p=0.045). While there was no association between NFL levels at first assessment and DN outcome, a doubling in NFL from beginning to end of study increased the odds of DN by 52% (p=0.026). Among TODAY participants in 2020, positive Spearman correlations (controlled for age, sex, T2D duration and BMI) were seen between NFL and MNSI-E (0.34, p=0.0010), HbA1c (0.48, p<0.0001), total cholesterol (0.25, p=0.0178), and LDL (0.30, p=0.0037), while negative correlations were found with multiple measures of HR variability (-0.42 to -0.46, p<0.0001).

Conclusions:
The findings that NFL levels are elevated in individuals with youth-onset T2D, and increase more rapidly in those who develop DN, suggest that NFL could be a valuable biomarker for DN.

References:
No

References 1:

References 2:

References 3:
References 4:


Keywords: Diabetic neuropathy, Type 2 diabetes, Neurofilament light
Cost Of Illness of Small Fiber Neuropathy in the Netherlands

Poster No:
97a

Authors:
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Introduction:
Damage of the thinly myelinated Aδ- and unmyelinated C-fibers results in small fiber neuropathy (SFN). Patients with SFN suffer from neuropathic pain and autonomic dysfunction. Neuropathic pain is associated with substantial health care costs, however studies on the burden of illness of SFN are scarce. The aim of this study was to examine the burden of illness of SFN and its association with age, anxiety and depression, quality of life (Qol) and pain.

Methods:
Total annual health care-, patient and family-, and societal costs per patient with a Pain Impact NRS (PI-NRS) of 0–3 (mild); 4–6 (moderate); and 7–10 (severe) were calculated by using baseline data of cost questionnaires of patients with SFN. Health care costs were obtained from the Dutch guideline for cost research, with the cost reference year of 2020. Productivity costs were calculated using the friction costs method. Severity of health-related Qol was determined by utility scores of the EuroQol 5D (EQ-5D-5L). Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS).

Results:
A total of 156 patients (mean age 53.8 y, 17.4 – 80.8; male 33.3%) completed the cost questionnaires. Moderate or severe pain was reported in 78.8% of the patients. The total annual average societal cost of SFN per patient was €17,871 (95% CI €14,395 – €21,480). Severe pain was associated with significant higher health care costs, patient and family costs, and more productivity loss (p ≤ 0.001). Patients with severe pain reported significant lower EQ-5D-5L utility scores and depression scores (p < 0.001).

Conclusions:
Based on the prevalence rates of SFN in the Netherlands (53/100,000 inhabitants) and an adult population of 15.5 million residents in 2020, the total average annual health care costs of SFN amounted to €29.8 million, and from a societal perspective €147.7 million.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** Small fiber neuropathy, Neuropathic pain, Economic burden, Health care costs, Cost-of-illness study
Neuron-Keratinocyte Communication in the Epidermis in Painful Diabetic Neuropathy

Poster No:
98a

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Institutions:
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Introduction:
Painful diabetic neuropathy (PDN) is one of the most common and intractable complications of diabetes. PDN is characterized by small-fiber degeneration, which can progress to complete loss of cutaneous innervation and is accompanied by neuropathic pain. Uncovering the mechanisms underlying axonal degeneration in PDN remains a major challenge to finding effective and disease-modifying therapies. Sensory nerve afferents normally extend into the epidermis in close juxtaposition to keratinocytes, but degenerate in diabetic skin. Our aim is to identify the changes in gene expression profiles and the interactions between dorsal root ganglion (DRG) neurons and keratinocytes to explore the mechanisms by which keratinocytes communicate with cutaneous afferents and how this communication impacts axonal degeneration underlying neuropathic pain in PDN.

Methods:
We used a mouse model of PDN where mice were fed a regular diet (RD, 11% fat) or a high-fat diet (HFD, 42% fat) for 10 weeks during which these mice develop glucose intolerance, mechanical allodynia, small fiber neuropathy. Using single-cell RNA (scRNA-seq) sequencing approach we captured DRG and keratinocytes gene expression profiles and generated interactome maps. We validated scRNA-seq results using RNAscope on DRG and skin frozen sections.

Results:
scRNA-seq identified both neuronal and non-neuronal clusters and several differentially expressed genes between RD and HFD from the DRG. We were able to identify several clusters of immune cells and keratinocytes at different stages of differentiation. We generated interactome maps between DRG neurons and the peripheral cells to highlight ligand-receptor interactions and we looked to identify genes that were differentially expressed in these interactions.

Conclusions:
Taken together our data highlights the importance of studying neurons in conjunction with the cells in the tissues with which they interact with to identify ligand-receptor interactions that may lead to the identification of neuron signaling in a chronic pain state such as PDN.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: neuropathic pain, DRG, high fat diet, Neuron-Keratinocyte Communication, single cell RNA sequencing
Post-onset gene therapy improves myelination in a CMT4C model.

Poster No: 99a

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Institutions: ¹The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

Introduction: CMT4C is a demyelinating neuropathy caused by autosomal recessive mutations in the SH3TC2 gene expressed specifically in myelinating Schwann cells of the peripheral nervous system (PNS). The Sh3tc2⁻/⁻ mouse model of CMT4C develops an early onset peripheral neuropathy with slowing of motor and sensory nerve conduction velocities, hypo- and demyelination, and widening of the nodes of Ranvier. This phenotype is progressive with increasing myelin pathology from 2 and 12 months of age.

Methods: We have developed and validated a novel AAV9-miniMpz.SH3TC2.myc vector for Schwann cell-targeted expression of SH3TC2 leading to functional improvements in the model of CMT4C. Here, we tested its efficacy to also improve myelination at early as well as at late stages of the neuropathy.

Results: The AAV9-miniMpz.SH3TC2.myc vector was delivered into 4 weeks or 4-month-old Sh3tc2⁻/⁻ mice by a single lumbar intrathecal injection and effects on myelination were assessed 2 or 4 months after injection, respectively. Morphological analysis revealed significant improvement in g-ratios, myelin thickness, and ratios of demyelinated fibers in lumbar roots, femoral and sciatic nerves of Sh3tc2⁻/⁻ mice both in early and late treatment groups. Furthermore, treated mice in both age groups showed improved nodal molecular architecture with normalization of nodal widening compared to mock-treated animals.

Conclusions: This study provides proof of principle for the effectiveness of gene replacement therapy to improve myelin pathology in the Sh3tc2⁻/⁻ model when delivered both at early as well as at later stages of the disease. These results are of clinical relevance for treating CMT4C.

References: No

References 1: 

References 2: 

References 3: 

References 4: 

Grant Support: Charcot-Marie-Tooth Association

Keywords: Charcot-Marie-Tooth, Gene therapy, AAV, Schwann cell, sh3tc2 gene
Mitochondrial Dysfunction Is A Feature Of Paclitaxel And Oxaliplatin-Promoted Chemotherapy-Induced Peripheral Neurotoxicity

Poster No: 100a

Authors: Silvia Giatti¹, Maria Elena Pero²³, Cristina Meregalli⁴, Marianna Dionisi⁵, Laura Monza⁴, PAOLA ALBERTI¹, Beatrice Riva⁵, Roberto Melcangi¹, Paola Marmiroli⁶, Carla Distasi³, Francesca Bartolini³, Guido Cavaletti⁴

Institutions: ¹Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy, ²Department of Veterinary Medicine and Animal Production, University of Naples, Naples, Italy, ³Department of Pathology & Cell Biology, Columbia University, New York, NY, ⁴Experimental Neurology Unit School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy, ⁵Department of Pharmaceutical Sciences, University of Eastern Piedmont, Novara, Italy, ⁶Department of Biotechnology and Bioscience, University of Milano-Bicocca, Monza, Italy

Introduction: Chemotherapy-induced peripheral neurotoxicity (CIPN) is one of the dose-limiting side effects for several effective anticancer drugs. In case of severe neuropathy, chemotherapy dose reduction/withdrawal can occur, with possible negative effects on oncological prognosis. Incomplete knowledge of CIPN pathogenesis is the main reason why therapeutic strategies are not currently available. Herein we evaluated the consequences of CIPN on oxidative stress and mitochondria dynamics using in vivo and in vitro models.

Methods: Adult male Wistar rats were treated with chemotherapeutic agents (paclitaxel (PTX) – 10 mg/kg 1 qw, i.v; oxaliplatin (OHP) – 5 mg/kg 2qw, i.v; 5 fluorouracil (5FU) – 50 mg/kg 1 qw i.p, the latter used as non CIPN-promoting chemotherapeutic drug) or vehicle for 4 or 6 weeks and multimodal assessment of CIPN was performed (neurophysiology and behavioral test). Oxidative stress, gene and protein expression were evaluated in dorsal root ganglia (DRG) of treated animals; moreover, in vitro analyses of mitochondria motility were performed.

Results: PTX-treated rats showed allodynia and neurophysiological alterations. Molecular analyses of DRG isolated from PTX-treated rats indicated lack of oxidative stress; however, the expression of the key markers associated with mitochondrial dynamics was altered. Conversely, OHP- or 5FU-treated rats did not show similar mechanical allodynia, nor presented modifications in markers associated with mitochondrial dynamics. However, OHP selectively affected mitochondrial electron transport chain protein levels and induced oxidative stress. We measured mitochondria motility in cultured adult DRG neurons exposed to doses at which OHP induced axonal degeneration in vitro and found that OHP promoted mitochondrial motility prior to axonal degeneration.

Conclusions: Altogether our data support the notion that allodynia specifically correlates with perturbation of mitochondria dynamics and suggest that seemingly unrelated CIPN drugs may converge on induction of abnormal mitochondrial function in DRG neurons.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This research is supported by PRIN Grant n. 2017ZFJCS3.

Keywords: mitochondrial dynamics, oxidative stress, allodynia, dorsal root ganglia, mitochondria motility
Nephropathy In Chronic Inflammatory Demyelinating Polyradiculoneuropathy Associated With Nodal And Paranodal Antibodies: A Systematic Review

Poster No:
101a

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Introduction:
In a few patients with CIDP with antibodies anti contactin-1 (CNTN-1) and neurofascin-140/186 (NF-140/186) the presence of a concomitant nephropathy has been reported. We performed a systemic review of the literature on the concurrent presentation of CIDP and nephropathy.

Methods:
We searched Pubmed up to December 2021 and included all cases of CIDP and nephropathy. Data were extracted according to a predefined protocol and authors were contacted via email and asked to provide missing information. Included CIDP patients with nephropathy with and without antibodies against nodal-paranodal proteins were compared with 52 seronegative CIDP patients followed at our center.

Results:
A total of 50 published cases of CIDP in association with nephropathy were found (30 with antibodies, 20 without). Twenty-seven patients had anti-CNTN-1 and 3 patients anti-NF-140/186 antibodies. Kidney biopsy disclosed membranous glomerulonephritis in all patients with anti-CNTN-1 and focal segmental glomerulosclerosis in all anti-NF-140/186 positive patients. Compared to seronegative CIDP patients, those with CIDP associated with nephropathy and nodal-paranodal antibodies more frequently were males, had an older age at clinical onset, higher CSF proteins levels, more frequently reported ataxia and tremor, had more severe disability at symptoms onset, less frequent treatment response. About 30% of them died at follow-up. Patients with CIDP associated with nephropathy without antibodies had higher CSF proteins levels, more severe disability at symptoms onset, and less frequent treatment response compared to seronegative CIDP patients. Nephropathy was severe and showed a poor treatment response in both the two groups of patients.

Conclusions:
CIDP associated with nephropathy is a rare and severe syndrome, with a poor treatment response, and may be found both in patients with and without antibodies against nodal–paranodal proteins. Nephropathy seems more frequent in patients with anti-CNTN-1 antibodies. Histological pattern seems to correlate with the type of nodal/paranodal antibody.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, Nodal and paranodal antibodies, Nephropathy
Guillain-Barré Syndrome as a Paraneoplastic Presentation of Adenocarcinoma of Endometrium

Poster No:
102a

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Introduction:
Guillain-Barré syndrome (GBS) is serious autoimmune disorder in which the immune system attacks peripheral nervous system (PNS). Hodgkin's lymphoma is the cancer most often associated with GBS, however the relationship to other malignancies is still unclear. We report a case with GBS and endometrial adenocarcinoma.

Methods:
Fifty-one years old female patient applied to neurology outpatient department with weakness of arm and legs. This weakness is acute and progressive. In medical history, she was operated due to mass in the uterus fifteen days ago. Neurological examination revealed bilateral facial paralysis and moderate tetraparalysis. Deep tendon reflexes were also absent. F waves were too long in her electroneuromyography (EMG) at admission. Lumbar puncture yielded cerebrospinal fluid with normal protein (24 mg/dL), glucose (66 mg/dL), chlorine (114 mg/dL) normal red blood cell count (0 per/µL), and one white blood cell (mononuclear) count (1 per/µL).

Results:
The patient was diagnosed with GBS because of progressive weakness. The repeated EMG also revealed demyelinating neuropathy. The pathology of the uterine mass was found to be endometrial adenocarcinoma grade 2. Intravenous immunoglobulin (0.4 g/kg/day) was given to the patient for five days and marked improvement was seen in her neurological examination. Chemotherapy was also planned. The detailed investigation of metastasis including breast were negative. Screening for anti-onconeural antibodies (antiHu, anti-Ri, anti-Yo, anti-amphiphysin and antiCV2) performed by immunohistochemistry and western blotting. Anti-Yo was positive, the others were negative.

Conclusions:
This is the first case in English literature with GBS and Anti Yo (+) endometrial adenocarcinoma.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:
Keywords: Guillain-Barré Syndrome, Paraneoplastic neuropathy, Inflammatory Neuropathy
Activation of 20-HETE Synthase Triggers Oxidative Injury and peripheral Nerve Damage in Type 2 Diabetic Mice

Poster No:
103a

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Introduction:
Diabetic Peripheral Neuropathy (DPN) is characterized by peripheral nerve dysfunction. Reactive Oxygen Species (ROS) overproduction has been suggested to orchestrate diabetic complications including DPN. Untargeted antioxidant therapy has exhibited limited efficacy, highlighting a critical need to explore ROS sources altered in a cell-specific manner in DPN. Cytochromes P450 (CYP) enzymes are prominent sources in which research has shown the implication of 20-HETE synthase, CYP4A, in diabetes-induced renal, retinal, and cardiovascular injuries. The following study aims to investigate the role of CYP4A and its metabolite 20-HETE in diabetes-induced sciatic nerve injury, and the mechanistic pathway altered.

Methods:
We assessed peripheral nerve functionality in a murine model of Type 2 Diabetes Mellitus (T2D). Non-obese T2D mice (MKR) were treated with a CYP4A-inhibitor (HET0016) or AMPK-activator (Metformin) after which sensorimotor modalities were assessed by behavioral testing via the Raised Beam Walking, Plantar Hyperalgesia, and Grip Strength tests. Nerve Conduction Velocity was recorded for electrophysiological assessment. ROS production was assessed by HPLC, DHE staining and NADPH Oxidase Activity Assay. CYP4A expression, myelin protein profiles, phosphorylated AMPK levels, and autophagy were examined in sciatic nerves via western blot or immunohistochemistry.

Results:
Peripheral nerves of MKR mice reflect increased CYP4A and 20-HETE levels, concurrent with altered myelin proteins and sensorimotor deficits. This was associated with increased ROS production and altered Beclin-1 and LC3 protein levels, indicative of disrupted autophagic responses in tandem with AMPK inactivation. AMPK activation via Metformin restored nerve integrity, reduced ROS production, and regulated autophagy. Interestingly, similar outcomes were revealed upon HET0016 treatment whereby ROS production, autophagic responses, and AMPK signaling were normalized in diabetic mice.

Conclusions:
Altogether, the results highlight hyperglycemia-mediated oxidative injury in DPN through a novel CYP4A/20-HETE/AMPK pathological axis. Targeting this axis may be of clinical potential in predicting and alleviating DPN in patients with T2D.

References:
No
References 3:

References 4:

Grant Support:

**Keywords:** Diabetic Peripheral Neuropathy, Insulin resistance, 20-HETE, AMPK, Oxidative Stress
Exploring SARM1 inhibition in mouse models of CMT

Poster No:
104a

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Institutions:
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Introduction:
Inhibiting SARM1 has been shown to be axon protective in mouse models following challenges including injury, chemotherapy-induced neuropathy, and diabetic/metabolic neuropathy. Here we test inhibiting SARM1 as a treatment for Charcot-Marie-Tooth disease (CMT).

Methods:
Sarm1 knock-out (KO) mice were bred to models of Kif1A/HSN2C, Fig4/CMT4J, and Gjb1/CMT1X. Mice were then evaluated through lifespan, body weight, grip strength and neurophysiology. Histopathology is on-going. We are also starting treatment of additional CMT mouse models with a SARM1 dominant-negative AAV (dn-SARM1 AAV).

Results:
The knockout of Sarm1 did not increase lifespan or body weight in Kif1A or Fig4 mutant mice, and neurofilament levels remain elevated in Kif1A/-, Sarm1/- mice. Gjb1 studies are on-going, but preliminary data show no striking improvements in NCVs, body weight or grip strength. In preliminary positive control studies with the dn-SARM1 AAV, wild-type mice were treated at birth and the sciatic nerve was crushed at 8 weeks. Histologically, axon integrity was protected, but functionally, there was no EMG following distal nerve stimulation. We are continuing dn-SARM1 AAV studies on other models of CMT, such as Gars/CMT2D.

Conclusions:
SARM1 inhibition in mouse models of HSN2C, CMT4J, and CMT1X have shown little overt benefit in disease pathology, but histopathology results are still pending. Studies with dn-SARM1 AAV in other models of CMT and injury are on-going.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Charcot-Marie-Tooth Association: CMT_SARM1-01-1151100

Keywords: SARM1, CMT, gene therapy
Interleukin-10 Promoter Polymorphisms and Haplotype Patterns in Patients with Guillain–Barre’ Syndrome

Poster No:
105a

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Introduction:
Interleukin-10 (IL-10) is an immunoregulatory cytokine with both pro- and anti-inflammatory effects that play a crucial role in the pathogenesis of Guillain-Barré syndrome (GBS). We investigated whether the three common polymorphisms -1082G/A (rs1800896), -819C/T (rs1800871) and -592C/A (rs1800872) in the promoter region of IL-10 have influence the susceptibility, severity and clinical outcome of GBS.

Methods:
We determined IL-10 promoter polymorphisms in 152 patients with GBS and 152 healthy controls from Bangladesh by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) and allele-specific oligonucleotide-PCR (ASO-PCR). Haplotype patterns and frequencies were analyzed using Heatmaply package of R statistics. Allele frequencies were analyzed using chi-square test and Fisher's exact test. Serum level of IL-10 was measured by enzyme linked immunosorbent assays using unpaired t-test with Welsh's correction.

Results:
IL-10 promoter polymorphisms -1082G/A, -819C/T and -592C/A were not associated with GBS susceptibility. The -819TT genotype associated with susceptibility; but, P value lost its significance after Bonferroni correction (P=0.029, OR=2.73, 95% CI=1.15-6.45; Pc=0.08). The homozygous -819TT genotype was prevalent in axonal variant of GBS compared to demyelinating subtypes and healthy controls (P=0.042, OR=8.67, 95% CI=1.03-72.97; Pc=0.123 and P=0.005, OR=4.2, 95% CI=1.55-11.40; Pc=0.015, respectively). Haplotype analysis revealed nineteen patterns of genotypes with different frequencies in 3 loci. The high IL-10 expression haplotype combinations (GCC/GTA, GCC/ATA and GCC/GCA) influence the severity of the disease (P=0.008, OR=3.22, 95% CI=1.4-7.43; Pc=0.024). Serum expression of IL-10 was elevated in GBS and in disease severity (GBS, [12.16±45.71] pg/mL vs. control, [0.65± 5.17] pg/mL, p=0.0027 and severely-affected, [15.25±51.72] pg/mL vs. mildly-affected, [3.59± 19.79] pg/mL, p=0.046; respectively). Genotype distribution showed no association with serum level of IL-10.

Conclusions:
The -819TT genotypes influence axonal variant of GBS, and high frequency of IL-10 expression haplotype combination (GCC/GTA, GCC/ATA and GCC/GCA) with elevated serum IL-10 may play a pivotal role in the pathogenesis of GBS.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain-Barré syndrome, Interleukin-10, Polymorphism, Haplotype patterns, Axonal GBS
Pathophysiological effects of anti-neurofascin155 IgG3 and IgG4 in vivo

Poster No:
106a

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Introduction:
The paranodal axoglial complex, consisting of contactin-1, contactin-associated protein-1 and neurofascin155 (NF155), is a target for autoantibodies in inflammatory neuropathies. Paranodal autoantibodies mostly belong to the IgG4 subclass, rarely to the IgG3 subclass, but both can be highly pathogenic. To find out more about the pathogenicity of IgG3 and IgG4 autoantibodies against NF155 in vivo, we performed passive transfer experiments.

Methods:
Lewis rats were intrathecally injected with purified IgG of a patient with anti-NF155 IgG4, a patient with anti-NF155/186-(Pan) IgG3 or purified IgG from a control without autoantibodies, for three weeks. Subsequently, nerve conduction studies (NCS) and behavioral tests, including Catwalk and Rotarod for the assessment of motor function and Von-Frey and Hargreaves for sensory assessment, were performed. Lumbar nerve roots were collected to study autoantibody binding.

Results:
Shortly after treatment with IgG of the anti-NF155-IgG4-positive patient, animals developed symptoms such as gait ataxia and paraparesis. Behavioral tests revealed motor and sensory deficits in animals treated with anti-NF155 IgG4 compared to controls. No alterations in NCS of the sciatic nerve were observed. Positive binding of patient IgG at paranodes was found in lumbar nerve roots L3, L4 and L5 of rats injected with IgG of the anti-NF155-positive patient. In contrast to the effect of anti-NF155 IgG4, we did not detect any motor or sensory deficits in rats treated with IgG of the patient with anti-pan-NF IgG3, although autoantibody binding at the nodes was detectable.

Conclusions:
Our results give evidence that anti-NF155 IgG4 autoantibodies get access to the paranodes after chronic exposure and induce sensory and motor impairment that is most probably mediated by autoantibody binding. Only nodal but no paranodal binding was detectable after intrathecal injection of IgG3 of a patient with anti-pan-NF autoantibodies and no corresponding symptoms were detectable indicating that nodal binding alone may not be sufficient to induce symptoms.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Inflammatory neuropathies, anti-neurofascin, Passive transfer, Autoantibody
Effects of Extracorporeal Shock Wave Therapy on neuroregeneration after median nerve reconstruction in the rat using autografts or conduits

Poster No:
107a

Authors:
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Institutions:
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Introduction:
Several studies evaluating the effects of Extracorporeal Shock Wave Therapy (ESWT) on nerve regeneration in the sciatic nerve model of the rat showed proregeneratory effects of this non-invasive treatment method. Effects of ESWT on nerve conduits remain mostly unstudied so far. A feasible alternative to the murine sciatic nerve model, which has some severe disadvantages regarding animal welfare and evaluation of experimental outcome, is the median nerve model of the rat. The aim of this work was to evaluate the effects of ESWT following reconstruction of the median nerve in rats.

Methods:
In 123 male Lewis rats a 7-mm segment of the right median nerve was resected and the nerve defect was bridged with either an autologous nerve graft, muscle-in-vein conduit, chitosan-conduit, or silk fibroin conduit. Half of the animals in each group received a single application of ESWT (defocused, electrohydraulic applicator, 300 impulses, 3 Hz, 0.1 mJ/mm2). Functional recovery during the 12-weeks observation period was assessed via the grasping test, computerized gait analysis and electrophysiological evaluations.

Results:
Regarding grasping strength and computerized gait analysis, no significant effects of ESWT were apparent when comparing the different groups. Electrophysiological evaluations did also not reveal any significant differences between reconstructive techniques, although autologous nerve grafts + ESWT were superior to both groups treated with muscle-in-vein conduits (p<0.05) and animals treated with silk fibroin conduits (p<0.05).

Conclusions:
No significant effects of ESWT on functional nerve regeneration were observable in our study which could be related to the animal model we used. Additionally, the exact modes of action and optimum application forms of ESWT remain to be elucidated in future studies. The same applies to the materials used to manufacture nerve conduits. Noteworthy, evaluation of functional recovery via the grasping test was impeded in our study due to the animals' limited motivation to participate in the procedure.

References:
No

References 1:
Grant Support: The authors are grateful to the Austrian Workers’ Compensation Board (AUVA) for supporting them with an “AUVA Forschungskonto” (Grant Number: FK 26/19 ESWT).

Keywords: Nerve Injury, Animals, ESWT, Neurotmesis, Median Nerve
Schwann cell LRP1 is essential for conserving myelin and mitochondrial integrity in aged peripheral nerves

Poster No:
108a

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Introduction:
Mitochondria are dynamic organelles, the abundance, size, and function of which are regulated by mitochondrial fission, fusion, and mitophagy. In the PNS, structurally abnormal mitochondria in Schwann cells (SCs) have been associated with peripheral neuropathy. The endocytic and cell-signaling transmembrane receptor, low-density lipoprotein receptor-related protein-1 (LRP1), is expressed in uninjured nerve and is substantially up-regulated in SCs after PNS injury. SC LRP1 contributes to the SC Repair Program. Herein, we assessed the activity of SC LRP1 in the aging PNS.

Methods:
Adult female scLRP1flox/flox-Mpz-Cre-positive (scLRP1-/-) and scLRP1flox/flox-Mpz-Cre-negative (scLRP1+/+) mice (12-24 month-old) were studied (n=4 mice/genotype). Aged sciatic nerves were placed in Karnovsky's fixative and embedded in epoxy resin. Ultrathin transverse nerve sections (60 nm) were cut and post-stained. Sections were viewed using a JEOL1200EX II transmission electron microscope and photographed using a Gatan digital camera. Electron micrographs (~2000) were used for all quantifications. For analysis of Remak bundles and myelinated fibers, at least 6 random fields per mouse were evaluated.

Results:
scLRP1-/– mice demonstrated progressive failure of myelin maintenance and diverse abnormalities in unmyelinated SCs (cytoplasmic protrusions, collagen pockets). However, the overall number of myelinated and unmyelinated fibers, and Remak bundles was unchanged. The abundance of mitochondria was significantly increased in myelinating (P<0.01) and non-myelinating (P<0.01) SCs. Importantly, the increase in abundance of mitochondria was not limited to SCs, but also identified in unmyelinated (P<0.01) and myelinated axons (P<0.05). An increased fraction of mitochondria in scLRP1-/– mouse nerves appeared swollen with loss of well-defined cristae; these changes may be observed in pre-apoptotic cells. scLRP1-/– nerves demonstrated an increase in number of vacuoles in Remak bundle axons (P<0.01).

Conclusions:
These ultrastructure studies demonstrate that SC LRP1 contributes to myelin maintenance and axonal integrity in aging nerves, at least in part via pathways that regulate mitochondrial abundance and function.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support: 1 I01 RX002484 Veterans Administration

Keywords: Schwann cells, mitochondria, peripheral neuropathy, aging, Remak bundles
Usefulness Of The Skin-Wrinkling Test In Patients With Small-Fiber Neuropathy And Gaucher Disease: Case Report

Poster No:
109a

Authors:
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Institutions:
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Introduction:
Purpose: Gaucher disease (GD) is an autosomal recessive disease characterized by an inborn metabolic error. Pain is one of the most frequent symptoms in this condition, generally attributed to skeletal involvement. However, it may present neuropathic characteristics in some patients. Therefore, recent studies analyzed the occurrence of peripheral polyneuropathy in patients with GD, especially small-fiber polyneuropathy (SFN), when faced with normal electroneuromyography (ENMG) and neurological examination. The methods used to assess SFN in these studies were mainly skin biopsy and quantitative sensory testing.

Methods:
Methods: In this case report, we present a case of SFN attributed to GD after excluding other etiologies. In addition, we demonstrate the usefulness of the skin-wrinkling test performed by immersion in water in the evaluation of this patient.

Results:
Results: A 27-year-old woman diagnosed with GD at 5 years of age was referred for evaluation after the onset of a new pain, with neuropathic characteristics. Given the compatible clinic and normal neurological examination and ENMG, a diagnosis of probable SFN was made. The skin-wrinkling test recorded by photographs was performed, in which the palms of the hands were photographed at time 0 to verify basal changes in the fingers and 30 minutes after immersion in water at 40ºC for comparison. The wrinkling of each finger, except for the first one, was graded into three categories: 0.0, no wrinkling; 0.5, slight wrinkling; and 1.0, clear wrinkling. The patient had a mean wrinkling of 0, demonstrating small-fiber involvement.

Conclusions:
Conclusion: Given the exclusion of other etiological possibilities described for SFN, the hypothesis was an association between SFN and DG, recently described in the literature and possibly underdiagnosed. Although only skin biopsy can confirm the diagnosis of SFN, the skin-wrinkling test can be useful for the complimentary assessment of pain in patients with GD, owing to its easy application and wide availability.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support: none

Keywords: Skin-wrinkling test, small fiber neuropathy, Gaucher disease, electroneuromyography, Pain

Poster No:
110a

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Introduction:
Our aim was to verify the use of the eponym 'Landry-Guillain-Barré-Strohl syndrome' in the medical literature, in recognition of the four authors who initially described the syndrome, in connection with the book of the same name written 50 years ago.

Methods:
This is a narrative review study that investigated the Pubmed and Lilacs medical databases with the descriptors: Acute polyradiculoneuritis of unknown cause and 'Landry-Guillain-Barré-Strohl syndrome' title of the book written by three Cuban doctors in 1972 and published in 1976. We searched the articles with the same name and interviewed the only living author of the book.

Results:
In 1972, then resident of neurology Otto Hernández Cossio, finished writing the clinical descriptions of the 76 patients included in the book, which together with the pathological examinations by Drs. Joaquim Galarraga Inza and Rafael Estrada Gonzalez compose the 273 page book, besides the chapter with the electrophysiological studies by Professor Estrada and the correlation and discussion of the results. Only 37 articles with the eponym LGBS were found.

Conclusions:
Recommendations to avoid the use of eponyms in the names of diseases or syndromes, has become a common fact, but the Guillain-Barré syndrome persists from university chairs to lay people. It would be difficult to have arrived at current knowledge about the syndrome if, in the works of Haymalter and Kernohan, Waksman and Adams, Asbury, Arnason and Adams. Our paper pays homage to the four physicians who in the 19th and early 20th centuries masterfully described it, as well as the three Latin neuroscientists who published the first book using the eponym with the names of the four original authors.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:
Keywords: Polyradiculoneuritis, History of Neurology, Medical eponyms
The role of ATF4 target-gene expression on neuropathy phenotype in mouse models of Charcot-Marie-Tooth disease type 2D

Poster No:
111a

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Institutions:
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Introduction:
The integrated stress response (ISR) is activated in motor neurons of mouse models of tRNA synthetase-associated Charcot-Marie-Tooth disease (CMT). The ISR precipitates two major cellular consequences – shutdown of cap-dependent translation and ATF4 target-gene expression. It is unclear whether the neuropathy phenotype is due to decreased translation, or expression of ATF4 targets.

Methods:
Gars/CMT2D mice will be crossed to motor neuron-specific ATF4 knockouts to determine if ATF4 target-gene expression is necessary for the neuropathy phenotype. Conversely, motor neuron-specific transgenic ATF4-overexpressing mice will be assessed to determine if ATF4 target-gene expression is sufficient to cause the phenotype. Neuromuscular performance, nerve histology, ATF4 target-gene expression, and translation levels will be assessed in these mice.

Results:
Initial litters are just arriving from these crosses. For the meeting, I plan to present pilot data from the transgenic ATF4-overexpressing mice showing neuromuscular performance and levels of ATF4 and its targets in motor neurons. I also expect to have litters and maybe preliminary data on neuromuscular performance and ATF4 levels the Gars/CMT2D mice crossed to ATF4 knockouts.

Conclusions:
While it is clear the ISR contributes to tRNA synthetase-associated neuropathy, it is unknown whether this is due to the global decrease in cap-dependent translation, or the increased expression of ATF4 targets. The results of this project will refine our understanding of the pathomechanism underlying tRNA synthetase-associated CMT.

References:
Yes

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease, ATF4, integrated stress response, GARS
Motor Neuron Disease or Sensory Neuropathy? L-Serine as a modulating factor

Poster No:
112a

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Institutions:
¹USZ, Zürich, Switzerland, ²University of Zurich, Institute for Clinical Chemistry, Schlieren, Switzerland

Introduction:
Hereditary Sensory Neuropathy Type 1 (HSAN1) is a progressive sensory neuropathy caused by mutations in the enzyme Serine-palmitoyltransferase (SPT). SPT catalyzes the rate-limiting step in the de-novo synthesis of sphingolipids. HSAN1 mutations induce a permanent change in the substrate specificity of SPT shifting from the canonical substrate L-Serine to the alternative L-Alanine. This forms an atypical class of neurotoxic 1-deoxySphingolipids. In contrast, amyotrophic lateral sclerosis (ALS) is a progressive, neurodegenerative disease affecting lower and upper motor neurons. Clinical hallmarks include progressive muscle atrophy, speech and swallowing difficulties, fasciculation, altered reflexes, and spasticity. Recently, we reported five heterozygous variants in SPT identified in eight unrelated families with childhood ALS.

Methods:
We analyzed the sphingolipid profile in blood of affected individuals and cellular models expressing the SPT-ALS variants by high-resolution mass spectrometry. We used stable isotope labelling to characterize activity of the mutants and their impact on sphingolipid de-novo synthesis.

Results:
Different from SPT variants that cause HSAN1, the dominantly-acting SPT-ALS variants cluster in exon 2. This domain is important for the interaction with the regulatory SPT subunit ORMDL3. Consequently, all SPT-ALS variants showed a reduced homeostatic control causing an excessive de-novo formation of ceramides and other SL species. Restricting the SPT substrate L-Serine, reduced the formation of canonical SL but caused an increased formation of 1-deoxySL instead. This indicated that low L-serine might cause a phenotypic shift from a motor to a sensory phenotype. This was confirmed in an SPT-ALS family which members showed either a sensory or a motor phenotype despite having an identical mutation.

Conclusions:
Mutations in SPT can either cause the sensory neuropathy HSAN1 or result in motor neuron degeneration and childhood ALS. Limiting L-serine availability causes a metabolic and phenotypic shift from the motor to the sensory phenotype.

References:
Yes

References 1:

References 2:
References 3:

References 4:

Grant Support: Foundation Suisse de recherche sur le maladies musculaires (FSRMM) to M.L; the Swiss National Science Foundation (SNF 31003A_179371) and the European Joint Programme on Rare Diseases (EJP RD+SNF 32ER30_187505) to T.H.

Keywords: HSN1, ALS, Sphingolipids, Peripheral Neuropathy
C698R Lrsam1 knock-in mouse model for CMT2P

Poster No:
113a

Authors:
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Institutions:
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Introduction:
Missense mutation C694R in the RING domain of the LRSAM1 gene results in a dominantly inherited peripheral neuropathy, Charcot-Marie-Tooth disease type 2P (CMT2P). In this study, we have generated a C698R Lrsam1 knock-in mouse, which was extensively characterized.

Methods:
Mice with a heterozygous C698R Lrsam1 mutation were generated by CRISPR/Cas9 technology; and evaluated clinically using Rotarod and hindlimb clasping tests, physiologically by nerve conduction studies, morphologically on sciatic nerve semithin section, and its nerve regeneration via a crushed nerve injury model.

Results:
Heterozygous (Lrsam1+/C698R) and homozygous knock-in (Lrsam1C698/C698R) mice exhibited normal motor functions as determined by behavioral tests and normal nerve conduction studies. Axonal density and myelin thickness were not significantly different between mutants and wild-type mice by sciatic nerve morphometric analysis up to 17 months of age. However, after a crush nerve injury, Lrsam1+/C698R mice at 20 months of age had a mild but significantly reduced compound nerve action potential (CMAP) and conduction velocity (CV) during recovery.

Conclusions:
C698R mutation results in mild impairment of nerve regeneration in mice. Every person encounters numerous minor nerve injuries during life. Thus, an accumulative effect from the injuries may explain the late-onset axonal polyneuropathy in patients with CMT2P.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This research is supported by grants from the National Institute of Neurological Disorders and Stroke (R01NS115748) and the Department of Veterans Affairs (IBX003385A).

Keywords: Charcot-Marie-Tooth disease type 2P, Lrsam1 gene, Axonal degeneration, Knock-in mouse
In vitro anti-glycolipid antibody production by Guillain-Barré syndrome patients’ derived B cells

Poster No:
115a

Authors:
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Introduction:
Anti-ganglioside antibodies are found in approximately half of the patients with Guillain-Barré syndrome (GBS) and are presumed to initiate nerve damage. Antibody levels vary considerably between patients both at disease onset and during follow-up but the reason for this is unknown. We hypothesize that patients with high titer antibodies have circulating B cells which have the potential to produce anti-glycolipid antibodies in vitro.

Methods:
B cells from six GBS patients were sorted into plasmablasts and CD27+ and CD27- B cells. Cells were cultured in vitro with a cytokine cocktail ± CpG to stimulate antibody production. Anti-GM1 and anti-GQ1b antibodies were present in the serum of five and one patient respectively.

Results:
Anti-GM1 IgG antibodies were detected in the culture supernatant of peripheral blood plasmablasts from half of the patients. These cells did not require stimulation with CpG. Anti-GM1 IgG antibodies were also produced by CD27+ B cells from the same patients but only after CpG stimulation. CD27- B cells did not produce anti-glycolipid antibodies in vitro. Follow up samples were investigated from two patients who demonstrated in vitro anti-GM1 antibody production. In one patient anti-GM1 antibodies were still produced by plasmablasts and CD27+ cells isolated one week after start of treatment. Serum anti-GM1 IgG antibody titers only decreased by one (2-fold) dilution step or remained the same after one week in patients who demonstrated in vitro antibody production.

Conclusions:
These data indicate that GM1-specific B cells circulate in the peripheral blood of GBS patients at the time of hospitalization and, in some patients, remain present for at least one week. The presence of GM1-specific cells within the CD27+ population of B cells may suggest ongoing B cell activation and differentiation. The data provide a rationale for B-cell targeted therapy in case standard treatment is not effective in reducing pathogenic antibody levels.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support: GBS/CIDP Foundation International

Keywords: Guillain-Barre syndrome, B cells, Antibodies
Utilizing kinase inhibitors to ameliorate neurofilament aggregation in an iPSC-derived motor neuron model of Charcot-Marie-Tooth disease type 2E

Poster No:
117a

Authors:
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Introduction:
Charcot-Marie-Tooth disease type 2E is an autosomal dominant form of axonal CMT caused by missense variants in the NEFL gene. NEFL encodes neurofilament-light polypeptide (NF-L), a structural protein that is of critical importance in processes such as neuronal development, axonal radial growth and axoskeletal stability. We are specifically interested in the p.N98S variant of CMT2E, which results in a severe neuropathy with childhood onset. Our lab recently uncovered that iPSC-derived motor neurons from CMT2E NEFL N98S patients exhibit both widespread kinome dysregulation and protein aggregation phenotype (see Medina et al. abstract). Due to a serine substitution at position 98, we postulate that upregulated kinases could be responsible for aberrant NF-LN98S phosphorylation, as phosphoserines in NF-L head domain are known regulatory sites of NF-L assembly and disassembly.

Methods:
To this end, select kinases with either known roles of phosphorylating the NF-L head domain or roles in protein aggregation in related neuromuscular disorders were targeted for inhibition using small molecules. Supernatant NF-L was used to evaluate the effect of kinase inhibition on axonal integrity in both 2D and 3D Spinal Spheroid (SpS) iPSC-derived motor neurons from either CMT2E patients or healthy controls.

Results:
of six small molecules investigated to date, two compounds exhibited a therapeutic benefit by decreasing supernatant NF-L, while three compounds increased supernatant NF-L.

Conclusions:
Ongoing work includes automation of image analysis for NF-L aggregate quantification using the CellInsight CX5 HCS Platform. Additionally, kinases that have been computationally identified to phosphorylate mutant NF-L based on structural motif and human protein-protein interaction network analysis are currently being evaluated for supernatant NF-L reduction and aggregate reduction. Overall, identification of kinases involved in the progression of CMT2E is key to finding valuable druggable targets and may shed the light on the mechanism of CMT2E, which remains to be elucidated.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: iPSCs, Charcot-Marie-Tooth disease, axonal, Type 2E, Drug repurposing, Neurofilament, Kinase
Severe Congenital Myasthenic Syndromes caused by AGRIN mutations affecting secretion by motoneurons

Poster No:
118a

Authors:
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Introduction:
Congenital myasthenic syndromes (CMS) are predominantly characterized by muscle weakness and fatigability and can be caused by a variety of mutations in genes required for neuromuscular junction formation and maintenance. Among them, AGRN encodes AGRIN, an essential synaptic protein secreted by motoneurons. We have identified CMS patients with variants of unknown significance (p.R1671Q, p.R1698P and p.L1664P) in the LG2 domain of AGRIN. Possible effects of AGRN mutations in motoneurons had not been investigated yet. We report the characterization of in vitro and in vivo models to evaluate the pathogenicity of AGRN variants and investigate their potential pathophysiologic mechanisms.

Methods:
As mutations into proline predicted possible protein misfolding and secretion defects, we used the overexpression of mini-AGRIN and full-length AGRIN variants in neuroblastoma cell line, murine primary motoneurons culture, and in ovo embryonic motoneurons to investigate AGRIN variant subcellular localization and secretion efficiency. Finally, we used human motoneurons derived from a patient's induced pluripotent stem (iPS) cells to confirm our results and hypothesis.

Results:
AGRN variants overexpression studies in vivo and in vitro revealed that AGRIN is indeed partially misfolded, mislocalized and prevented normal secretion by motoneurons suggesting their pathogenicity. Conditioned media with AGRIN mutants trigger significantly less myotube cluster of acetylcholine receptors (AchR). Interestingly, mutant AGRIN secreted fraction was fully functional as a rescue of AGRIN content in the media rescue also the AchR cluster amount. Finally, patient motoneurons derived from iPS cells and coculture with human myotubes confirm the defect in AGRIN secretion at the neuromuscular junction.

Conclusions:
Our results show that AGRIN mutations can cause CMS by primarily affecting the ability of the presynaptic compartment to secrete AGRIN. Interestingly, secreted AGRIN mutants are still functional to trigger AchR cluster. Altogether this work opens a new therapeutic avenue that aims to facilitate AGRIN secretion.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: AGRIN, Congenital Myasthenic Syndrome, motoneuron, secretion defect, iPSC
Biomarkers associated with disease severity and outcome in Guillain-Barré syndrome: a prospective cohort study

Poster No:
119a

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Introduction:
Guillain-Barre syndrome (GBS) is an immune-mediated polyneuropathy with variable clinical manifestation, prognosis and outcome. Despite of the proven efficacy of intravenous immunoglobulin (IVIg), 20% patients remain disabled with 2-19% mortality. Biomarkers associated with disease prognosis and the clinical outcome of GBS have become important to improve clinical management and effective treatment at early stage of GBS. In current study, we investigated the biomarkers to predict the disease severity and clinical outcome in early phase of GBS.

Methods:
We included 107 GBS patients in a prospective cohort study during 2019-2021 in Bangladesh. Detailed neurological examinations, hematological parameters and serological markers investigations including serum albumin, IgG and C-reactive proteins were performed at baseline and pre-defined follow-up. Statistical comparisons between intended biomarkers and disease prognosis were performed using spearman correlation, ANOVA and student t-test.

Results:
The median age of 107 patients was 31 years (IQR: 22-40) with male predominance (67%); 43 patients were treated with IVIg, 20 with plasmapheresis and 44 patients received only supportive care. Hemoglobin and serum albumin levels were negatively correlated with GBS disability score at enrolment (p<0.001) and 4 weeks (p<0.001). Whereas, increased absolute neutrophil, neutrophil lymphocyte ratio (NLR) and C-reactive protein (CRP) were significantly correlated with disease severity at early stage of disease (p<0.001) and poor prognosis at 4 weeks (p<0.001). Serum albumin was significantly increased at 13 weeks and 26 weeks in both IVIg treated and supportive care patients; however, elevated serum albumin levels were not correlated with the clinical improvement of GBS. No significant correlation was observed between disease outcome and serum IgG levels, platelet, and liver function enzymes.

Conclusions:
Decreased hemoglobin, serum albumin, elevated neutrophil, NLR and CRP levels can be considered as potential early predictors in poor prognosis of GBS. Large sample size is required to validate the clinical relevance of these biomarkers in future.

References:
Yes
References 1:

References 2:

References 3:

References 4:

Grant Support: 5K43TW011447-03; Emerging Global Leader Award (K43) - Fogarty International, NIH, USA

Keywords: Guillain-Barre syndrome, Biomarkers, Disease severity, Clinical outcome, Prognosis
NCAM1 and GDF15 are biomarkers of Charcot-Marie-Tooth Disease in patients and mice

Poster No:
120a

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Introduction:
Molecular markers, scalable for clinical use are critical for the development of effective treatments for Charcot-Marie-Tooth disease (CMT). We identified proteins in the sera of mouse models of CMT1A (C61 het), CMT2D (GarsC201R, GarsP278KY), CMT1X (Gjb1-null) and CMT2L (Hspb8K141N), and from CMT patients with genotypes including CMT1A (PMP22d), CMT2D (GARS), CMT2N (AARS).

Methods:
We performed multitargeted proteomics on both sample sets to identify proteins elevated across multiple mouse models and CMT patients. Selected proteins and additional potential biomarkers, such as growth differentiation factor 15 (GDF15) and cell free mitochondrial DNA were validated by ELISA and quantitative PCR, respectively.

Results:
We propose that neural cell adhesion molecule 1 (NCAM1) is a candidate biomarker for CMT, being elevated in Gjb1-null, Hspb8K141N, GarsC201R and GarsP278KY mice, and in patients with demyelinating (CMT1A) and axonal (CMT2D, CMT2N) CMT. NCAM1 may reflect disease severity, demonstrated by a progressive increase in mouse models with time and positive correlation with neuropathy severity (CMTES) in patients. Serum NCAM1 may reflect muscle regeneration, triggered by denervation, which could potentially track disease progression or the effect of treatments. We found that member proteins of the complement system were elevated in Gjb1-null and Hspb8K141N mouse models,
as well as in patients with both demyelinating and axonal CMT. However, complement proteins did not correlate with patient severity (CMTES scale). Although the complement system does not seem to be a prognostic biomarker, elevated complement expression at the sarcolemma of CMT patients may indicate an involvement in pathophysiology. We also identify serum GDF15 as a highly sensitive diagnostic biomarker, which was elevated in all CMT genotypes as well as in Hspb8K141N, Gjb1-null, GarsC201R and GarsP278KY mouse models.

Conclusions:
Further large and longitudinal patient studies should be performed to establish the value of these proteins as diagnostic and prognostic molecular biomarkers for CMT.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: biomarkers, Charcot-Marie-Tooth disease, serum, proteomics, translational
Expanding the clinical spectrum: TTN mutations associated with neuropathy and neuropathic pain

Poster No:
121a

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Introduction:
The TTN gene is a large gene that encodes for titin, which plays an important role in the sarcomere. Although mutations in the TTN gene can cause several muscle disorders including cardiomyopathies and myopathies in general, the following abstract attempts to expand the clinical spectrum of TTN mutations by including the possibility of neuropathies being associated with TTN mutations.

Methods:
We report three unrelated individuals with known TTN mutations and one individual with a TTN variant who were evaluated with clinical, laboratory, electrophysiological, or genetic testing.

Results:
The mean age of onset was 40. All individuals reported neuropathic pain in their lower extremities. A woman who presented in her 50's had clinical and electrophysiological findings suggestive of Charcot Marie Tooth disease with bilateral foot drop and hand intrinsic weakness as well as sensory loss. One individual was a gentleman who presented in his 60's with breathing difficulties, shoulder, back and foot pain, and cardiac abnormalities with electrodiagnostic findings of a sensorimotor polyneuropathy. A young girl in her 20's had scoliosis, migraines, and back as well as foot pain who refused electrodiagnostic testing. The fourth individual was a young gentleman in his 20's who developed cramps, fasciculations and a sensorimotor polyneuropathy on exam; a muscle biopsy was performed and suggestive of denervation and neuropathic changes.

Conclusions:
The TTN gene is large with a complex structure. Given its large size, mutations in this gene may be associated with variable clinical presentations as well as neuropathies. Further investigation is indicated in expanding the clinical spectrum of TTN mutations.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, Neuropathy, TTN, neuropathic pain
Small Molecule HGF/MET Positive Modulator Effectively Reduces Pain-Related Behaviors in a Rat Diabetic Neuropathy Model

Poster No:
122a

Authors:
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Introduction:
Hepatocyte growth factor (HGF) signaling through the MET receptor promotes neuroprotective, neurotrophic, and anti-inflammatory mechanisms. We have developed a series of small-molecule compounds that are positive modulators (PMs) of HGF/MET to harness this system's therapeutic potential. This pathway is relevant to several chronic pain disorders, including diabetic neuropathy, which feature components of oxidative stress, nerve damage, and inflammation. Here, we investigate the in vivo efficacy of ATH-1019, an HGF/MET PM, in treating neuropathic pain in a rat model of streptozotocin (STZ)-induced diabetic neuropathy.

Methods:
Diabetes was precipitated with a single dose of STZ (55 mg/kg; IV). Neuropathic pain-related behaviors were established by day 14 post-STZ. ATH-1019 was administered once daily at 4 doses (1, 0.1, 0.025, and 0.00625 mg/kg; orally; n=12/group) from day 14 to 28. Mechanical allodynia was assessed using von Frey filaments (1.4, 4, 10, 15, 26, 48, 60 g). Thermal hyperalgesia was measured using a hot plate test (52.5°C). These behaviors were captured 1-hour post dose on days 21 and 28 (after 7 and 14 days of treatment, respectively). In addition, on day 25 (treatment day 11), behaviors were evaluated prior to dosing, at a time when ATH-1019 had been completely eliminated from plasma.

Results:
The increased mechanical allodynia observed in STZ-treated animals was effectively reversed by ATH-1019 after 7 and 14 days of treatment, with 67 and 78% recovery, respectively, at the best dose. ATH-1019 also reduced thermal hyperalgesia at these time points. These results were obtained with the compound still in circulation and could indicate acute and/or chronic effects of ATH-1019. Examining pain-related behaviors before dosing on day 11 of treatment revealed that ATH-1019 significantly modified pain even when fully cleared from the plasma.

Conclusions:
Overall, the HGF/MET PM ATH-1019 was found to significantly reduce pain-related behaviors at multiple doses in a rat model of STZ-induced diabetic neuropathy.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Neuropathy, Neuropathic pain, Hepatocyte growth factor, Streptozotocin-induced diabetes, ATH-1019
Distribution of resources to enroll participants with a dominant language other than English within the Inherited Neuropathy Consortium

Poster No:
123a

Authors:
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Introduction:
Diversity in research participants should be integral to the research process, beginning with natural history studies. A barrier to recruitment has been identified in the Diversity Core of the Inherited Neuropathy Consortium (INC): enrolling participants with a dominant language other than English (DLoE). Translation of consent forms and interpretation services may help increase the feasibility of participating in this cohort. This study aimed to assess the translation and interpreter services available at the worldwide enrolling sites of the INC.

Methods:
An electronic survey was distributed to all INC sites. The survey requested languages spoken of clinic staff, and whether document translation and/or interpreter services were available for both clinical and research purposes. A write in option was provided.

Results:
Fourteen sites completed the survey (response rate of 82%). The second and third most common languages were Spanish and Italian (three and two sites, respectively). Half of the respondents did not have clinic staff who spoke languages other than English. Only five of the seven sites (35.7%) with document translation services had the capacity to do so for research purposes. Four of these sites also had in-person interpreter services available for research; the remaining site, in addition to seven others, had virtual interpreter services available for research. Several sites (42.8%, n = 6) commented that, though interpreters are available for clinical visits, they might not be available for research visits due to lack of funding (n = 3), personnel (n = 1), or not specified (n = 2).

Conclusions:
When there are inconsistencies in translation and interpreter services at enrolling sites, large international multi-site studies can benefit from combining resources to enroll participants in their dominant language.

References:
Yes

References 1:
Inherited Neuropathy Consortium (INC)

References 2:
References 3:

References 4:

Grant Support: NIH, MDA, CMTA

Keywords: Diversity, Inclusion, Accessibility, Research participation, Charcot-Marie-Tooth
Allele-specific inactivation of dominant CMT2E mutations via CRISPR targeting common polymorphisms

Poster No:
124a

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Introduction:
We developed allele-specific CRISPR gene editing to inactivate a dominant NEFL mutation in human induced-pluripotent stem cells (iPSC) from a patient with CMT2E, achieving rescue of pathologic phenotypes in motor neurons. This is a promising therapeutic strategy for dominant axonal CMT, but targeting each individual mutation is not feasible. Targeting pairs of common polymorphisms for excision of disease alleles could enable a mutation-independent strategy.

Methods:
We generated iPSCs from CMT2E patients and healthy controls and performed whole genome sequencing. Cell lines heterozygous for common polymorphisms were transfected with ribonucleoprotein (RNP) complex of Cas9 with synthetic guide RNA. Genome editing was measured by targeted sequencing or by droplet-digital PCR. Motor neurons were differentiated from iPSC via inducible expression of a tripartite transgene integrated at a safe-harbor locus.

Results:
Directly targeting the NEFL-N98S mutation with RNP efficiently edited the mutant allele, while targeting NEFL-E396K produced minimal editing, thus necessitating an alternative strategy. Analysis of publicly available data revealed a haplotype block including the NEFL locus that contains a large number of common single nucleotide polymorphisms (SNP) that could be utilized for allele-specific excision to inactivate NEFL. Three of our CMT2E lines were heterozygous for this common haplotype, one with N98S and two with E396K mutations. Allele-specific RNP targeting SNPs flanking the NEFL gene were tested in pairwise fashion to identify those with the highest rates of allele-specific excision. Genome edited N98S and E396K cells were differentiated into motor neurons to measure mutant allele knockdown and phenotypic rescue.

Conclusions:
CRISPR gene editing designed to target pairs of common SNPs for DNA excision enabled allele-specific editing of a disease mutation that failed to be edited by direct targeting. This strategy could be deployed as a general therapeutic approach for a large percentage of patients independent of their individual disease mutations.

References:
No

References 1:

References 2:
References 3:

References 4:

**Grant Support:** Charcot Marie Tooth Association NINDS R01 NS119678-01  NIEHS U01 ES032673

**Keywords:** Charcot-Marie-Tooth, Induced Pluripotent Stem Cells, Motor Neurons, CRISPR, Gene editing
Preclinical evaluation of CLZ-2002, Neuronal Regeneration Promoting Cells in a CMT IA mouse model

Poster No:
125a

Authors:
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Introduction:
Charcot–Marie–Tooth (CMT) disease is a hereditary disease that occurs in 1 in 2,500 people, and the phenotype and genetic causes are very heterogeneous. CMT1A is a type of inherited neurological disorder that affects the peripheral nerves and is caused by having an extra copy (a duplication) of the PMP22 gene. Human tonsil-derived mesenchymal stem cells (TMSCs) are useful for stem cell therapy in various disease and can differentiate into Schwann cell-like cells (SCs).

Methods:
We investigated the potential of TMSC-SCs for peripheral nerve and muscle regeneration in C22 mice, a model for CMT1A. TMSC-SCs were manufactured in GMP facility and named Neuronal Regeneration Promoting Cells (NRPCs), CLZ2002 for development. We transplanted NRPCs into the bilateral thigh muscles in C22 mice and observed behavioral observation, sciatic nerve function test, nerve conduction test, and morphological analysis based on tissue staining and electron microscopy findings in C22 mice.

Results:
Motor functions of thigh muscles in NRPC-transplanted groups were much improved compared to the sham group at 12 weeks post-transplantation. Restoration of the sciatic nerve structure in C22 mice was observed using transmission electron microscope. The ratio of myelinated axons among total axons was significantly increased in the NRPC-transplanted groups compared to the sham group. The NRPC-transplanted groups had also significantly reduced G-ratio values compared to the sham group. Regeneration of sciatic nerve and muscle observed in all NRPC-transplanted groups, which was appeared in a dose-dependent manner.

Conclusions:
The sciatic nerve regenerations in C22 mice surely induced by remyelination of peripheral nerves following NRPCs transplantation. Transplantation of NRPCs could enable peripheral nerve and muscle regeneration in patients with CMT1A.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support: This research was supported by a grant from the Korea Health Technology R&D Project (HI20C0039), Ministry of Health and Welfare.

Keywords: Charcot-Marie-Tooth disease, Cell Therapy, Mesenchymal Stem Cells, Preclinical study, Schwann Cells
AAV9-MEDIATED POST-ONSET GENE REPLACEMENT THERAPY BENEFITS TRANSGENIC MODELS OF CMT1X NEUROPATHY

Poster No:
126a

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Introduction:
CMT1X is a common form of inherited demyelinating peripheral neuropathy resulting from mutations affecting the gap junction protein connexin 32 (Cx32). Patients with CMT1X express mutant forms of Cx32 in Schwann cells, that could potentially interfere with virally delivered wild type (WT) Cx32 through dominant-negative effects. In previous work we showed improvements in pre-onset treated R75WKO and N175DKO models of CMT1X expressing Golgi-retained mutant Cx32.

Methods:
In order to study the efficacy of post-onset AAV9-mediated gene addition therapy to rescue the demyelinating neuropathy in CMT1X models, we delivered by lumbar intrathecal injection an AAV9 carrying the GJB1 gene under the myelin protein zero promoter (Mpz) in 6-month-old mutant mice expressing the R75W or N175D mutations on a Gjb1-null background. Assessment of therapeutic effect was performed 4 months after treatment at the age of 10 months, by behavioral, electrophysiological and morphological studies.

Results:
Post-onset treated R75WKO and N175DKO mice showed improvement in the force generated by the hindlimbs but not in the rotarod analysis. Improvement was also detected in electrophysiological analysis where motor nerve conduction velocities were improved. Finally, morphological analysis indicated improvement in all PNS tissues examined in both mutant lines.

Conclusions:
In conclusion this study provides additional proof of principle for a clinically translatable gene therapy to treat CMT1X also after the onset of the neuropathy even in the presence of endogenously expressed Golgi-retained Cx32 mutants.

References:
No

References 1:

References 2:

 References 3:

References 4:
**Grant Support:** The project was co-funded by Muscular Dystrophy Association (Grant MDA 603003 to KAK) and Charcot-Marie-Tooth Association

**Keywords:** Gene therapy, Schwann cells, Charcot-Marie-Tooth disease, AAV9
IVIg-exposure and thromboembolic event risk: findings from the UK Biobank

Poster No:
127a

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Introduction:
Arterial and venous thromboembolic events (TEEs) have been associated with intravenous immunoglobulin (IVIg) use. We previously calculated the risk of TEEs associated with exposure to IVIg and now present the impact of IVIg on overall TEE risk. In the UK guidelines, low risk is <10% incidence of cardiovascular disease within the next 10 years and high risk is ≥20% probability of event within the next 10 years.

Methods:
We included participants from UK Biobank recruited over 3 years (n=502, 492). The study endpoints were incidence of myocardial infarction, other acute ischemic heart disease, stroke, pulmonary embolism, and other venous embolism and thrombosis. Predictors included known TEE risk factors: age, sex, diagnosis of hypertension, smoking status, type 2 diabetes mellitus, hypercholesterolemia, cancer, and past history of TEE. IVIg was added in the sensitivity analysis.

Results:
In the prior TEE category, IVIg exposure was independently associated with increased risk of incident TEE (OR= 3.69, p=0.03) on multivariate analysis. The number needed to harm by exposure to IVIg in this group was 5.8 (95% CI, 2.3-88.3). IVIg exposure did not increase risk of TEE in those without previous history of TEE. If everyone in the past history group was exposed to IVIg, then the median risk of recurrent event in those <60 years of age increases from 6.1% to 19.3% and in those >60 from 9.1% to 26.9% (moving nearly 50% of individuals into >20% risk of recurrent TEE). A similar change in risk was seen if the cohort was divided by gender.

Conclusions:
IVIg is associated with increased risk of further TEE in individuals with prior history of an event with one further TEE for every 6 people exposed. In practice, this will influence how clinicians consent for and manage overall TEE risk upon IVIg exposure in patients already at increased risk.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: immunoglobulin, cardiovascular risk, thromboembolic disease
Utility of Plasma Neurofilament Light Chain in Determining Subclinical Disease Activity in Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Poster No:
128a

Authors:
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Introduction:
To explore associations between plasma neurofilament light chain (pNfL) and disease activity in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and examine its usefulness in determining disease remission.

Methods:
We examined pNfL in untreated CIDP patients (n=10) before and after intravenous immunoglobulin (IVIg) induction treatment, differences in pNfL in patients on maintenance IVIg treatment (stable patients n=15, unstable patients n=9), and in clinically stable IVIg treated patients (n=10) in whom we stopped IVIg to determine their disease activity and need for maintenance IVIg.

Results:
Untreated patients with CIDP: pNfL was significantly higher in patients than an age-matched, healthy control group and comparable to control group values post IVIg induction. Clinically stable and unstable patients with CIDP on IVIg treatment: pNfL was significantly greater in unstable patients than stable patients. A pNFL value above 16.6 pg/mL identified unstable treated CIDP from stable treated CIDP (sensitivity= 86.7%, specificity= 66.7%, area under ROC= 0.73). Treatment withdrawal group: There was a strong and statistically significant correlation between pNfL concentration at time of IVIg withdrawal and the occurrence of relapse, suggesting an association of higher pNfL with active disease.

Conclusions:
pNfL concentrations may be a sensitive, clinically useful biomarker in assessing subclinical disease activity.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: neurofilament light chain, CIDP, disease activity, remission
Neurodegeneration in HSAN1 due to ATL1 (Gly66Gln) mutation is associated with defective ER-protein quality control and compromised autophagy

**Poster No:**
129a

**Authors:**
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**Introduction:**
Atlastin-1 (ATL1) functions as a GTPase and is crucial for endoplasmic reticulum (ER) shaping and ER-microtubule interactions. Mutations in ATL1 have been reported to cause hereditary sensory and autonomic neuropathy type 1D (HSAN1D) as well as hereditary spastic paraplegia 3A (SPG3A). ATL1 mutation have been linked to abnormal ER morphology; still the molecular pathomechanism of defective ER structures and their pathological consequences contributing to HSAN1D and SPG3A have not been investigated in detail so far.

**Methods:**
We used biochemical and immunocytochemistry approaches followed by live cell imaging in cell culture models overexpressing normal and mutant ATL1 proteins. We corroborated our findings with comparative ultrastructural analysis on cell culture models and on biopsy samples.

**Results:**
We observed that over-expression of mutant ATL1 (Gly66Gln) forms protease resistant large, globular ER associated aggregates in cell culture models, which further leads to ER stress and structural abnormalities of ER and associated compartments. Interestingly while endogenous ATL1 protein is degraded by ubiquitin proteasome system (UPS), mutant ATL1 impairs UPS, induces proteotoxicity and cell death. Autophagy, which activates as a compensatory mechanism, also compromises at multiple steps, probably due to deformities of ER and persistent proteotoxic stress. Extensive workup of skin, sural nerve and muscle biopsy material of a rare Gly66Gln HSAN1 patient revealed prominent loss of myelinated and unmyelinated sural nerve fibres, but only minor neurogenic muscular atrophy. Ultrastructural analysis on this biopsy revealed signs of altered autophagy in axons as well as prominent alterations of Schwann cell nuclei/nuclear envelope. In line with this, HSAN1 patient's fibroblasts showed similar defects.

**Conclusions:**
Overall, our results support the notion that neurodegeneration in HSAN1 due to ATL1 mutation is closely linked with the deformed ER and associated functions including autophagy. Neurons and distal axons are particularly vulnerable to such pathomechanism, thus explaining the degenerative phenotype in HSAN 1 and related diseases.

**References:**
No

**References 1:**
References 2:

References 3:

References 4:

Grant Support:

Keywords: Atlastin-1, HSAN1, ER stress, proteotoxicity
COVID-19 vaccination and Guillain-Barré syndrome: analyses using the National Immunoglobulin Database

Poster No:
130a

Authors:
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Introduction:
Vaccination against viruses has rarely been associated with Guillain-Barré syndrome (GBS). Association with COVID-19 vaccination is unknown. We performed a population-based study of National Health Service (NHS) England data and a UK multicentre surveillance study, to investigate the relationship between COVID-19 vaccination and GBS.

Methods:
Firstly, we present a retrospective analysis of every GBS patient in England in the National Immunoglobulin Database (NID) linked with COVID-19 vaccination data. NID GBS cases December 2020 – July 2021 were linked to data from England's National Immunisation Management System (NIMS) to identify COVID-19 vaccination exposure. For the NID/NIMS linked dataset, GBS temporally associated with any COVID-19 vaccine within a 6-week risk window were identified. Secondly, we prospectively collected incident UK GBS cases January – November 2021 in a separate multicentre surveillance database regardless of vaccine exposure, and explored GBS phenotypes to identify COVID-19 vaccine-associated GBS features.

Results:
996 GBS cases were recorded in the NID January–October 2021. A spike of cases above the 2016-2020 average occurred in March–April 2021. In England, among all GBS cases, 198 occurred within 6 weeks of first-dose COVID-19 vaccination (0.618 cases per 100,000 vaccinations, 176 ChAdOx1 nCoV-19, 21 tozinameran, 1 mRNA-1273). Excess GBS cases occurred with a peak at 24 days; first-dose ChAdOx1 nCoV-19 accounted for the excess. The absolute number of excess GBS cases was 98-140 cases for first-dose ChAdOx1 nCoV-19 January–July 2021. First-dose tozinameran and second-dose any vaccination showed no excess GBS risk. The separate multicentre surveillance dataset (121 patients) identified no phenotypic or demographic differences between vaccinated and non-vaccinated cases.

Conclusions:
First-dose ChAdOx1 nCoV-19 vaccination is associated with excess GBS risk of 0.576 (95%CI 0.481-0.691) cases per 100,000 doses. No specific clinical features, including facial weakness, are associated with vaccination-related GBS compared to non-vaccinated cases. The pathogenic cause of the ChAdOx1 nCoV-19-specific first-dose link warrants further study.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: COVID-19 vaccination, Guillain-Barre syndrome
Creation of a preliminary POEMS-specific RODS using the UK POEMS cohort

Poster No:
131a

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Introduction:
The Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein and Skin changes syndrome (POEMS) is a rare haematological condition which almost always manifests with a typical neuropathy, which may be very disabling. At present, no disability scales exist which are specific to POEMS. We intend to use our national UK POEMS cohort to create a preliminary POEMS-specific Rasch-built Overall Disability Scale (RODS).

Methods:
A 146-point activity questionnaire, which has been used in the creation of various other RODS, will be administered to our national POEMS cohort in the UK. Recruitment is ongoing and we are aiming for over 30 responses. Obtained data will be subjected to Rasch analysis. Items displaying misfit statistics, disordered thresholds, item bias or local dependency will be systematically removed.

Results:
We aim to create an initial POEMS-RODS of between 20 and 30 items fulfilling model expectations and with good validity and reliability.

Conclusions:
We will present an initial POEMS-RODS and discuss our plans to validate this with a larger international cohort.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: POEMS, Rasch
Acute Inflammatory Demyelinating Polyneuropathy with Reversible Conduction Failure: a Manifestation of Nodopathy

Poster No:
132a

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Introduction:
Reversible conduction failure (RCF) has been reported in acute motor axonal neuropathy (AMAN) and it has been regarded as one of the signs of nodopathy. Several reports of RCF in acute inflammatory demyelinating polyneuropathy (AIDP) suggested that AIDP could be a manifestation of nodopathy. We conducted this study to find the frequency of RCF in AMAN and AIDP and to compare the clinical features between AMAN and AIDP with or without RCF.

Methods:
We enrolled 63 patients with AMAN or AIDP from January 2011 to January 2021 retrospectively. Diagnosis of AMAN/AIDP with or without RCF was based on serial electrodiagnostic findings (within 2 weeks and 1 month) according to Uncini's criteria. Disabilities were evaluated at nadir, one month, and six months after onset by Hughes functional grading scale. The clinical features and results of anti-ganglioside antibody tests were obtained by chart review.

Results:
Among 63 patients, 36 patients were diagnosed as AMAN (57.1%) and 27 patients were diagnosed as AIDP (42.9%). RCF was observed in 14 out of 36 (38.9%) in AMAN and 5 out of 27 (18.5%) in AIDP. Onset age of AIDP with RCF (47.6±14.7) was significantly lower than that of AIDP without RCF (65.0±14.4) and it was similar with AMAN with RCF (50.7±13.5). Diarrhea was more frequent in AIDP with RCF and AMAN than in AIDP without RCF as preceding infection. There were no significant differences in frequency of anti-ganglioside antibody status among the groups.

Conclusions:
AIDP with RCF was not rare and AIDP with RCF was comparable with AMAN with RCF in terms of clinical features. AIDP could be one of the manifestations of nodopathy. The dichotomous current electrodiagnostic criteria, classifying demyelinating or axonal neuropathy, is not sufficient to define nodopathy and further study is needed to revise electrodiagnostic criteria of Guillain-Barré syndrome.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** acute inflammatory demyelinating polyneuropathy, reversible conduction failure, nodopathy, Guillain-Barré syndrome, electrodiagnostic criteria
Chemical tools to Investigate the Molecular Mechanisms of HDAC6 in Health and Disease

Poster No:
133a

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Introduction:
Histone deacetylase 6 (HDAC6) modulates a variety of non-histone substrates such as α-tubulin, Miro1 and ubiquitin, and is involved in protein degradation. Pharmacological inhibition of HDAC6 rescues axonal transport deficits in several models of peripheral neuropathies. However, we still lack knowledge of the underlying mechanisms and expression patterns of HDAC6.

Methods:
We designed and synthesized a library of fluorescent HDAC6 ligands based on structure-activity relationships of known HDAC6 inhibitors. The chemical probes were evaluated for HDAC6-selectivity in multiple biochemical assays and live cell imaging.

Results:
A first generation of fluorescent HDAC6 compounds was successfully designed and synthesized. Inhibition of HDAC6 was demonstrated by increased acetylation-levels of α-tubulin in neuronal-like cells and biochemical in vitro assays. The fluorescent ligands stain the cytoplasm in both fixed and living cells and we evaluated their pharmacodynamic properties. Optimized imaging properties (i.e. signal-to-background ratio and brightness) allowed visualization of endogenous HDAC6 in living cells. We detected an increased signal when overexpressing HDAC6 in cells, further implying selectivity of the ligand. Live tracking of the fluorescent compound visualized compartments moving between the cell soma and neurites in iPSC-derived motor neurons. Taken together, our findings indicate the fluorescent compound visualizes HDAC6. Further evaluation in disease-relevant, cell-based and animal-based models will be performed.

Conclusions:
With this imaging tool, we will be able to monitor endogenous HDAC6 localization, distribution and dynamics in a live cell environment. This will lead to a deeper understanding of the mechanisms of HDAC6 inhibition, its rescue of axonal transport deficits and its therapeutic potential in peripheral neuropathies.

References:
Yes

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: HDAC6, live-imaging, motor neuron, chemical biology, fluorescent
CSF IL-8 In Acute And Chronic Inflammatory Polyneuropathies

Poster No:
134a

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Introduction:
There is a lack of reliable biomarkers for acute and chronic inflammatory polyneuropathies. Interleukin-8 (IL-8) is released by activated macrophages and acts as a neutrophil chemoattractant. Our pilot proteomics study revealed high levels of IL-8 in cerebrospinal fluid (CSF), but not in plasma in a small GBS cohort. To further investigate the roll of IL-8 in inflammatory polyneuropathies we preformed this study.

Methods:
Study population: Guillain-Barré syndrome (GBS, n=26), chronic inflammatory demyelinating polyneuropathy (CIDP, n=23), paraproteinemia-related demyelinating polyneuropathy (PDN, n=6), multifocal motor neuropathy (MMN, n=6), healthy controls (HC, n=44), non-inflammatory polyneuropathies (NIP, n=29), multiple sclerosis (MS, n=33), amyotrophic lateral sclerosis (ALS, n=31). Study design: retrospective cohort study. CSF was analyzed with ELISA method prior to and following immunomodulatory treatment.

Results:
1] IL-8 levels in GBS were higher compared to all subtypes of chronic inflammatory polyneuropathies (CIDP, PDN, MMN), and all control groups. 2] IL-8 levels in CIDP and PDN were higher compared to HC. 3] Post-treatment levels of IL-8 in GBS were lower than pre-treatment levels. However, in CIDP, post-treatment IL-8 levels remained as high as pre-treatment levels, and also higher compared to that in HC. 4] IL-8 levels correlated with impairment in GBS 0-12 months after diagnosis and at 18 months in CIDP.

Conclusions:
CSF IL-8 could be used as a diagnostic biomarker in patients with GBS, CIDP, and PDN, and a prognostic biomarker in patients with GBS and CIDP. Cerebrospinal IL-8 activation seems to be specific to immune-mediated polyneuropathies, but not immune-mediated disorders of the central nervous system, i.e., MS. IL-8 levels in the CSF reduce after immunomodulatory treatment in GBS. Further studies: Further investigation of IL-8 signaling pathways and it’s role in the pathogenesis of inflammatory polyneuropathies is called for.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: biomarker, interleukin-8, inflammatory polyneuropathies
A study of endemic sensory, optic and auditory neuropathy in the UK Black Caribbean community

Poster No:
135a

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Introduction:
Endemic optic, sensory and auditory neuropathy (Strachan's disease) is seen in black African and Caribbean individuals following dietary restriction. The syndrome has been defined clinically and histologically in Tanzania and also in Cuba following the fall of the former USSR. Despite vegan and vegetarian diets being common amongst British Caucasians and parts of the subcontinent, Strachan's disease is uncommon in these communities. The purpose of this study was to describe the clinical features of a UK cohort of Strachan's disease.

Methods:
The clinical, genetic, metabolic and pathological features of a cohort of UK patients with Strachan's disease were collected from five neuroscience centres in the UK.

Results:
Sixteen patients were identified with a clinical diagnosis of Strachan's disease (4 males and 12 females). All patients were black Caribbean and presented with a painful sensory axonal neuropathy. 15 out of 16 had bilateral optic neuropathy and four had sensorineural hearing loss. The cohort included two sets of unrelated siblings. Urine organic acid profiles measured acutely revealed raised ethylmalonic acid and urine lactate. Screening for known mitochondrial DNA and nuclear mitochondrial mutations was negative. Muscle biopsies from five patients revealed a reduction in mitochondrial DNA copy number in one and ragged red fibres in another. Perivascular inflammatory cell infiltrate was evident in four out of ten sural nerve biopsies. Acute treatment with high dose B vitamins appeared to halt progression and in some resulted in symptomatic improvement.

Conclusions:
Strachan's disease is a cause of acute onset sensory and optic neuropathy in UK black Caribbean individuals. This study suggests that the disease is driven in part by mitochondrial dysfunction precipitated by nutritional deficiency and catabolic stress. The occurrence of the syndrome in siblings suggests a genetic predisposition.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Strachan's, sensory neuropathy, optic neuropathy, genetic
Involuntary movements in Multifocal Motor Neuropathy (MMN) are associated with a marked reduction in axonal fast K+ currents

Poster No: 136a

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Introduction: We aimed to assess the changes in axonal membrane excitability associated with involuntary movements in Multifocal Motor Neuropathy (MMN). MMN patients can develop fasciculations, myokymia, and pseudodystonia1, 2. Axonal excitability studies just distal to conduction block (CB) were abnormal3 although the link to involuntary movements has not been established.

Methods: EMG, ultrasound (US), nerve conduction studies, and axonal excitability at the wrist by threshold tracking and mathematical modelling4 were studied in 2 cases of MMN with proximal conduction block (CB) of the median and ulnar nerves and with involuntary movements of hand muscles. A group of 7 MMN patients without involuntary movements were used as controls.

Results: EMG showed neurogenic MUPs, fibrillations, fasciculations, trains of discharges, and loss of motor units in the right abductor pollicis brevis (APB). Motor CB and temporal dispersion were present in the ulnar and median nerves at the axilla, whereas sensory conduction was normal. The US showed enlargement of the nerves at the axilla and brachial plexus but normal caliber at the wrist. As compared to MMN patients without involuntary movements, the MMN patients with involuntary movements showed larger peak threshold deviations during depolarizing electrotonus and a larger superexcitability during the recovery cycle. These excitability abnormalities at wrist could be modeled as a 4.5-fold reduction in the axonal fast K+ currents.


References: No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Multifocal Motor Neuropathy, Spontaneous activity, Involuntary movements, Excitability, Potassium current
A new mouse model of CMT2Z with a MORC p.S87L mutation

Poster No:
137a

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Introduction:
The microrchidia (MORC)-family CW-type zinc finger 2 (MORC2) gene is related to DNA repair, adipogenesis and epigenetic silencing via the human silencing hub (HUSH) complex. The MORC2 gene missense mutation is known to cause peripheral neuropathy of Charcot-Marie-Tooth disease type 2Z (CMT2Z). However, there have been reports of peripheral and central neuropathy in patients. The etiology of MORC2 mutation-mediated neuropathy remains uncertain. In vivo studies using appropriate animal models are essential to study the mechanism and therapeutic approaches.

Methods:
Although genetically engineered mouse models of CMT have been developed, no mice with p.S87L have been developed. We established Morc2a p.S87L mutant mice. We examined motor skills of Morc2a p.S87L mice using rotarod performance tests, Hindlimb clasping analysis, and Y-maze spontaneous alternation test. Nerve conduction studies (NCSs) were performed. The sciatic nerves from wild type mice and Morc2a p.S87L mutant mice were biopsied, and pathological examinations were performed using light and electron microscopy.

Results:
Because the Morc2a p.S87L missense mutation leads to severe neuropathy in humans, we selected p.S87L as a target mutation in the design of our mouse model. Morc2a p.S87L mice displayed the clinical symptoms expected in human CMT2Z patients, such as axonal neuropathy, muscle atrophy and weakness. Notably, we observed severe central neuropathy with cerebella ataxia, cognition disorder and motor neuron degeneration in the spinal cord. Morc2a p.S87L mice develop peripheral and central neuropathies associated with neuronal DNA damage and apoptosis, followed by p53/cytochrome c/caspase 9/caspase 3-mediated apoptosis.

Conclusions:
This study presents a new mouse model of CMT2Z with a Morc2a p.S87L mutation. We suggest that neuronal apoptosis is a possible target for therapeutic approach in MORC2 missense mutation.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

**Keywords:** Neuronal apoptosis, CMT2Z, DIGFAN, Morc2a, S87L
Fat fraction and Cross-sectional area analysis of the sciatic nerve in Charcot-Marie-Tooth disease type 1A patients using MRI

Poster No:
138a

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Introduction:
CMT type 1A (CMT1A) results from duplication of the peripheral myelin protein 22 (PMP22) gene on chromosome 17. CMT1A is a demyelinating neuropathy, that typically demonstrates nerve hypertrophy as an increased cross-sectional area (CSA) on imaging studies compared with normal controls. Our purpose in this study was to assess the fat fraction (FF) and CSA of the sciatic nerve in CMT1A patients using Dixon-based proton density fat quantification MRI and to elucidate its potential association with clinical parameters.

Methods:
Thigh MRIs of 18 CMT1A patients and 18 age- and sex-matched volunteers enrolled. Analyses for FF and CSA of the sciatic nerve were performed at three levels (proximal, middle, distal). CSA and FF were compared between the two groups and among the different levels within each group. The relationship between the MRI parameters and clinical data were assessed in the CMT1A patients.

Results:
The CMT1A patients showed significantly higher FF at level 3 (p = 0.0217) and significantly larger CSA at all three levels compared with the control participants (p < 0.0001). Comparisons among levels showed significantly higher FF for levels 2 and 3 than for level 1 and significantly larger CSA for level 2 compared with level 1 in CMT1A patients. CSA at level 3 correlated positively with the CMT neuropathy score version 2 (CMTNSv2).

Conclusions:
In conclusion, the sciatic nerve FF of CMT1A patients was significantly higher at level 3 compared with both the controls and the measurements taken on more proximal levels. Our result showing a distal tendency for increased FF in CMT1A patients could suggest a distal predominance of increased interfascicular fat. Sciatic nerve CSA at level 3 correlated significantly and positively with CMTNSv2, suggesting its potential value as an imaging marker for clinical severity.

References:
No

References 1:

References 2:
Keywords: Charcot-Marie-Tooth disease, cross sectional area, Intraepineurial fat quantification, CMT1A, sciatic nerve
Addressing Diversity, Equity and Inclusion within the Inherited Neuropathy Consortium

Poster No:
139a

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Introduction:
The Inherited Neuropathy Consortium (INC) Diversity Committee is working to address representation of underserved demographic groups among subjects enrolled in the INC and related networks, in turn improving delivery of clinical care to patients with Charcot-Marie-Tooth disease (CMT) from these populations. Our committee is comprised of 10 members including six members from four INC sites in three countries who represent several disciplines and roles within the consortium. The other four committee members are leaders from major CMT patient advocacy groups in the United States and Italy.

Methods:
Our committee frequently collaborates with the Rare Disease Clinical Research Network (RDCRN) Diversity committee to share efforts and ideas across all RDCRN consortia. Current committee initiatives include (1) Implementing the use of updated and more descriptive race/ethnicity sub-categories that can be used in the United States, the United Kingdom, Italy and Australia; (2) Assessing knowledge and comfort levels for study team members who collect demographics data; (3) Developing and validating CMT-specific virtual assessments into Spanish and Italian; (4) Providing resources for document translation and visit support to sites with staff who are bilingual and able to serve as centers for virtual enrollment and assessment of non-English speakers, and (5) Creating and developing the INC Diversity Intern position.

Results:
Collaborations with other groups outside of the INC are aimed at helping other consortia build their own diversity committees and sharing information and project ideas that may be applicable to a broader patient population. Collaborators include NeuroNext, Accelerate Clinical Trials in Charcot-Marie-Tooth Disease (ACT-CMT), the Asian Oceanic Inherited Neuropathies Consortium (AOINC), and the Rare Disease Clinical Research Network (RDCRN) Cross Consortia Collaboration Committee.

Conclusions:
Future plans include initiatives aimed at addressing diversity among investigators, site staff, students, and our committee itself, development of marketing materials aimed at specific populations, and collaborations with patients.

References:
No
Grant Support: The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01). The INC also receives funding from the Muscular Dystrophy Association and the Charcot-Marie-Tooth Association.

Keywords: Diversity
Serum Neurofilament Light Chain Associated With Outcome In Guillain-Barré Syndrome Across Regional And Disease Spectrums

Poster No:
140a

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Introduction:
Guillain-Barré syndrome (GBS) is an acute classical complement-mediated peripheral nerve disease with a diverse regional presentation. Neurofilament light chain (NfL), a biomarker of neuronal damage, is elevated in GBS.

Methods:
Serum samples were collected prospectively from 35 healthy controls and 97 GBS patients, 82 from Bangladesh and 15 from Europe and North America (EU/NA). Patients ≥17 years, with onset of weakness ≤2 weeks and a GBS disability score (GBS-DS) of ≥3 were included. Serum NfL (sNfL) was assessed using single-molecule array and its association with GBS-DS was evaluated by Spearman's coefficient, unadjusted for known prognostic factors and irrespective of treatment administered.

Results:
All patients had elevated sNfL, which correlated with GBS-DS (r=0.5395, p<0.0001), peaked 12.5 days after admission, declined by week 4, and normalized by week 26. Baseline mean sNfL was 932.1±1274.2 pg/mL (1-1200x controls). In this monophasic disease, peak sNfL (psNfL) provided more informative correlations than baseline sNfL with GBS severity (r=0.136, p<0.001), age (r=-0.371, p<0.001), ability to improve in GBS-DS at week 4 (r=0.480, p<0.0001) or 8 (r=0.351, p<0.001), and GBS-DS at month 6 (r=0.55, p<0.0001). Higher psNfL was seen in patients with acute motor axonal neuropathy (AMAN) vs. acute inflammatory demyelinating polyneuropathy (AIDP) (1986.0 vs. 1050.0 pg/mL; p=0.07). At 6 months, 45.6% of patients could run (GBS-DS≤1), displaying a median psNfL of 362.2 vs. 1417.0 pg/mL (p=0.0025). Consistent with a psNfLBangladesh:psNFLEU/NA ratio of 5.95, median psNfL was 766.0 vs. 2298.0 pg/mL (p=0.088) in Bangladesh and 182.2 vs. 455.1 pg/mL (p=0.142) in EU/NA. These levels corresponded with the 40th percentile rank in sNfL distribution in both populations, which were similar in electrophysiological subtypes.

Conclusions:
Serum NfL mirrored disease course and correlated with severity, axonal variants, and functional outcome in a heterogeneous population. Integration of sNfL in a universal GBS disease model is warranted.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support: Annexon Biosciences, Inc.

Keywords: Guillain-Barré syndrome, neurofilament light, prognostic biomarker, complement
A Rare Case of Long-Standing Multifocal Motor Neuropathy and concomitant Waldenstroms macroglobulinemia and Anti-MAG Neuropathy

Poster No:
141a

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Introduction:
Multifocal motor neuropathy (MMN), Waldenstroms macroglobulinemia (WM) and anti-MAG (anti-myelin-associated-glycoprotein) neuropathy are rare conditions with distinct clinical presentations. We present a case of previously unreported concomitant MMN with anti-ganglioside IgM antibodies (anti-GM1) together with WM neuropathy with anti-MAG antibodies.

Methods:
This report evaluates a case of a 63-year-old male who presented with over a ten year history of progressive muscle weakness which started in his distal upper extremities. Three years prior to initial visit he developed right foot drop and an unstable gait.

Results:
Examination was significant for distal greater than proximal weakness in bilateral upper and lower extremities. He had atrophy throughout his forearms and hand intrinsics, absent reflexes throughout and a wide based gait with slap foot on the right. He had minimal sensory deficits of left upper extremity. Electrodiagnostic studies revealed a chronic, severe, non-length-dependent sensorimotor, demyelinating more than axonal, polyneuropathy. Laboratory workup revealed significantly elevated GM1 IgM antibody, IgM kappa monoclonal gammapathy and elevated anti-MAG antibodies. Bone marrow aspiration and biopsy suggested diagnosis of indolent B-cell lymphoma, leading to the diagnosis of WM.

This patient's clinical course and workup is suggestive of a long-standing history of multifocal motor neuropathy accounting for his progressive muscle weakness with a superimposed more recent sensory neuropathy associated with WM and anti-MAG antibody. He was first started on rituximab, cyclophosphamide and dexamethasone, later started on intravenous immune globulin.

Conclusions:
This is the first report of this combination of rare autoimmune neuropathies and antibody profile that includes MMN, WM, anti-MAG, and anti-GM1 antibodies.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** Multifocal motor neuropathy, Waldenstrom's macroglobulinemia, Anti-MAG neuropathy
Various Peripheral Nerve Complications Associated with COVID-19 Vaccination: a case study

Poster No:
142a

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Institutions:
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Introduction:
COVID-19 vaccination plays a key role in defeating the pandemic worldwide. It is clear, that benefits of all approved COVID-19 vaccines outweigh the risks. Nevertheless, we should be aware of the vaccination-associated complications. Multiple organ systems can be affected, one of them being the peripheral nervous system. We are presenting three patients with peripheral nerve involvement following the administration of mRNA COVID-19 vaccine.

Methods:
We have performed throughout clinical neurologic examination followed by electromyography (EMG) and lumbar puncture (LP) with cerebrospinal fluid (CSF) analysis in three patients (one female, two males) who were hospitalized at our department.

Results:
The first patient, 42 years old male, with acute onset of weakness of the whole body one week after the first dose of mRNA vaccine was diagnosed with acute inflammatory demyelinating polyneuropathy (AIDP). The second patient, 50 years old male, with acute onset of L5 radicular syndrome two weeks after the first dose of mRNA vaccine was diagnosed with postvaccination radiculitis. The third patient, 56 years old female, with slowly progressing paresthesia and weakness of all limbs over three months after the second dose of mRNA vaccine was diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP). In all patients serum anti-ganglioside antibodies were positive. Albuminocytologic dissociation in CSF was present in the first two patients. The first patient was successfully treated with plasmapheresis, the other two patients received IV and oral corticosteroids with prompt clinical improvement.

Conclusions:
Peripheral nerve complications associated with COVID-19 vaccination are rare, but they might be severe. Clinical history together with EMG and CSF analysis are important for confirmation of the diagnosis. The treatment, if started early, can be very effective. We should be aware of such vaccination-associated complications to diagnose them and treat them as soon as possible.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: COVID-19, mRNA, vaccine, complication, GBS
Coincidence of Acute Inflammatory Demyelinating Polyneuropathy and SORD Neuropathy: a case study

Poster No:
143a

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Introduction:
Two brothers with clinical symptoms of hereditary neuropathy (HNP) were referred to our Center. The clinical symptoms in the older brother (16 years old) were mild (toe walking, contractures of Achilles tendons, hammer toes) and showed slow progression. The younger brother (10 years old) was almost asymptomatic except for development of foot deformity (pes equinovarus) and clinically occasional stumbling. After a foot surgery his clinical symptoms worsened rapidly resulting in persistent quadriparesis. Genetic cause of HNP with participation of acute inflammatory demyelinating polyradiculoneuropathy (AIDP) was considered in the younger brother.

Methods:
In both brothers clinical and paraclinical examinations were performed. Analysis of particular genes was followed by a custom neuromuscular gene panel analysis and whole-exome sequencing (WES) afterwards. The results were verified by Sanger sequencing. Detailed immunological and cerebrospinal fluid examination and magnetic resonance imaging (MRI) of lumbosacral spine were added in the younger brother with a one-year delay from the deterioration.

Results:
EMG findings worsened and changed extensively during the rapid deterioration in the younger brother. Cerebrospinal fluid analysis showed mild elevation of protein levels, normal white blood cell count and blood-brain barrier disorder; serum anti-sulfatide antibodies were positive. The MRI of the spine was normal. Intravenous immunoglobulin therapy was given with the delay with minimal clinical effect. After a couple of years, WES analysis revealed two causal variants p.Ala153Asp (c.458C>A) and p.Ala253Glnfs*27 (c.757del) in heterozygous state in the SORD gene in both brothers.

Conclusions:
The SORD variants explained HNP in both brothers. The rapid worsening and the progression of upper limb weakness is ascribed to coincidence of HNP and AIDP in the younger brother. Even in patients with HNP we should be vigilant when an abnormal deterioration of the clinical symptoms occurs. In such a case, the possibility of coincidence of HNP and AIDP should be considered.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support: MEYS 8F20002 under the frame of EJP RD, the European Joint Programme on Rare Diseases. In addition, this project has received funding from the European Union’s Horizon 2020 research and innovation programme under the EJP RD COFUND-EJP No 825575.

Keywords: Acute inflammatory demyelinating polyradiculoneuropathy, Charcot-Marie-Tooth disease, Hereditary neuropathy, SORD Deficiency
Skin biopsy and quantitative sensory assessment disclose early non-length dependent denervation in patients with ATTRv: data from an Italian cohort

Poster No:
144a

Authors:
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Introduction:
Study of intraepidermal nerve fiber density (IENFD) by skin biopsy is a promising tool in the evaluation of patients with ATTRv polyneuropathy (ATTRv-PN). We retrospectively analyzed IENFD and quantitative sensory test (QST) data from an Italian cohort of ATTRv-PN patients and asymptomatic carriers to provide insights into early nerve pathological and functional changes in this disease.

Methods:
IENFD and QST data of 20 ATTRv-PN patients and 20 asymptomatic carriers were retrospectively analyzed together with clinical and paraclinical data (disease stage and severity, neuropathic pain scales, and sural SNAP amplitude).

Results:
Considering an estimated time to the predicted age of onset of symptomatic disease of 20.27 + / − 7.9 years, small nerve fiber loss seems to be unexpectedly early in carriers. Moreover, carriers showed skin denervation at the proximal (thigh) site, suggesting a non-length-dependent neuropathic process. IENFD at ankle correlated with disease severity and other paraclinical variables such as sural nerve potential amplitude and QST parameters. Patients at earlier stages of the disease did not show significant differences in ankle IENFD compared with asymptomatic carriers, but significant differences were noted in terms of QST parameters, small fiber neuropathy symptoms, and neuropathic pain.

Conclusions:
Skin biopsy can detect an early non-length-dependent small fiber nerve loss in ATTRv-PN and, together with QST, could provide a useful tool to identify the disease onset and progression.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: ATTRv, Polyneuropathy, Small fiber neuropathy, Skin biopsy, QST
Carpal Tunnel Syndrome. An Early Marker for Amyloidosis

Post No:
145a

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Introduction:
Amyloidosis are systemic conditions and carpal tunnel syndrome (CTS) could precede in years the onset of the principal complications and it could be an important and early marker of the illness. The objective of this work was to determine the frequency of amyloid deposition in patients with CTS

Methods:
We evaluated consecutively patients with clinical and electromyographic criteria for CTS during September 2019 to January 2020 and their samples from anterior carpal ligament and synovial were studied using congo red staining and polarized light microscopy. In the patients where amyloid was detected we performed genetic testing for transthyretin (TTR) mutations, immunoelectrophoretic with immunofixation in blood and urine and multidisciplinary evaluation.

Results:
Thirty patients were included, 19 women, mean age 70 (range 42-89 years). Sixty percent of them had bilateral CTS. We identified 3 patients (10%) with amyloid, 2 men. During the follow up one of them had cardiac valve replacement and chronic diarrhea, other cardiac insufficiency and syncope and required permanent pacemaker. Only 1 patient had twin brothers with bilateral CTS. Genetic testing for TTR was negative in 2 patients and in 1 is pending. Light chains study was negative in the 3 patients. We did not found evidence for peripheral neuropathy and vitreous deposition. The patients are completing cardiac evaluation with scintigraphy

Conclusions:
Ten percent of our population had CTS without evidence of monoclonal gammopathy. Genetic studies will discriminate between amyloidosis associated to TTR mutations or wild type allowing in both cases an early treatment. Carpal tunnel syndrome could be an early marker for systemic amyloidosis.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: amyloidosis, carpal tunnel, wild type, transthyretin, mutations
Skin amyloid deposits and nerve fiber loss as markers of neuropathy onset and progression in hereditary transthyretin amyloidosis

Poster No:
146a

Authors:
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Introduction:
Our objective is to assess skin biopsy as marker of disease onset and severity in hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN), a treatable disease.

Methods:
In this single center retrospective study, skin Congo red staining and intraepidermal nerve fiber density (IENFD) were evaluated in symptomatic ATTRv-PN patients and asymptomatic TTR gene mutation carriers between 2012 and 2019. Non-ATTRv subjects with small fiber neuropathy suspicion who underwent skin biopsy in the same timespan were used as controls.

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

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

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: hereditary transthyretin amyloidosis, skin biopsy, amyloid deposition, small fiber loss, biomarkers
Physician Behaviors Support Need for CIDP Confirmation Committee to Adjudicate Clinical Trial Entry

Poster No:
147a

Authors:
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Institutions:
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Introduction:
Accurate diagnosis of CIDP is critical for enrollment in treatment trials. Accordingly, the ongoing ADHERE trial (NCT04281472) established an independent CIDP Confirmation Committee (CCC) to confirm the diagnosis as part of patient screening. We performed a physician-reported online survey to ascertain current CIDP diagnostic and management practices in the US, with retrospective physician-reported chart reviews.

Methods:
This 95-item, anonymous questionnaire assessed frequency of clinical guideline usage, diagnostic test utilization, treatment practices, and physician-perceived disease burden and treatment limitations. Participating physicians also provided data on 2-3 real-world patients. Eligible patients required a diagnosis of definite/probable CIDP confirmed by electrodiagnostic studies, active treatment, and ≥12 months of management by the participating physicians. Eligible physicians were board-certified neurologists, practicing for ≥2 years, managing ≥5 patients with CIDP, and conducting nerve conduction studies (NCS) in ≥10% of patients and has data access.

Results:
In September 2021, 60 neurologists across 26 states answered the questionnaire and reported their evaluation/treatment of 150 patients. 53.3% worked in community practices and 46.7% in academic institutions. 72.7% of patients across practices reportedly had definite CIDP, 20.7% probable, and 6.6% possible. Despite CIDP diagnosis, 7.4% never had NCS. Only 15.0% of neurologists always used the 2021 EFNS/PNS guidelines when diagnosing CIDP; another 75.1% were familiar but used them inconsistently. Treatment response data were inconsistent. Of the 150 charts reviewed, 16.0% of patients had a monophasic course, and 89.3% had some symptom relief with treatment. However, roughly one-third were deemed to have inadequate disease control on therapy.

Conclusions:
In this self-report survey of physician behavior around CIDP diagnosis and treatment, only a small minority of neurologists always use CIDP diagnostic criteria. Described clinical experience reinforce concerns about accuracy of CIDP diagnosis in practice. Our findings support the need for a CCC for diagnostic confirmation prior to patient enrollment in clinical trials.

References:
No

References 1:
Grant Support: This study was funded by argenx SE, which is the manufacturer of an investigational agent being studied in CIDP that is not currently approved for use by any regulatory agency.

Keywords: CIDP, physician behavior, practice pattern, survey, guideline
Gli1 Regulates the Postnatal Acquisition of Peripheral Nerve Architecture

Poster No:
148a

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Introduction:
Peripheral nerves are organized into distinct compartments. The endoneurium contains fascicles of axons, Schwann cells (SCs), and endoneurial fibroblasts (EFs) within an extracellular matrix (ECM). These fascicles are enclosed by the perineurium, a cellular sheath comprised of layered perineurial glia (PNG). SC secretion of Desert Hedgehog (Dhh) regulates this organization. In Dhh knockout mice, development of the perineurium is defective and the endoneurium is organized into many small compartments termed minifascicles. Minifascicles are also observed following nerve trauma and a 'minifascicular' neuropathy has been reported in patients with Dhh mutations. We investigate the role of Gli1, an important transcriptional effector of the canonical hedgehog pathway, in the organization of peripheral nerves.

Methods:
Mouse models were utilized for genetic fate-mapping of Gli1-expressing cells. Gli1 and Dhh null mice, as well as inducible knockout and over-expressor lines were analyzed by qRT-PCR, immunohistochemistry, EdU incorporation, and electron microscopy to assess the role of this signaling axis. The integrity of the nerve barriers was tested using protein tracers.

Results:
We identify PNG, EFs, and pericytes as Gli1-expressing populations. Dhh and Gli1 levels coordinately increase with myelination. Unexpectedly, Gli1 expression in EFs persists in Dhh knockouts. Unlike Dhh nulls, Gli1 nulls have a normal epineurium and perineurium and an intact nerve barrier. Like Dhh nulls, Gli1 nulls form minifascicles, which form via proliferation and progressive remodeling of EFs. Gli1 also regulates endoneurial ECM, nerve vascular organization, and has modest, non-autonomous effects on SC sorting and myelination. In adult nerves, induced deletion of Gli1 is sufficient to drive minifascicle formation.

Conclusions:
Gli1 is expressed non-canonically and functions cooperatively with Dhh to drive normal endoneurial development; it is dispensable for perineurial development. EFs are the cells that form minifascicles with nerve pathology. Thus, Gli1 is required for both the development and maintenance of appropriate peripheral nerve architecture.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support: NS103353 to B.Z. and NS100867 to J.L.S.

Keywords: Gli1, endoneurium, perineurium, Schwall cell, fibroblast
A Mouse Strain with Decreased Scarring Abilities Demonstrates Superior Peripheral Nerve Healing

Poster No:
149a

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Introduction:
Outcomes of peripheral nerve injury (PNI) remains to be largely unchanged for decades. PNI disproportionately affects young, and healthy adults and represents a major morbidity cause in hand trauma. Recently described, scar formation following PNI poses a physical barrier to axonal regeneration. Murphy Roths Large (MRL/MpJ), known as ‘super-healing’ mice, have shown the ability to heal with minimal or no scar formation in wound and tendon healing. This study seeks to investigate whether this attribute improves peripheral nerve regeneration.

Methods:
The MRL/MpJ was compared to the C57BL/6J strain (controls). 120 mice were divided into two groups: 1) Nerve Repair (NR, n=60) and 2) Nerve Graft (NG, n=60). The right sciatic nerve (SN) was divided and either microsurgically repaired (NR) or, had a 5mm segment excised, reversed and re-interposed (NG). Functional recovery was assessed by the Sciatic Functional Index (SFI) at post-operative weeks (POW) 1, 3, 6, 9, and 12. SNs were subsequently harvested and processed to calculate axon counts and the ‘g’ ratio for each end-point.

Results:
The MRL/MpJ strain demonstrated significantly superior SFI scores at POW 1, 3 (NR group) and at POW 6 (NG group). Axon counts were significantly higher in the C57BL/6J strain at POW 3 and 6 (NR group), and at POW 6, 9, and 12 (NG group). The MRL/MpJ strain demonstrated a significantly better axonal myelination at POW 3, 6, 9, and 12 (DR group) and at POW 6 and 12 (NG group).

Conclusions:
This study demonstrates superior axonal regeneration in the MRL/MpJ strain. The results support the concept of quality being more important than the quantity of regenerating axons following peripheral nerve injury. More future work implementing a mechanistic that targets nerve scarring is warranted using the MRL/MpJ strain.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: nerve regeneration, nerve grafts
A Role of Axonal Load in Regeneration Through Autologous Grafts

Poster No:
150a

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Introduction:
Two-stage free functional muscle transfers for long-standing facial palsy can yield unpredictable results. Early work demonstrates incomplete regeneration across neurorrhaphies in native nerve and higher donor axonal counts correlating with improved outcomes, but axonal count in nerve grafts has not been as thoroughly reviewed. Purpose of this study was to investigate the impact of varying axonal counts in autologous grafts on functional outcomes of repair.

Methods:
Six-week old YFP-16 female mice were allocated into three groups: Direct Nerve Repair (DNR, n=50), Small Nerve Graft (SNG, n=50), and Large Nerve Graft (LNG, n=50). All grafts were inset into the posterior auricular nerve with ear movement recovery (EMR) monitored as functional outcome. At various post-operative weeks (POW), excised specimens were imaged with electron microscopy. Axonal counts were measured proximal (PAC) to, distal (DAC) to, and within grafts (GAC). Total Success Ratio (TSR) was calculated to determine how many axons regenerated across the graft.

Results:
In DNR, DAC was significantly lower than PAC at all POWs, with maximum TSR of 80%. TSR for LNG and SNG were significantly lower at all POWs when compared to DNR, with maximums of 56% and 38% respectively. LNG had a significantly larger DAC than SNG at POW12 and beyond. A direct relationship was present between DAC and EMR for all values.

Conclusions:
Higher native axonal count of autologous nerve grafts resulted in higher percentage of regeneration across neurorrhaphies. This finding builds on previous reports that utilizing large diameter grafts can lead to central ischemia and necrosis. The findings suggest that there is an optimal size for non-vascularized nerve grafts.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:
Keywords: nerve regeneration, nerve grafts
A young Romanian man with dysautonomic onset as first case in Italy of Glu54Gln Transthyretin amyloidosis

Poster No:
151a

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Introduction:
Hereditary Transthyrethin Amyloidosis (ATTRv) with Glu54Gln mutation has been described in Romanian patients. Clinical features of this variant are early onset, mixed phenotype, aggressive progression and short survival.

Methods:
We report on the first patient (a 41-year-old Romanian man) diagnosed in Italy with the Glu54Gln mutation of the TTR gene whose only clinical manifestations at onset were pain, erectile dysfunction and diarrhoea. For the erectile dysfunction, he underwent surgical varicocele repair without benefit. For diarrhoea and weight loss (about 20 Kg), colonoscopy and esophagastroduodenoscopy were performed (non-atrophic gastritis). Despite the patient reported a family history of unspecified amyloidosis, ATTRv was not considered. For severe back pain, a rheumatologist suggested a 99mTc-HMDP bone scan. For high myocardial uptake (Perugini score 3), he was referred to our attention by the nuclear medicine specialist.

Results:
At neurological examination we found orthostatic hypotension and lower limbs areflexia (NIS = 8). Genetic test identified the c.220G>C (Glu54Gln) mutation of TTR gene. Blood tests showed increased NT-proBNP and absence of monoclonal gammopathy. EKG showed right atrial enlargement and incomplete right bundle branch block. Echocardiography evidenced hypertrophic left ventricle with preserved systolic function, thickened valve systems and a global longitudinal strain with apical sparing. Ophthalmological examination was normal. Neurophysiology showed a mild sensory axonal neuropathy at lower limbs. Echography showed increased cross-sectional area at the proximal sciatic nerve and brachial plexus in supraclavicular space.

Conclusions:
Despite a positive family history, the patient was diagnosed only after 18 months from symptoms onset. The case is exemplificative of diagnostic delay due to the lack of awareness of ATTRv. An early diagnosis is crucial especially for genotypes with more aggressive disease. An asymptomatic 50-year-old patient's sister with negative neurological and neurophysiological evaluations carried the same TTR mutation as the proband. The patient in currently on Patisiran therapy, the sister in regular follow-up.

References:
Yes

References 1:

References 2:
Torres-Courchoud I, Martínez-Gil R, Aíbar-Arregui MA, Andrés-Gracia A, Torralba-Cabeza MA. Cardiac Involvement Secondary to a Familial Form of Transthyretin Amyloidosis Resulting From the Glu54Gln Mutation. Rev Esp Cardiol (Engl Ed). 2017 Apr;7

References 3:

References 4:

Grant Support:

Keywords: TTR
Aldose Reductase Inhibitor AT-007 Prevents Mitochondrial Dysfunction And Neurodegeneration in Sorbitol Dehydrogenase Deficiency-Induced Neuropathy

Poster No:
152a

Authors:
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Introduction:
Sorbitol dehydrogenase (SORD) deficiency has been identified as the most frequent autosomal recessive form of hereditary neuropathy, affecting roughly 10,000 patients worldwide. Loss of SORD causes high sorbitol levels in cells due to the inability to convert sorbitol to fructose in the two-step polyol pathway, leading to neurodegeneration. However, underlying mechanisms of sorbitol-induced neurodegeneration have not been fully elucidated.

Methods:
A Drosophila model of SORD deficiency was characterized by locomotor assay and brain imaging. Reactive oxygen species (ROS) staining in the brain and muscle was performed to understand the pathological changes at the molecular level. To reduce sorbitol accumulation by inhibiting conversion from glucose, a next-generation central nervous system (CNS) penetrant aldose reductase inhibitor (ARI) developed by Applied Therapeutics, Inc, named AT-007, was applied to patient-derived fibroblasts and flies. Sorbitol levels in cells and fly brains were measured, and neurological phenotypes of flies were analyzed.

Results:
In a Drosophila model of SORD deficiency, we showed age-dependent locomotor impairment and progressive synaptic degeneration in the brain. In addition, we found an accumulation of ROS in the CNS and muscle, indicating mitochondrial dysfunction. AT-007 significantly reduced sorbitol levels in patient-derived fibroblasts and the Drosophila model. Moreover, we demonstrated that feeding with AT-007 in Drosophila significantly improved locomotor activity, mitigated synaptic degeneration, and reduced ROS levels.

Conclusions:
Our findings establish the underlying disease pathogenesis and provide a potential treatment strategy for patients with SORD deficiency.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

**Keywords**: sorbitol, neurodegeneration, hereditary neuropathy, reactive oxygen species, mitochondrial dysfunction
Modulating Molecular Chaperones: A Potential Therapeutic Approach For X-Linked Charcot-Marie-Tooth (CMT1X) Disease

Poster No:
153a

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Introduction:
CMT1X is an inherited peripheral neuropathy caused by mutations in the GJB-1 gene that encodes for connexin 32 (Cx32). Despite being the second most common form of CMT neuropathies, there are no pharmacologic treatments for CMT1X. We have developed 'novologues' as orally bio-available novobiocin analogues that manifest neuroprotective activity by modulating the expression of heat shock protein 70 (Hsp70). The novologue, KU-596, is in clinical trials for treating a metabolic neuropathy and we examined if it may improve neuropathic symptoms in Cx32 deficient (Cx32def) mice and T55I x Cx32def mice, authentic mouse models of human CMT1X.

Methods:
4-month-old Cx32def and T55I x Cx32def mice were treated with either vehicle or KU-596 (0.3 mg/kg, 1mg/kg or 3 mg/kg) daily for 5 months. We measured grip strength (alternate weeks) and nerve electrophysiology as parameters for peripheral neuropathy in CMT1X mouse models.

Results:
Cx32def and T55I x Cx32def mice develop a significant reduction in grip strength (~0.8N), motor nerve conduction velocity (MNCV, ~45-50m/sec) and compound muscle action potential (CMAP, ~ 20-25mV) compared to wild-type mice (grip strength, ~1.6N; MNCV, ~60m/sec; CMAP, ~ 40mV). KU-596 therapy in Cx32def mice significantly improved grip strength (~1.5N), MNCV (~ 55-60 m/sec) and CMAP (~ 30mV). Treatment with KU-596 in T55I x Cx32def mice improved grip strength (~1.4N) and MNCV (~ 60m/sec) but did not significantly improve CMAP. To investigate whether these effects were Hsp70 dependent, Cx32def x Hsp70 knockout mice were treated with KU-596. While the deletion of Hsp70 did not affect the development of peripheral neuropathy, the therapeutic efficacy of KU-596 was Hsp70 dependent since, there was no improvement in MNCV or CMAP.

Conclusions:
Our data suggests that modulating Hsp70 with KU-596 may be beneficial for treating CMT1X and that efficacy may not be limited by the nature of the underlying genetic mutation in the GJB-1 gene.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Peripheral Neuropathy, Molecular Chaperones, CMT1X, Nerve Electrophysiology
An improved protocol of RNA extraction from rat laryngeal muscles: advances and limitations of RNA-Seq analysis in the larynx.

Poster No:
154a

Authors:
Ignacio Hernandez-Morato¹, Angela Kemfack¹, Yalda Moayedi¹, Michael Pitman¹

Institutions:
¹Columbia University, New York City, NY

Introduction:
Laryngeal functions are regulated by vocal fold (VF) movement, which is essential for respiration, airway protection, and voice production. VF motion is coordinated by contraction of antagonistic intrinsic laryngeal muscles (ILM), which are innervated by paired recurrent laryngeal nerves (RLN). The abductor muscle opens the glottis for respiration, and the remaining adductor muscles close it for phonation and airway protection. The rat model of RLN injury is an excellent and well accepted model of cranial nerve injury and reinnervation. However, global transcriptome of the ILM for the characterization of the key genes that may participate in the selective reinnervation of the larynx has been limited due to the inability to extract quality RNA under standard conditions.

Methods:
A protocol for high-quality RNA isolation was developed for the rat ILMs. Posterior cricoarytenoid, lateral and medial arytenoid muscles were dissected from Sprague Dawley rats. Multiple RNA extraction methods were compared by spectrophotometer and bioanalyzer assessment.

Results:
A suitable protocol was achieved by modifying multiple previously describe tissue preparations strategies that otherwise failed. The use of RNase inhibiting reagents after ILM dissection from the larynx are mandatory to avoid RNA degradation. Cell lysis and RNA purification required cryogenic grinding followed by integrated manual and rotor-stator homogenization for optimal RNA extraction. Pooling of three muscles produced sufficient RNA for RNA-Seq analysis for all samples, a 260/280 ratio of 2.14 ± 0.09, and a RNA integrity number between 7.0 and 8.6.

Conclusions:
This work established a reproducible and systematic protocol for high-quality RNA isolation from rat ILMs. This methodology is currently being applied in a broader study involving nerve regeneration following RLN injury for the identification of genes that participate in axonal pathfinding and selective reinnervation of the ILMs.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: RNA-Seq, laryngeal muscles, vocal fold paralysis, recurrent laryngeal nerve, reinnervation
Laterality of intrinsic laryngeal muscle innervation parallels differential expression of Homer2 and Myo1D.

Poster No:
155a

Authors:
Angela Kemfack1, Yalda Moayedi1, Richard Friedman1, Abhinav Joshi1, Michael Pitman1

Institutions:
1Columbia University, New York City, NY

Introduction:
The intrinsic laryngeal muscles (ILMs) controlling vocal fold movement are innervated by the recurrent laryngeal nerve (RLN). Following RLN injury, vocal fold (VF) paralysis due to aberrant reinnervation of the ILMs results in impaired voice and airway defense and significant patient morbidity. Clinically, idiopathic and post-intubation RLN injury cause VF paralysis at a significantly higher rate on the left side. Though the cause of this discrepancy is unknown, it suggests intrinsic neuromuscular differences between left and right ILMs. The present study pioneered a systematic protocol using RNA-Seq to investigate these genetic differences. Identifying high-value differentially expressed genes in normal ILMs and after RLN injury will inform research into the prevention and treatment of VF paralysis.

Methods:
Consistent, high-quality RNA from distinctive ILMs, previously unobtainable using standard techniques, was isolated from P15 and P60 rats. RNA extracts from left and right posterior cricoarytenoid, lateral thyroarytenoid, and medial thyroarytenoid muscles were sequenced using a high-throughput system (NovaSeq). For this preliminary study, differences in left versus right were studied (n=12).

Results:
Gene ontology and KEGG pathway analysis revealed phenotypically related biological mechanisms, including the establishment of left/right asymmetry and the FoxO signaling pathway. Significant genes of interest were identified in MTA and LTA muscles. Specifically, increased expression of Homer2 (p = 2.00E-05) was observed in the left MTA compared to the right. Homer2 indirectly inhibits FoxO signaling, which regulates neuromuscular junction stabilization. While Myo1D was slightly upregulated in the MTA (p = 0.00024), the left-right LTA comparison indicated downregulation (p = 4.40E-05). Myo1D is involved in left-right asymmetry and endocytic trafficking.

Conclusions:
Considering the laterality of VF paralysis, Homer2 and Myo1D are potential high-value targets for further investigation due to their function and differential expression that is consistent with discrepant left-right ILM innervation.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: recurrent laryngeal nerve, reinnervation, intrinsic laryngeal muscle, muscle regeneration, neuromuscular
NCAM1 is a cellular target engaged serum biomarker reflecting disease severity in CMT1A patients

Poster No:
156a

Authors:
Young Hee Kim1, Byeol-A Yoon1, Young Rae Jo1, Jong Kuk Kim1, Byung-Ok Choi2, Hwan Tae Park1

Institutions:
1Dong-A University, Busan, Korea, Republic of, 2Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of

Introduction:
Background and Objectives: Elevated serum concentrations of neural cell adhesion molecule 1 (NCAM1) and p75 neurotrophin receptor (p75) in patients with peripheral neuropathy have been reported to represent pathologic Schwann cells (SCs). This study aimed to determine the specificity of serum concentration elevation of either NCAM1 or p75 in demyelinating subtypes of Charcot-Marie-Tooth disease (CMT) and its correlation with disease severity.

Methods:
Methods: Blood samples were collected from 142 patients with inherited peripheral neuropathy and 55 healthy controls. Disease severity was measured using CMT neuropathy score version 2 (CMTNSv2), and serum concentrations of NCAM1 and p75 were analyzed by ELISA. Eight sural nerves from CMT patients were examined to determine the relation of histopathology and serum NCAM1 levels.

Results:
Results: We found that serum concentration of NCAM1, but not p75, was specifically increased in demyelinating subtypes of CMT disease (median: 7100 pg/ml, p<0.01), including CMT1A, but not in axonal subtype (6153 pg/ml, p>0.05), compared to the control (5064 pg/ml). However, serum NCAM1 elevation in CMT1A patients was not observed in the patients with severe phenotype (CMTNSv2>20). Immunofluorescent NCAM1 staining for the sural nerves of patients with CMT showed consistent increase of NCAM1-positive onion bulb cells in CMT1A (97.9% of myelinated fibers) compared to axonal subtype (9.9% of myelinated fibers), but the expression of NCAM1 in the onion bulb was decreased in a severe case of CMT1.

Conclusions:
Discussion: The development of disease severity-related serum biomarker such as NCAM1 reflecting pathological SC status holds potential for patient selection in clinical trials and for monitoring disease progression and treatment response.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** Neural cell adhesion molecule 1, Schwann cells, Inherited peripheral neuropathy, Charcot-Marie-Tooth disease
CKD-510, a Novel Selective HDAC6 Inhibitor, is Well-tolerated and Increased Acetyl-tubulin in Healthy Volunteers

Poster No:
157a

Authors:
Ka Young Hong1, Seieun Kim1, Jeong Ah Lim1, Yves Donazzolo2, Nina Ha3, Semi Kim1, Jiheon Choi1, Keunho Ryu1, Seongkon Kim1, Choon Kyung Oh1

Institutions:
1Chong Kun Dang Pharm., Seoul, Korea, Republic of, 2Eurofins Optimed, Gières, France, 3CKD Research Institute, Chong Kun Dang, Yongin si, Korea, Republic of

Introduction:
CKD-510 is an oral histone deacetylase 6(HDAC6) inhibitor and under development for treatment of Charcot-Marie-Tooth disease(CMT). HDAC6 is predominantly located in the cytoplasm and catalyze the removal of acetyl-moieties from non-histone proteins such as α-tubulin[1]. α-tubulin acetylation improves axonal transport via microtuble stabilization in the nerve. HDAC6 inhibition also improves myelination of peripheral nerve by reducing misfolded PMP22 aggregation[2-4]. CKD-510 is a novel non-hydroxamate HDAC6 inhibitor resulting in less toxicities and better PK properties than hydroxamate inhibitors. CKD-510 has shown outstanding functional improvement in CMT model mice which supports its therapeutic potential for CMT and here we present the key results of first-in-human study of CKD-510.

Methods:
A phase 1 study was a double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, and pharmadynamics of CKD-510 in healthy adults following a single dose(30-800mg) and 14-day multiple dose(100, 300, 600mg QD and 300mg BID) administration. Adverse events(AEs), clinical laboratory, vital signs, physical examination were evaluated. Blood samples were collected to measure plasma concentration and acetylation levels of α-tubulin.

Results:
A total of 87 subjects participated in the study. CKD-510 was safe and well tolerated up to 600 mg daily repeated dosing. All AEs were mild to moderate intensity and no dose-relationship for AEs was observed. There were no deaths or serious AEs. No clinically significant changes were reported in vital signs, clinical laboratory, physical examination and cardiac parameters. The CKD-510 plasma concentration reached maximum level after 1-4 hours, and mean half-life was 6-8 hours. Dose proportionality on exposure was linear. Acetylated α-tubulin increased in a dose-dependent manner and sustained by 24 hours following CKD-510 administration.

Conclusions:
CKD-510 was safe and well-tolerated following single and multiple doses in healthy subjects. Safety and PK/PD findings from this study supports to initiate phase 2 study with once daily dosing regimen for the treatment of CMT.

References:
Yes

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: HDAC6 Inhibitor
Sensory neuron-specific atg7 deficiency leads to sarm1-dependent axonal degeneration

Poster No:
158a

Authors:
HYE RAN KIM¹, HYE JIN LEE¹, Hwan Tae Park²

Institutions:
¹Peripheral Neuropathy Research Center (PNRC), Department of Molecular Neuroscience, College of Medic, Busan, Korea, Republic of,
²Dong-A University, Busan, Korea, Republic of

Introduction:
Autophagy dysfunction has closely related to the development of neurodegenerative diseases. However, It has not been clearly revealed how autophagy dysfunction leads to peripheral neuropathy. Here we show that conditional knockout mice of Atg7 gene in dorsal root ganglion (DRG) neurons with Advillin-Cre (Adv-Atg7KO) or DRG-specific Synapsin-Cre (Syn-Atg7KO) exhibited sensory neuropathy as revealed by the reduction of sensory nerve conduction velocity as well as defects of sensory-motor coordination around 1 month after birth. Although DRG neuronal cell death was not remarkable in Adv-Atg7KO mice, the peripheral nerve in these mice showed the reduction of the number of myelinated axons, and the appearance of a lot of 'band of Bungner', the evidence of Wallerian degeneration. In line with this, DRG neurons in these mice showed the induction of neuronal injury markers such as ATF3 and pSTAT3. Accordingly, axonal degeneration and the defect in sensory-motor coordination in Syn-Atg7KO mice were improved by the adeno-associated viral delivery of dominant-negative Sarm1, which has been known as a key activator of Wallerian degeneration. In summary, our findings suggest that sensory neuron-specific Atg7 deficiency leads to Sarm1-dependent axonal degeneration rather than neuronal cell death in young adult mice.

Methods:

Results:

Conclusions:
we show that autophagy impairment induced by the deletion of Atg7 gene in the peripheral sensory neurons leads to Sarm1-dependent axonal degeneration in myelinated axons. This study provides mechanistic insights on how autophagy dysfunction leads to axon degeneration and identifies a potential therapeutic target of axonal neuropathy associated with autophagy-related disorders.

References:
Yes

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: Autophagy, Dorsal root ganglion, Conditional knockout, axonal degeneration, Sarm1
Comparison Of Three State of the Art Small Fibre Measures in Type 2 Diabetic Polyneuropathy

Poster No:
159a

Authors:
Sandra Gylfadottir,1 Mustafa Itani,2 Jens Nyengaard,3 Søren Sindrup,4 Troels Jensen,4 Nanna Finnerup,5 Pall Karlsson5

Institutions:
1Dept. of Neurology, Aarhus University Hospital, Aarhus, Denmark, 2Dept of Neurology, Odense University Hospital, Odense, Denmark, 3Centre for Molecular Morphology Aarhus University, Aarhus, Denmark, 4Aarhus University, Aarhus, Denmark, 5Danish Pain Research Centre, Aarhus University, Aarhus, Denmark

Introduction:
There is no agreed gold standard for diagnosing small fibre involvement in diabetic neuropathy. Three quantitative tests: Intraepidermal nerve fibre density (IENFD), Cornea confocal microscopy (CCM) and thermal detection thresholds are considered to represent the key structural and functional tests detecting small fibre abnormality in diabetic polyneuropathy. It is unclear which test is best to identify small fibre damage in patients with early diabetic neuropathy. This study assessed and compared the use of CCM, IENFD and thermal detection thresholds in patients with newly diagnosed type 2 diabetes with and without neuropathy and in healthy controls.

Methods:
Diabetic patients from the Danish diabetic DD2 cohort underwent detailed neurological examination, electrophysiology, quantification of IENFD, CCM and quantitative sensory testing. Neuropathy diagnosis was classified according the Toronto consensus criteria (without relying on IENFD and thermal thresholds). All patients without neuropathy and with at least probable DPN were included in the study. Toronto clinical neuropathy score (TCNS) was used to grade severity of neuropathy.

Results:
214 diabetic patients with probable or definite diabetic neuropathy, 63 patients without neuropathy and 97 controls were included. Patients with neuropathy had lower CCM measures (length, density, branch), IENFD, cold and warm detection thresholds compared to controls and diabetics without neuropathy after adjusting for age, sex and BMI (p values: <0.005). There was no difference between controls and diabetics without neuropathy on all measures. The sensitivity of CCM measures ranged from 5.1-7.9%, specificity from 95.2-100%. The sensitivity and specificity for IENFD was 51.1% and 90.0%, respectively. For thermal thresholds the sensitivity and specificity was 30.4% and 85.7%, respectively. For all three tests positive predictive values ranged from 83.3-100% and negative predictive values from 23.2-37.2%.

Conclusions:
All three small nerve fibre tests have high specificity, but CCM has particularly low ability to identify neuropathy in patients with recently diagnosed type 2 diabetes.

References:
No

References 1:
Keywords: Diabetic neuropathy, Small fibres, Cornea confocal microscopy, Intraepidermal nerve fibre density, Thermal detection thresholds
Translation and Validation Of The Spanish Version of The Toronto Clinical Neuropathy Score (TCNS) and Modified Version (mTCNS).

Poster No:
160a

Authors:
Juan Idiaquez¹, Carolina Barnett-Tapia², Vera Bril²

Institutions:
¹Division of Neurology, University of Toronto and University Health Network., Toronto, Ontario,
²University of Toronto, Toronto, Ontario

Introduction:
The Toronto Clinical Neuropathy Score (TCNS) is an easy-to-use questionnaire aimed at screening and detecting diabetic sensorimotor polyneuropathy (DSP). A modified TCNS (mTCNS) has shown the highest sensitivity and specificity for the diagnosis of early DSP. This tool is not yet available in Spanish. To translate and cross-culturally adapt the TCNS and mTCNS to Spanish and evaluate their measurement properties.

Methods:
Translation of the original version into Spanish by three independent bilingual and bicultural Spanish translators. The translations were compared, discrepancies and ambiguities noted, and a preliminary Spanish translation was generated. Then a reverse translation was carried out by two independent bilingual and bicultural English translators. Both translators were blind to the original versions of TCNS and mTCNS. Finally, the reverse translations were compared to the originals by a review committee including the developer of the instruments. Subsequently, we performed a cross-sectional study of 34 patients with suspected DSP using the TCNS and the mTCNS, the Michigan Neuropathy Screening Instrument (MNSI, and nerve conduction studies (NCS). We used a Pearson linear correlation model and an internal consistency measure (Cronbach's alpha) to assess the reliability of the measures.

Results:
The Spanish versions of TCNS (TCÑS) and mTCNS (mTCÑS) have good internal reliability with Cronbach's Alpha of 0.8. A strong positive correlation was found between the TCÑS and mTCÑS and MMSI (r= 0.66) (p=0.0002) and NCS(r= 0.61) (p=0.0004).

Conclusions:
The TCÑS and mTCÑS are reliable and valid translations of the original TCNS. TCÑS and mTCÑS are valid ways to evaluate the presence and severity of DSP for epidemiological studies and clinical practice in Spanish-speaking diabetic patients.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Diabetes, Polyneuropathy, Spanish, Diagnosis
Diagnosis of Polyneuropathy with the Modified Toronto Clinical Neuropathy Score (mTCNS)

Poster No:
161a

Authors:
Juan Idiaquez¹, Vera Bril²

Institutions:
¹Division of Neurology, University of Toronto and University Health Network., Toronto, Ontario,
²University of Toronto, Toronto, Ontario

Introduction:
The mTCNS comprises symptoms and signs of polyneuropathy, including severity levels, and ranges from a normal of 0 to a maximum of 33 points. This scale is valid and reliable for the diagnosis and staging of diabetic sensorimotor polyneuropathy. Diagnostic cut-off values for the mTCNS in various polyneuropathies have not been fully evaluated. Objective: We aimed to explore diagnostic cutoff values with optimal sensitivity and specificity when using the mTCNS in the diagnosis of polyneuropathy (PNP).

Methods:
We performed a retrospective study of 190 patients with PNP and 20 healthy controls. Patients had clinical, electrophysiological, and small fibre (SF) assessments of their PNP. Sensitivity, specificity, likelihood ratios (LR) and the area under the receiver operating characteristics curve (AUC) were determined for different mTCNS cutoff values.

Results:
The mean age of all patients was 59.5±13y: SF (n=30) 53.0±15y and large fibre (LF) (n=160) 60.7±12y. The optimal mTCNS cutoff value for diagnosing PNP was ≥5 (sensitivity 94.2%, specificity 85.7%, LR+= 6.59, LR-= 0.07), SF ≥3 (sensitivity 96.7%, specificity 85.7%, LR+= 6.5, LR-= 0.02), and LF ≥5 (sensitivity 91.8%, specificity 100%, LR+= infinity, LR-= 0.08). The AUC is 98.7%.

Conclusions:
Values of 5 or more on the mTCNS have high sensitivity and specificity in the diagnosis of PNP.

References:
Yes

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Polyneuropathy, Diagnosis
Dexamethasone and Aprepitant Protect from Cisplatin Induced Peripheral Neuropathy in Breast Cancer

Poster No:
162a

Authors:
Nishi Bamania¹, Bari Chowdhury¹, Anand Krishnan¹

Institutions:
¹University of Saskatchewan, Saskatoon, Saskatchewan

Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) is a painful complication associated with several chemotherapy agents, including platinum drugs, vinca alkaloids, bortezomib, and new generation angiogenesis inhibitors. No effective therapy is currently available to prevent or cure this painful condition leading to premature withdrawal of the causative drug from the treatment regimen and suboptimal therapy for patients. In the case of cisplatin-induced peripheral neuropathy (CisIPN), the painful symptoms persist for years even after the withdrawal of the drug, leaving cancer survivors with poor quality of life. Neuroinflammation and substance P-NK1 axis were shown to contribute to CisIPN. The underlying cancer also compounds CisIPN. In this study, we evaluated the effects of the anti-inflammatory agent Dexamethasone (Dex) and substance P-NK1 axis inhibitor Aprepitant (Apr) in CisIPN in an orthotopic breast cancer model.

Methods:
CisIPN was induced in 20 female breast cancer animals by administering them with standard doses of cisplatin. Some of these animals were co-administered with either Dex or Apr along with cisplatin. These animals were then subjected to mechanical and cold sensitivity assessment using Von Frey filament and acetone assays. We also examined the involvement of the neuroprotectors MANF and Plastin-3 in Dex and Apr mediated treatment response in these animals.

Results:
We found that both Dex and Apr pre-treatment prevented CisIPN, evident by the protection of animals from cisplatin-induced mechanical and cold hypersensitivity. We also found that both Dex and Apr prevented the cisplatin-mediated suppression of the neuroprotectors MANF and Plastin-3.

Conclusions:
Our results indicate that both Dex and Apr protect against CisIPN by maintaining the expression of neuroprotector molecules. Dex and Apr may be considered as potential therapies for managing CisIPN.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: Cisplatin induced peripheral neuropathy, Dexamethasone, Aprepitant, Neuroinflammation
Sorbitol-Dehydrogenase (SORD) gene Mutation as a Curable Cause of Charcot-Marie-Tooth 2 (CMT-2) and Distal Hereditary Motor Neuronopathy (d-HMN)

Poster No:
163a

Authors:
Gulshan Yunisova¹, Şahin Avci¹, Ayfer Arduç¹, Hülya Kayserili², Piraye Oflazer²

Institutions:
¹Koc University Hospital, Istanbul, Turkey, ²Koç University, Koç University Hospital, Istanbul, Turkey

Introduction:
Sorbitol-Dehydrogenase (SORD) is an enzyme, which converts sorbitol to fructose in carbohydrate metabolism and has been associated with diabetic neuropathy due to sorbitol deposition in axons. However, in a very recent study, SORD gene mutations that cause dysfunction in this enzyme was reported as the most common cause of autosomal recessive hereditary neuropathy.

Methods:
We here report 2 additional patients from Turkey with hereditary motor neuronopathy and motor-predominant sensory-motor neuropathy phenotypes with SORD gene mutations.

Results:
First patient, 35-year-old male, presented with asymmetrical and slowly progressive gait difficulty onset being at the age of 15. Neurological examination showed distal, asymmetric muscle weakness, absent deep tendon reflexes, and pes cavus deformity. Electromyography (EMG) revealed predominantly motor axonal sensori-motor polyneuropathy. Whole exome sequencing (WES) identified a homozygous pathogenic variant (c.757delG, p.Ala253fs) in SORD gene. Second patient was 16 years old male who had difficulty in walking and climbing stairs for the past 5 years. Mild symmetrical weakness predominant in peroneal muscles of distal lower extremities was found. Deep tendon reflexes were preserved with normal sensory examination. Diffuse anterior horn/anterior root involvement was revealed by EMG along with normal conduction velocities. A homozygous (c.908C>G, p.Thr303Arg) variant of uncertain significance (VUS) in SORD gene was revealed by WES. Fasting sorbitol level in serum was about 100 times increased in both patients (19.0 mg/L and 14.3 mg/L, respectively. N<0.16 mg/L).

Conclusions:
SORD mutations were recently reported as one of the new, treatable cause of hereditary neuropathies. In this presentation, our aim is to point to this treatable cause of hereditary neuropathies, which presented with two distinct inherited and incurable diseases such as CMT-2 and d-HMN. The fact that there will be an effective treatment option, which can reduce sorbitol level, highlights the clinical impact of implementing next generation sequencing technologies to achieve definite diagnosis in neuromuscular disorders.

References:
Yes

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, d-HMN, SORD gene, sorbitol, hereditary neuropathy, neuronopathy, WES, NGS, treatment
Human iPSC-derived organoid model recapitulates rescuable key pathology features of CMT1A

Poster No:
164a

Authors:
Jonas Van lent1, Leen Vendredy2, Elias Adriaenssens1, Tatiana Da Silva Authier1, Bob Asselbergh3, Ludo Van Den Bosch4, Jonathan Baets1, Vincent Timmerman1

Institutions:
1University of Antwerp, Antwerp, Belgium, 2University of Antwerp, Antwerp, -, 3VIB-UAntwerp, Antwerp, Belgium, 4University of Leuven, Leuven, Belgium

Introduction:
Motor and sensory neuron cultures differentiated from patient-derived induced pluripotent stem cells (iPSCs) have proven valuable to study axonal CMT (CMT2). However, the generation of such models that also produce myelinating Schwann cells has proven to be particularly challenging. This has prevented the field from using human iPSC-derived cultures for studying dysmyelinating forms of CMT. Here, we present an iPSC-derived organoid culture that overcomes these challenges and which mimics the human peripheral nervous system (PNS). We used this model to study myelination defects in CMT1A-organoids and their response to PXT3003 and shRNA treatment.

Methods:
We differentiated and characterized organoid cultures from human iPSCs from the most common CMT type 1 causal gene coding the peripheral myelin protein 22 (PMP22), along with a healthy control iPSC line.

Results:
We developed an organoid model that contains neurons, muscle cells, Schwann cells, endothelial and glial cells. With the presence of myelinated neurons and neuromuscular junctions, the organoid model captures key features of the PNS, as confirmed by single-cell transcriptomics and immunocytochemistry. We used this model to study disease signatures of CMT1A, revealing early ultrastructural myelin alterations and onion bulb-like formations at later developmental stages. These hallmarks were not present in a differentiated CMT2A iPSC-patient line, supporting the notion that these alterations are specific to CMT1A. When we treated these cultures with PXT3003 or shRNAs targeting PMP22, we observed amelioration of these pathogenic features. Our data therefore suggest that the current clinical trial Phase III drug PXT3003 and gene-silencing can reverse myelination defects in human in vitro cultures.

Conclusions:
Our data describe the first organoid model containing various cell types of the PNS, including human Schwann cells that can myelinate peripheral nerves, and reveal myelination defects in CMT1A cultures. This organoid model is therefore able to capture the physiological complexity of the PNS and supports the therapeutic approach of reducing PMP22 expression.

References:
No

References 1:

References 2:
Keywords: Charcot-Marie-Tooth neuropathy, iPSC-derived organoid cultures, Myelinating Schwann cells, Short-hairpin RNAs targeting PMP22, PXT3003
Poster Session II
Tuesday 17 May
12.00 – 14.00
ICU Diagnosis of Neuromuscular Respiratory Failure

Poster No:
1b

Authors:
Sakhi Bhansali¹, Christopher Lamb¹, Jason Siegel¹

Institutions:
¹Mayo Clinic, Jacksonville, FL

Introduction:
Detailed neurological history and examination (H&P) are difficult to obtain for patients admitted to Intensive Care Unit (ICU) with acute neuromuscular respiratory failure (aNMRF), creating risk of delayed or inaccurate diagnosis. The aim of this systematic literature review was to identify key findings which helped most in diagnosis and whether these findings were recorded in Pre-ICU settings or after ICU transfer.

Methods:
We identified all indexed case reports and series where the cause of aNMRF was not diagnosed until the ICU. Patients eventually diagnosed with Guillain-Barre syndrome (GBS), Motor Neuron Disease (MND), and Myasthenia Gravis (MG) were identified, according to established criteria. We recorded the setting of the initial H&P and key diagnostic features identified for GBS, MG, and MND diagnoses.

Results:
Forty-two cases were evaluated. The initial history was first documented in the ICU in 13/42 (31%) cases and exam in 22/42 (52.4%) cases. No diagnosis was recorded for 28/42 prior to ICU (most often GBS), and 14/42 (most often MG) had misdiagnosis prior to ICU. MND had the least (0/8) and GBS (18/20, 90%) had the most evaluations performed Pre-ICU. Irrespective of the setting, H&P were concordant with the final diagnosis in 34/42 (81%) cases. H&P aligned most often with final diagnosis in GBS (17/20, 85%) and least often in MG (7/14, 50%). Hypo/areflexia (14/20, 70%), ptosis (5/14, 36%), and combined Upper and Lower motor neuron signs (5/8, 63%) were the most recorded findings in the ICU for GBS, Myasthenic Crisis, and MND, respectively.

Conclusions:
It is common that pertinent history and exam findings in patients with aNMRF are first identified after ICU admission. Despite limitations, H&P remains patients continue to have reliable features that can direct diagnosis.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:
Keywords: Guillain-Barré syndrome, Motor neuron disease, Myasthenia Gravis, Neuromuscular respiratory failure
Risk of relapse after SARS-CoV-2 vaccination in patients with chronic inflammatory neuropathies and safety and tolerability of the SARS-CoV-2 vaccines

Poster No:
2b

Authors:
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Institutions:
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Introduction:
To assess whether vaccination for SARS-CoV-2 increase the risk of relapse in chronic inflammatory neuropathies.

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

**Conclusions:**
Vaccination for SARS-CoV-2 does not appear to increase the short-term risk of relapse in CIDP and MMN.

**References:**
No

**References 1:**

**References 2:**

**References 3:**

**References 4:**

**Grant Support:**

**Keywords:** vaccination, SARS-CoV-2, COVID-19, CIDP, MMN
Diffusion tensor imaging analysis for cerebellar white matter abnormalities in Charcot-Marie-Tooth disease

Poster No:
3b

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Introduction:
Charcot-Marie-Tooth disease (CMT) is a hereditary peripheral neuropathy with clinical and genetic heterogeneities. Cerebral nervous system (CNS) symptoms have been reported in several CMT subtypes. Diffusion tensor imaging (DTI) study has been widely used in neuroscience field. We employed DTI to assess changes in white matter microstructure by leveraging its sensitivity to diffusion measurement on a microscopic scale.

Methods:
We enrolled 94 study participants including 47 healthy controls and 47 CMT patients. Clinical assessments were obtained by detailed history taking and physical examination. Brain volumetry and DTI were performed in 47 CMT patients with PMP22 duplication (n=10), MFN2 (n=15), GJB1 (n=11), or NEFL mutations (n=11) and 47 controls to investigate for structural changes of the cerebellum. We analyzed volumetric and DTI data using the statistical tools.

Results:
Volume in cerebellar white matter (WM) was significantly reduced in CMT patients with NEFL mutations. Abnormal DTI findings were observed in the superior, middle, and inferior cerebellar peduncles predominantly in NEFL mutations, and partly in GJB1 mutations. Cerebellar ataxia was more prevalent in the NEFL mutation (72.7%) than GJB1 mutation (9.1%), but not observed in other genotypic subtypes, which indicates that structural cerebellar abnormalities were associated with the presence of cerebellar ataxia. However, NEFL and GJB1 mutations did not affect cerebellar gray matter (GM), and neither cerebellar GM nor WM abnormalities were observed in PMP22 duplication or MFN2 mutations. We found structural evidence of cerebellar WM abnormalities in CMT patients with NEFL and GJB1 mutations and the association between cerebellar WM involvement and cerebellar ataxia in these genetic subtypes, especially in the NEFL subgroup.

Conclusions:
Therefore, we suggest that neuroimaging such as MRI volumetry or DTI can be helpful for early detection of cerebellar dysfunction in CMT patients with NEFL and/or GJB1 mutations, especially in cases harboring cerebellar ataxia.
References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease, Volumetry, diffusion tensor imaging, white matter, cerebellum
Modeling-Based Characterization Of Population Pharmacokinetics Of Intravenous Immunoglobulin G,10% In Patients With Multifocal Motor Neuropathy

Poster No:
4b

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Introduction:
Intravenous immunoglobulin G (IVIG),10% represents an effective therapy for multifocal motor neuropathy (MMN), a rare, immune-mediated peripheral neuropathy. This analysis characterized the pharmacokinetics (PK) of IVIG,10% in patients with MMN and assessed potential covariate effects using population PK (popPK) modeling.

Methods:
Overall, 309 serum trough concentrations of total immunoglobulin G (IgG) were available from 44 IVIG treatment-experienced adults with MMN, following IVIG,10% administration in a phase 3 randomized placebo-controlled trial (NCT00666263). IVIG dose ranged from 0.4 to 2.0 g/kg and was administered every 2, 3, or 4 weeks throughout the 60-week study. IVIG,10% popPK were described using nonlinear mixed-effects modeling. Patient baseline characteristics were tested as covariates in a systematic stepwise procedure.

Results:
IVIG,10% PK were well characterized by a one-compartment turnover model with constant endogenous IgG production. The model included first-order elimination with three structural parameters: volume of distribution (V1); the rate constant for elimination; and the latent IgG concentration in the absence of treatment (CBASE). Lean body mass was identified in covariate analysis to significantly affect V1 and was therefore included in the final popPK model. Random effects describing interindividual variability were estimated to be percent coefficient of variation (%CV) 32.6% and 17.7% for V1 and CBASE, respectively, and residual variability was described with a proportional model (%CV 9.5%). Fixed-effect parameters were estimated with good precision (percent relative standard error <11.2%).

Conclusions:
This is the first model describing IVIG,10% popPK in MMN, based on sparse serum trough concentrations of total IgG. The model described the observed data well and may provide a tool to predict individual IgG PK profiles in MMN under different dosing regimens. This model sets the foundation for future PK/pharmacodynamic modeling to understand the relationship between serum IgG concentrations and clinical efficacy outcomes in patients with MMN. Study/medical writing support funder: Takeda Development Center Americas, Inc.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: Population pharmacokinetics, Intravenous immunoglobulin G, Multifocal motor neuropathy
Serum peripherin is superior to NFL as a biomarker for axonal damage in inflammatory peripheral nerve disease

Poster No:
5b

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Introduction:
No reliable blood biomarkers are in current clinical use for the diagnosis and management of inflammatory neuropathies. Serum neurofilament light chain (NFL) is elevated in acute (Guillain-Barré syndrome, GBS) and chronic inflammatory neuropathies (chronic inflammatory demyelinating polyradiculoneuropathy, CIDP) and many other peripheral nervous system (PNS) and central nervous system (CNS) diseases. However, NFL is non-specific and cannot distinguish between CNS and PNS injury, with a slow elimination profile in the bloodstream which precludes sensitive monitoring of disease activity. Peripherin is an intermediate filament protein expressed almost exclusively in PNS neurons. We postulated that peripherin would be a more specific biomarker than NFL for peripheral nerve disease.

Methods:
We obtained longitudinal serum samples from GBS and CIDP patients. We assayed absolute serum peripherin and NFL levels using Single molecule array (Simoa), and compared these to normal controls and patients with multiple sclerosis (as a comparator group for patients with CNS inflammatory disease).

Results:
Serum peripherin displayed superior kinetic properties and specificity for GBS and CIDP compared with serum NFL in differentiating between CNS and PNS inflammatory disease.

Conclusions:
We postulate that peripherin may be a reliable and specific biomarker for peripheral nerve axonal damage which could supersede neurofilament in bioassays.

References:
Yes

References 1:
RYS Keh and D Smyth contributed equally to this work.
Keywords: Biomarkers, Inflammatory neuropathies, GBS, CIDP
Novel variants broaden the mutational spectrum of Hereditary Sensory and Autonomic Neuropathy disorders

Poster No:
6b

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Introduction:
Currently approximately 20 genes have been identified in which pathogenic sequence variants lead to a monogenetic disorder of lack of pain perception. This includes clinical entities such as hereditary sensory and autonomic neuropathies (HSAN) and congenital insensitivity to pain (CIP). Clinically, the various disorders manifest themselves through repeated trauma and mutilation. Yet, small individual patient cohorts and the lack of standardized phenotype information hinder the complete elucidation of these genetic disorders.

Methods:
The European Network on Inherited Sensory Neuropathies and Insensitivity to Pain (ENISNIP) was established by seven research centers and two patient advocacy organizations specialized on HSAN/CIP and it aims at accumulating the knowledge from clinicians, geneticists, basic scientists and patients. For the present work, existing sequencing datasets of the ENISNIP project partners and collaborating research institutions were screened and novel likely pathogenic alterations in the already known HSAN/CIP genes were compiled.

Results:
In 43 patients, we identified 45 likely disease-causing novel variants in the following HSAN/CIP genes: ATL3, DST, FLVCR1, NGF, NTRK1, PRDM12, RAB7A, SCN9A, SPTLC2 and WNK1. All variants were rare or absent from control cohorts and none had previously been reported in the literature. If applicable, the pathogenicity was corroborated by segregation analyses within the families.

Conclusions:
Through compiling the existing sequencing data within the network, here we report on 45 novel pathogenic variants in known HSAN/CIP genes. This work thus expands the mutational spectrum of HSAN/CIP, gives insights in the pathogenicity and facilitates future diagnosis of affected patients of these rare disorders.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Hereditary sensory and autonomic neuropathy, Congenital insensitivity to pain
Update on the Dutch Guillain-Barré syndrome Mimics Study

Poster No:
7b

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Introduction:
Accurate and rapid diagnosis of Guillain-Barré syndrome (GBS) is often difficult due to the heterogeneity of the disease course, the comprehensive differential diagnosis and the lack of a confirmative test. The Dutch GBS Mimics Study aims to (i) describe the differential diagnosis of GBS, (ii) establish discriminating factors between GBS and GBS mimics and (iii) validate existing clinical criteria for GBS.

Methods:
The GBS Mimics Study is an ongoing national, multicenter, prospective cohort study in which all patients with GBS in the differential diagnosis can be included. Detailed clinical and diagnostic data are collected at the time of first contact and the time of diagnosis. The diagnoses GBS or GBS mimic are checked for each patient by an independent team of neurologists.

Results:
From the preliminary analysis of the first 337 included patients, n=193 (57%) had a final GBS diagnosis and n=144 (43%) a GBS mimic diagnosis. Frequent mimics were chronic inflammatory demyelinating polyneuropathy (n=18), metabolic causes (e.g. vitamin deficiencies; n=13), malignant or paraneoplastic diseases (n=13), (post)infectious/auto-immune myelitis (n=12) and infectious polyradiculitis (e.g. neuroborreliosis; n=10). At time of first contact, limb weakness was present in 71% of GBS and 68% of GBS mimics patients. Hypo- or areflexia was seen more often in GBS (89%) than in GBS mimics patients (66%), p<0.001. A more extensive analysis of potential discriminating factors between GBS and GBS mimics will be presented at the upcoming PNS meeting.

Conclusions:
This study provides important insights into the differential diagnosis of GBS and intends to define early distinguishing features between GBS and its mimics. Patient inclusion and data quality checks are ongoing. The results may help to improve the diagnostic process in daily practice, and may be valuable to evaluate existing clinical criteria.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Guillain-Barré syndrome, Differential diagnosis
Early recognition of Guillain-Barré syndrome with treatment-related fluctuations and acute-onset chronic inflammatory demyelinating polyneuropathy

Poster No:
8b

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Introduction:
Guillain-Barré syndrome (GBS) is a typical monophasic disorder, but secondary deteriorations can occur since 10% may have treatment-related fluctuations (TRFs) and in 5% the diagnosis is eventually changed to acute-onset chronic inflammatory demyelinating polyneuropathy (A-CIDP). Early recognition of patients at risk for TRF or A-CIDP has implications, as prognosis differs and additional treatment options may be considered. This study aimed (i) to describe the clinical characteristics of GBS-TRF and A-CIDP compared to monophasic GBS and (ii) to define distinguishing factors between GBS-TRF and A-CIDP.

Methods:
Prospectively collected data from the first 1000 patients in the International GBS Outcome Study (IGOS) were used. Patients with alternative diagnoses, protocol violations or insufficient data were excluded. Additional questionnaires were sent to the local investigators when TRF or A-CIDP was reported.

Results:
Of the 950 eligible patients, 874 had monophasic GBS, 40 (4%) GBS-TRF and 36 (4%) were ultimately diagnosed with A-CIDP. Cranial nerve involvement at study entry was less frequently present in GBS-TRF (35%) and A-CIDP (26%) than in monophasic GBS (50%), \(p=0.003\). A-CIDP patients significantly more often had sensory deficits at study entry (89%) compared to GBS-TRF (65%) and monophasic GBS (60%). Both GBS-TRF (16 days, IQR 8-33) and A-CIDP (18 days, IQR 7-35) patients had a longer time from symptom onset until nadir compared to monophasic GBS (7 days, IQR 4-12). Nine GBS-TRF patients had a deterioration after 8 weeks from onset, but remained diagnosed with GBS. Patients with \(\geq 3\) TRFs (\(n=2\)) were diagnosed with A-CIDP. The GBS disability score at study entry did not differ between the three groups. Mechanical ventilation was required in 11% A-CIDP, 18% GBS-TRF and 18% monophasic GBS patients.

Conclusions:
Although GBS-TRF and A-CIDP patients have overlapping characteristics, there are distinctive features. More extensive analyses are ongoing and these results will be presented at the upcoming PNS meeting.

References:
No

References 1:

References 2:
Keywords: Guillain-Barré syndrome, Acute-onset chronic inflammatory demyelinating polyneuropathy, Treatment-related fluctuations
Distal hereditary motor neuropathy due to novel YARS gene mutation

Poster No:
9b

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Introduction:
Distal hereditary motor neuropathies (dHMN) comprise a heterogeneous group of diseases that share the common feature of a length-dependent predominantly motor neuropathy. The causative genes of dHMN have implicated proteins with diverse functions, including aminoacyl-tRNA synthetase (ARS) genes which are the essential first step of protein translation. Although cases of dHMN have previously been described in other ARS genes, a tyrosyl-tRNA synthetase (YARS) mutation has only ever been reported as a dominant intermediate sensorimotor Charcot-Marie-Tooth neuropathy (CMT).

Methods:
We describe the clinical and electrophysiological profile of a patient with a novel YARS gene mutation that exhibits a unique phenotype characterized by a dHMN.

Results:
The patient is a 26-years-old male, with no relevant medical records, who at 24 years of age developed a difficulty for standing on his heels and a slightly abnormal gait. The patient reported no symptoms in the arms or sensory effects. Upon examination, the patient presented a weakness that was exclusive to the extension of his first toe as well as atrophy in his foot muscles. The electrophysiological study showed a purely motor neuropathy with normal sensory conduction. Amplitudes of compound muscle action potentials were severely decreased in the legs. The patient's father presented identical clinical symptoms and the nerve study conduction also showed a purely motor neuropathy. A genetic study was carried out in the index patient using NGS study of genes involved in CMT. This showed c.587A>G (p.E196G) mutation in heterozygosis of the YARS gene, stablished as likely pathogenic.

Conclusions:
Mutations in YARS gene have been described in two large unrelated US and Bulgarian pedigrees as a cause of a dominant sensorimotor intermediate Charcot-Marie-Tooth neuropathy. Our case is the first description of a strictly dHMN phenotype due to a mutation (c.587A>G) in the YARS gene.

References:
Yes

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: Distal hereditary motor neuropathies, Charcot-Marie-Tooth neuropathy, Tyrosyl-tRNA synthetase mutation
Timed Up and Go Test: effective tool for gait assessment in chronic inflammatory demyelinating polyneuropathy

Poster No:
10b

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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) is an entity that requires special clinical monitoring given the wide phenotypic variability and the disparate response to treatment among patients. Gait impairment is very important in CIDP and we lack an effective tool since no gait test has been validated for autoimmune neuropathies. From the point of view of CIDP, in which there may be multifactorial gait impairment the Timed Up and Go Test may provide significant value to assess the globality of the deficits.

Methods:
This is a descriptive observational study carried out between June and December 2021, which included patients with confirmed diagnosis of CIDP. The registry included demographics, gait tests, validated clinical scales in CIDP and physical examination and electromyography findings of these patients.

Results:
A total of 24 patients were recruited. The mean age was 60.6 years, and 37.5% were women. Correlation was observed between the TUG test and the other two gait tests evaluated: 10-meter walk test (r:0.95; p<0.001) and Six-Minute Walk Test (r:-0.87; p<0.001). Correlation was also demonstrated with the validated clinical scales of CIDP: INCAT (r:0.71; p<0.001) and I-RODS (r:-0.69; p<0.001), as well as with manual grip strength (r:-0.62; p=0.001). Likewise, correlation was observed between the TUG test and the quality of life measured by the EuroQol Thermometer for self-assessment of health status (r:-0.53; p=0.009) and the Activities-specific Balance Confidence Scale (r:-0.81; p<0.001). Finally, a greater affection of the TUG was observed in those patients with an alteration in vibratory sensitivity (p=0.015) and axonal degeneration in nerve conductions studies, both motor (p=0.007) and sensitive nerves (p=0.029).

Conclusions:
The present study is the first to analyze the TUG test for patients with CIDP. The study observes that the TUG test could become an effective tool for gait assessment in CIDP and, consequently, for monitoring the clinical evolution of patients.

References:
Yes

References 1:
Allen JA, Merkies ISJ, Lewis RA. Monitoring Clinical Course and Treatment Response in Chronic Inflammatory Demyelinating Polyneuropathy During Routine Care: A Review of Clinical and Laboratory Assessment Measures. JAMA Neurol. 2020 Sep 1;77(9):1159-1166.
References 2:

References 3:

References 4:

Grant Support:

Keywords: Chronic inflammatory demyelinating polyneuropathy, Outcome, Gait impairment, Timed Up and Go Test
Impact of Pain on Symptom Burden in Chemotherapy-Induced Peripheral Neuropathy

Poster No:
11b

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Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) manifests in the extremities as numbness, tingling or shooting or burning pain. However, there remains limited understanding of the impact of different CIPN phenotypes on symptom severity and burden, which may have rehabilitation and treatment implications for cancer survivors. Therefore, the purpose of this study was to identify differences between painful and non-painful CIPN and investigate potential behavioural changes associated with the painful CIPN phenotype.

Methods:
587 participants (mean age=57.3±12.9) were assessed cross-sectionally 5.5±3.1 months post-treatment with neurotoxic chemotherapy. CIPN severity was graded using a clinical-grading scale (NCI-CTCAE), a neurological examination score (Total Neuropathy Score-clinical version (TNSc)) and a patient-reported outcome (EORTC-QLQ-CIPN20). Structured-interview questions examined the impact of CIPN symptoms on exercise, sleep, and treatment-seeking behaviour. Participants were classified as 'painful-CIPN' or 'non-painful CIPN' based on responses on EORTC-QLQ-CIPN20 questions concerning numbness, tingling and shooting-or-burning pain. Group comparisons were investigated using Mann-Whitney U test or Chi-square test.

Results:
Among 587 participants, 26% (n=149) reported painful CIPN, 49% (n=290) reported non-painful CIPN, and 25% (n=148) reported no CIPN. Painful-CIPN group scored higher on CIPN severity measures, including NCI-CTCAE (painful-CIPN=median:2.0(IQR:1.0-2.0)/nonpainful-CIPN=1.0(1.0-2.0);p<0.001), TNSc (painful-CIPN=5.0(3.0-7.5)/nonpainful-CIPN=4.0(3.0-6.0);p=0.002) and EORTC-QLQ-CIPN20 (painful-CIPN=22.2(14.9-33.3)/nonpainful-CIPN=12.3(7.0-19.3);p<0.001). Participants with painful-CIPN were twice-as-likely to report their symptoms affected their ability to exercise (p=0.008), almost three-times-as-likely to report trouble sleeping due to their symptoms (p<0.001) and almost three-times-as-likely to seek treatment for their symptoms in comparison to participants with non-painful CIPN (p<0.001).

Conclusions:
Participants with painful-CIPN phenotype reported higher scores across all CIPN severity measures, including behavioural changes to exercise, sleep, and treatment-seeking behaviour. This highlights the importance of accurate identification of different CIPN phenotypes, in hopes of informing better treatment and rehabilitation options for cancer survivors with painful CIPN.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support:

**Keywords:** Chemotherapy-Induced Peripheral Neuropathy (CIPN), Pain, Phenotype, Outcome Measures
Risk of recurrences of Guillain-Barré Syndrome or exacerbations of CIDP and MMN after SARS-CoV-2 vaccination.

Poster No:
12b

Authors:
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Introduction:
Concerns on safety of SARS-CoV-2 vaccinations are common in patients with a history of Guillain Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and multifocal motor neuropathy (MMN). This study aims to determine the risk of recurrence of GBS, and exacerbations in CIDP and MMN following SARS-CoV-2 vaccination.

Methods:
We conducted a prospective, observational multicenter cohort study in three academic hospitals in collaboration with the national patient organization for neuromuscular diseases. Individuals, aged 18 years or older, with a prior diagnosis of GBS, CIDP or MMN were eligible to participate. Participants completed a questionnaire consisting of four subsets at different time points: (a) baseline, (b and c) within 48 hours before any SARS-CoV-2 vaccination, and (d) six weeks after their last SARS-CoV-2 vaccination. Participants unwilling to get vaccinated were asked to complete the last subset (d) four months after baseline (a). Outcomes of interest are any reported recurrence of GBS, exacerbation of CIDP or MMN related symptoms, treatment initiation or alteration, and hospitalization.

Results:
Questionnaires were sent to 1,160 individuals. In total, 656 participants (57%) were included in analyses. Over 1,000 vaccinations were reported by 585 individuals. None of 247 participants with a history of GBS reported a recurrence. Of 323 participants with CIDP, 13 (4%) reported an exacerbation of symptoms within six weeks following vaccination. For five (1.5%) of these patients this resulted in either restart or alteration of their maintenance treatment. One out of 166 participants (0.6%) with MMN reported an exacerbation, but did not require treatment alteration or hospital admission.

Conclusions:
In this study, no risk of a recurrence of GBS and a low risk of an exacerbation of CIDP or MMN following SARS-CoV-2 vaccination was found. Reported exacerbations might be due to spontaneous disease related fluctuations. Our data indicate no additional recommendations regarding SARS-CoV-2 vaccinations in patients with a history of immune-mediated neuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain-Barré Syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, SARS-CoV-2 vaccination, recurrence
An attempt To Simplify Diagnosis And Classification Of Peripheral Nerve Vasculitis

Poster No:
14b

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Introduction:
Peripheral nerve vasculitis remain rare and their diagnosis is a real challenge. The main purpose of this study was to evaluate the respective value of different parameters used to establish the diagnosis of peripheral nerve vasculitis, including complementary pathological techniques (special stains, immunohistochemistry). The secondary objective was to determine a minimal set of laboratory criteria to make the diagnosis of peripheral nerve vasculitis.

Methods:
This retrospective study included 67 patients who underwent neuromuscular biopsy, divided into 4 groups: definite vasculitis, probable vasculitis, CIDP and neurolymphomatosis. A review of all cases was performed to collect all clinical, biological, electrophysiological, and histological criteria proposed by the PNS in 2010.

Results:
Clinical and laboratory criteria discriminating vasculitis from control groups were asymmetry, axonal involvement, biological inflammation, T cells in vessel wall, and haemosiderin deposits in nerve. The two criteria that distinguished definite from probable vasculitis were presence of ovoids and endoneurial haemosiderin deposits. Among the complementary techniques, only multiple HE cut levels, immunohistochemistry for typing the inflammatory infiltrate and Perls staining were useful.

Conclusions:
We were able to propose a new, slightly simplified pathological classification of vasculitis, and recommendations on the management of biopsy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Peripheral Nerve vasculitis, Biopsy, Classification, Diagnosis
The overlooked involvement of small fibers in CANVAS

Poster No:
15b

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Introduction:
CANVAS, a rare disorder responsible for late onset ataxia of autosomal recessive inheritance, has gained recent attention due to the identification of its genetic cause. We have investigated the involvement of small fibers, which has been previously largely overlooked in the sensory neuronopathy of CANVAS.

Methods:
We investigated 8 patients from 6 unrelated families, who were referred to our department for diagnosis of a sensory neuropathy and/or unexplained cough and were found to carry the mutations of CANVAS. Investigations included clinical and routine laboratory analyses and skin biopsy at the distal leg and proximal thigh. Additionally, four of our patients underwent nerve biopsy.

Results:
The 8 patients had clinical and/or laboratory evidence of sensory neuronopathy. All but one had neuropathic pain that had started in an asymmetric fashion in two. Chronic cough was a prominent feature in our eight patients and had started years before neuropathic symptoms in all but one. Similarly, pain was one of the main concern in most of our patients. The course of the disease was slow and ataxia remained mild in all. Five patients were initially thought to have immune-mediated sensory neuronopathy and received immunotherapy. Skin biopsy showed a near complete and non-length-dependent loss of intraepidermal nerve fibers. Moreover, nerve biopsy findings suggested a prominent involvement of small myelinated and unmyelinated fibers.

Conclusions:
The burden of disease in CANVAS extends far beyond cerebellar ataxia and vestibular manifestations. Indeed, our study shows that small fiber involvement might be prominent in patients with this disorder, as demonstrated by sensory symptoms and skin and nerve biopsy. Additionally, chronic cough, which is encountered in a majority of patients, may be also linked to small fiber impairment at the upper airway level.

References:
No
TRPA1 Rare Variants in Chronic Neuropathic Pain Patients

Poster No:
16b

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Introduction:
This study aimed at identifying new genetic risk factors for neuropathic pain (NeuP) to better understand underlying mechanisms and drug-targetable sites.

Methods:
We collected 456 patients with NeuP characterized by Pain Intensity Numeric Rating Scale (PI-NRS) >0, classified according to pain distribution as 'length-dependent' (hand, feet), 'non-length-dependent' (diffuse) and 'atypical' (mouth, pelvic), and 216 healthy controls (HC) aged over 50. All the subjects were analyzed by target sequencing of 107 genes involved in pain signaling or modulation. Rare genetic variants (GnomAD frequency <0.01) were selected and classified following ACGS recommendations.

Results:
TRPA1 showed a significant overrepresentation of rare variants with functional or disrupting impact on the protein product in NeuP patients as compared to HC. In particular, we identified 27 non-synonymous variants exclusively present in 35 patients (7.7%), whereas no rare variant was found in HC. The majority of the variants are clustered in the N-terminal domain containing the ankyrin repeats, essential for the channel function and regulation. Interestingly, 20 (57%) patients harboring TRPA1 variants complained of non-length-dependent NeuP, 13 (37%) reported cold-induced or cold-accentuated pain, and 14 (40%) neuropathic itch.

Conclusions:
TRPA1 encodes for a polymodal Ca2+ channel, mainly expressed in sensory neurons and epithelial cells, involved in acute and chronic pain and inflammation. It is activated by various noxious stimuli, chemical agents, and intense cold. The only genetic disease associated to TRPA1 channelopathy is the Familial Episodic Pain Syndrome. Highthroughput studies on SNPs frequency found no association with NeuP susceptibility. Conversely, focusing on rare and high-impact mutations, our study suggests for the first time that TRPA1 variants are associated with complex painful conditions, particularly in patients with non-length-dependent symptoms, cold-induced pain, and severe itch. Identification of functionally relevant mutations is crucial for fully understanding the properties of this channel and designing efficient therapies rescuing TRPA1 channelopathies.
References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: pain, neuropathy, itch, genetics, TRPA1
Genetic heterogeneity of ATTRv-pn in a large Brazilian cohort: preliminary results

Poster No:
17b

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Introduction:
Genetic heterogeneity of ATTRv-pn in a large Brazilian cohort: preliminary results

Methods:
We collected clinical and molecular data from 15 reference centers spread around the entire country. Here we present a preliminary analysis of our molecular findings

Results:
We found 442 ATTRv-pn patients, from 162 families, that carried 11 different mutations. The most prevalent mutation was the Val30Met, followed by the Val122Ile (44 families) and the Ile127Val (44 families). The remaining variants were very rare present in only two families (Asp38Tyr, Arg123His) or in only in one family (Asp38Tyr, Thr70Ala, Val71Ala, Glu89Lys, Glue112Ala, Glu109Lys). Interestingly the Vao122Ile and the Ile127Val seems to be highly concentrated at the northeastern region.

Conclusions:
This a large Brazilian cohort of ATTRv-pn. As expected, the Val30Met is the most prevalent mutation, certainly due to our strong Portuguese descent. However, a great number of other variants were found, reflecting the multi ethnicity of our population. Interestingly the second and the third most frequent mutations seem to be highly concentrated at the Northeastern states, probably reflecting their founder populations.

References:
No
References 1:
References 2:
References 3:
References 4:

Grant Support: This study was partially supported by Pfizer

Keywords: TTR, Amyloidosis
Autoantibody screening in neuralgic amyotrophy patients

Poster No:
18b

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Introduction:
Neuralgic amyotrophy (NA) is a rare disorder of the peripheral nervous system with unknown pathophysiology. Fifty percent of NA cases are triggered by various immune-mediated events (infectious diseases, vaccines, or others), including hepatitis E virus infection. The objective of this study is to screen for autoantibodies targeting peripheral nerve antigens in a cohort of patients with NA associated with acute hepatitis E (HEV-NA).

Methods:
Autoantibody screening was performed in serum samples from 10 HEV-NA patients, obtained before treatment onset. The screening included testing for immunohistochemistry on monkey peripheral nerve sections, immunohistochemistry on swine sciatic nerve, immunocytochemistry on murine dorsal-root ganglia (DRG) neurons and neuroblastoma-derived human motor neurons. We analyzed the staining patterns of NA patients (n=10) and healthy controls (HC, n=39).

Results:
Mean age was 49 years; 90% of patients were male, most frequently (n=6; 60%) suffering from bilateral brachial paresis. Most patients were treated in the acute phase with IVIg (50%) or corticosteroids (40%). IgM reactivity against axons of monkey nerve tissue was detected in 30% of NA patients vs 2.6% of HC (p=0.051), whereas no IgG reactivity against axons of monkey nerve tissue was found. IgM reactivity against Schwann cells (SC) was present in 10% of NA patients vs 2.33% of HC (p=0.37) and IgG reactivity against SC was present in 20% of NA vs 4.65% of HC (p=0.10). No differences were found between IgG or IgM reactivities in DRG neurons. Non-specific reactivities in swine sciatic nerve were found in NA patients. Results from neuroblastoma-derived human motor neurons will be presented at the congress.

Conclusions:
Our study shows that some HEV-NA patients have a heterogeneous repertoire of autoantibodies directed against axons and Schwann cells. Further immunologic studies in larger, collaborative NA cohorts are needed to find potential humoral biomarkers.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: neuralgic amyotrophy, autoantibody
GENETIC PROFILING OF A BRAZILIAN COHORT OF INHERITED DEMYELINATING NEUROPATHIES

Poster No:
19b

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Introduction:
Charcot Marie Tooth disease and related disorders are the most common inherited neuromuscular disorder. Its genetic epidemiology has been well described in European, Asiatic and at the North American countries, but little is known in other regions, specialty in South America. In this study we have analyzed the genetic background of the inherited demyelinating neuropathies in a Brazilian referral centre for Neurogenetics disorders.

Methods:
This is a retrospective analysis of the genetic epidemiology of the inherited demyelination disorders followed in a Brazilian university hospital. Upper limb motor CV velocities were used for electrophysiological classification.

Results:
We have studied so far 1319 CMT1/CMT4 patients. Initially we tested for PMP22 duplication/deletion. If negative, we Sanger sequenced PMP22, MPZ and GJB1 genes. More recently, we initiated with target panels and exome sequencing. Among the 1319 CMT1/CMT4 patients, there where 791 females, age at first consultation ranged from 1.8 to 71 years old (mean=31). There were 646 PMP22 duplications, 103 PMP22 deletions, 62 GJB1, 26 MPZ, 7point mutations in PMP22 gene, 5 in LITAF, 2 in SH3TC gene and several isolated mutations in other genes. Additional 294 patients do not have a known gene. It is worth to know that at least 4 of our patients had an associated inflammatory neuropathy, responding well to treatment. Additional 5 patients presented a concomitant leprosy neuropathy.

Conclusions:
Our population of patients with inherited demyelinating neuropathies have a genotypic epidemiology that is very similar to studied populations from Europe and US. This is somewhat expected. Although the Brazilian population is extremely mixed, the European component is particularly strong at southeast region, where this study has been done. We still need to figure the genotypic distribution of other areas of the country with different ancestry.

**References:**
No

**References 1:**

**References 2:**

**References 3:**

**References 4:**

**Grant Support:**

**Keywords:** Demyelinating Charcot Marie Tooth, CMT, Genetic epidemiology
Defining the molecular mechanism of GARS1-related Charcot-Marie-Tooth disease

Poster No:
20b

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Introduction:
Aminoacyl-tRNA synthetases (ARSs) are essential enzymes required to charge tRNA molecules to cognate amino acids in the cytoplasm and mitochondria. Although ARSs are essential and ubiquitously expressed, loss-of-function (LOF) missense and small, in-frame deletion mutations in five dimeric ARS enzymes have been associated with dominant peripheral neuropathy (also known as Charcot-Marie-Tooth disease [CMT]). CMT is a genetically and clinically heterogeneous inherited peripheral neuropathy characterized by the progressive loss of motor and sensory function. Mutations in glycyl-tRNA synthetase (GARS1) have been associated with distinct clinical phenotypes where individuals can present with later-onset CMT or infantile spinal muscular atrophy.

Methods:
While protein translation and the integrated stress response have been implicated in GARS1-related CMT, the mechanism by which mutations in GARS1 lead to distinct clinical phenotypes is unclear. Since all five implicated ARSs function as dimers and since the majority of CMT-associated ARS variants cause a loss-of-function effect, we propose the possibility of a dominant-negative mechanism. To test dominant-negative effects of pathogenic glycyl-tRNA synthetase (GARS1) variants, we will develop a humanized yeast model and test GARS1 mutations for the ability to repress a wild-type copy of GARS1. To better understand the distinct clinical phenotypes, we will assess the dominant toxicity of a series of pathogenic GARS1 alleles to determine if toxicity in our yeast model correlates with disease severity. Finally, we will identify pathways that, when manipulated, improve GARS1 function by performing experimental evolution and gain-of-function studies using a hypomorphic GARS1 allele and yeast growth assays.

Results:
Here, we will present our unpublished data on development of our humanized model and on initial assessments of pathways that can improve GARS1 function.

Conclusions:
These studies will aid in defining the molecular mechanism of GARS1-related CMT and in identifying the genetic underpinnings responsible for the observed clinical heterogeneity.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** CMT, aminoacyl tRNA synthetases
PACSIN1-binding to LRP1, a pro survival receptor in Schwann cells, transactivates TrkC via a SRC family kinase-dependent pathway

Poster No:
21b

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Introduction:
Low-density lipoprotein receptor-related protein (LRP1) binds numerous ligands, some of which transactivate receptor tyrosine kinases (RTKs) via Src family kinases (SFKs) in neurons. Using affinity precipitation and LC-MS/MS, we identified PACSIN1 as an intracellular neuronal protein released from injured axons, which binds to LRP1. Binding of ligands to LRP1 may support Schwann cell (SC) reprogramming into the Repair Phenotype. The goal of this study was to determine whether PACSIN1 activates cell-signaling via LRP1 and thus, may trigger SC reprogramming in PNS injury.

Methods:
Injured rat sciatic nerve extracts were isolated using an approach that does not cause de novo cell lysis and affinity-precipitated with Fc-fusion proteins containing the ligand-binding domains of LRP1 (CCR2 and CCR4). By this approach, PACSIN1 was identified as an LRP1 ligand. The cell-signaling pathway activated by purified PACSIN1 was characterized in primary cultured SCs. The effects of Lrp1 silencing and the SFK inhibitor, PP2, on PACSIN1-induced ERK1/2, C-Jun, and TrkC phosphorylation were examined.

Results:
Purified PACSIN1 caused phosphorylation of TrkC and ERK1/2 in a concentration- and time-dependent manner. Silencing Lrp1 expression blocked the effects of PACSIN1 on TrkC and ERK1/2 phosphorylation without affecting the activity of neuro-trophin-3, a direct TrkC ligand. PP2 also blocked PACSIN1-induced ERK1/2 and TrkC phosphorylation in SCs, indicating an essential role for SFKs. PACSIN1 activated c-Jun, a key factor in the SC Repair Program in an SFK- and LRP1-dependent manner.

Conclusions:
PACSIN1 activates cell-signaling in SCs via LRP1. The effects of PACSIN1 on TrkC phosphorylation demonstrate that RTK transactivation is conserved in the LRP1 signaling pathway across different nervous system cells. The specific RTK targeted in SCs (TrkC) is novel. Activation of ERK1/2 and c-Jun by PACSIN1 suggests a major role for PACSIN1 as an initiator of the SC Repair Program in PNS injury.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support: 1 I01 RX002484 Veterans Administration

Keywords: Schwann cells, cell signaling, pacsin, lrp1, mass spec
Proximo-distal chronic juvenile motor neuropathy associated with C9ORF72 short expansion

Poster No:
22b

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Introduction:
Dominant hexanucleotide repeat expansions in C9ORF72 have been described in familial amyotrophic lateral sclerosis (fALS), frontotemporal dementia (FTD), or an association of those two diseases; with a large variability in symptoms and severity. Patients usually have hundreds to thousands of repeats, while shorter expansions (2–24) have been reported in unaffected people. Hereditary motor neuropathies (HMN) are a group of heterogeneous diseases and an increasing number of reports suggests a genetic overlap between HMN and fALS.

Methods:
We report the case of a 36 years old female with a childhood onset chronic proximo-distal HMN probably related to a short C9ORF72 expansion.

Results:
She displayed proximal deficit, frequent falls and upper limbs tremor before the age of 10, without known familial history. Symptoms were very slowly progressive. At 36 she presents with a distal amyotrophic deficit in the upper limbs, and a proximo-distal deficit in the lower limbs (4/5 MRC scale), with brisk reflexes, bilateral Hoffman sign, no Babinski, bulbar nor cognitive symptoms. Electroneuromyography shows a very stable motor neuropathy (2017-2021), CK, hexoaminidases activity, cerebral and medullar MRI were normal. Muscular biopsy revealed pure neurogenic abnormalities. NGS for HMN genes was negative, targeted analysis of SMN1 and VCP were normal, exome sequencing did not reveal any variant in known HMN and fALS genes. C9ORF72 analysis was performed considering the pyramidal signs, and revealed an heterozygous GGGGCC expansion of around 36 repeats.

Conclusions:
A such chronic and early phenotype has never been reported so far in C9ORF72-related diseases, but exhaustive explorations did not find any other cause, and both genetic and clinical findings remain in the scope of a motoneuron condition. As their genotypic and phenotypic descriptions grow more and more diverse, it appears there might be a wide-spectrum continuum between HMN and fALS. This is particularly important to consider, given the promising therapeutic strategies emerging in both diseases.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

**Keywords:** Hereditary Motor Neuropathy, Familial Amyotrophic Lateral Sclerosis
Changes in PBMCs and serum following different methods of apheresis in patients with immune mediated neurological diseases

Poster No:
23b

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Introduction:
Immune-mediated neurological diseases, such as Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Guillain-Barre syndrome (GBS) and Multiple Sclerosis (MS) are characterized by the damage of myelin due to autoimmune processes. Therapeutic apheresis is a commonly used therapy, that removes pathogenic agents such as immunoglobulins, inflammatory cytokines or complement from the patient’s blood. The methods available vary in the specificity of the extinction; plasma exchange (PE) reduces solvent factors while immunoadsorption (IA) reduces more specific pathological agents. At present, no studies are available analyzing the course of protective and destructive factors, comparing the different methods, and correlating the results with clinical outcome parameters.

Methods:
Patients with different immune mediated neurological conditions (CIDP, GBS, MS; n=56) and controls (n=16) before, during and after apheresis therapy were included. Pro- and anti-inflammatory cytokines, different neurotrophic factors, hormones, and vitamins are measured in serum. Immune cell subpopulations were determined via flow cytometry. Clinically relevant parameters, electrophysiological examinations and MRI imaging were evaluated.

Results:
Preliminary results suggest that concentration of the pro-inflammatory serum factors such as IL-17 and TNF-alpha are below detection levels, while IFN-gamma is only detectable in particular patients and reduced by both apheresis methods. The anti-inflammatory cytokine IL-10 was detected in similar concentrations before and after first PE, while it increased after first IA in some patients. Comparable results were measured for hepatocyte growth factor (HGF). The HGF level was not altered after PE but increased in most patients after IA. Immune cell populations are currently under investigation.

Conclusions:
A better understanding of the effects caused by different apheresis methods may help to improve patient's outcome regarding a specialized therapy dependent on patients' characteristics. Some may benefit from more specific removal of destructive factors while others may rely on the preservation of protective and regenerative factors in an acute therapy for demyelination conditions in neurology.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

**Keywords:** CIDP, GBS, apheresis, plasmaseparation, plasma exchange
Screen and Care in hereditary TTR-mediated amyloidosis: an Italian multicentre project

Poster No:
24b

Authors:
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Introduction:
The goal of the project is to spread awareness of the importance of screening for hereditary TTR-mediated amyloidosis (hATTR). Twenty-four physicians, referring to ten coordinators, participated in educational meetings, collected data from patients who underwent a neurologic(cardiologic examination within the past six months, described the signs/symptoms that raised suspicion of hATTR and then identified patients with confirmed hATTR.

Methods:
An educational form to help a common and organized data gathering was used to register: reason for referral, family history of neuropathy(cardiomyopathy; previous diagnosis/diagnostic elements; instrumental exams performed; signs/symptoms that raised the suspect of hATTR; neurophysiological examination, EKG; confirmation of hATTR and mutations. The aim of the data collection was to assess (a) The number of suspected/confirmed cases of hATTR (b) the signs/symptoms leading to the suspect of hATTR (c) The possible difference in the frequency of signs/symptoms leading to the suspect of hATTR in the populations with confirmed/not confirmed hATTR (d) The mutations observed in patients with confirmed hATTR.

Results:
(a) Data were collected from 10,841 patients, hATTR was suspected in 104 (0.95%) and confirmed in 15/104 (14,4%) patients. (b) The following signs/symptoms led to the suspect of hATTR: numbness/tingling; difficulty in walking; hyposthenia; balance disorders with walking difficulties; altered sensitivity to hot/cold; neuropathic pain. (c) None of the signs/symptoms described in (b) were statistically more frequent in the population with confirmed hATTR. (d) The mutations observed were: GLU109GLN; ILE88LEU; PHE84ILE; VAL50MET; HIS110ASN; VAL40ALA

Conclusions:
Once hATTR is suspected, the diagnosis is confirmed in a significant percentage of cases. Even if signs/symptoms leading to suspect of hATTR did not appear significantly more frequent in the confirmed group, probably because of the small size of confirmed group, the results outline the importance of a
careful clinical evaluation and the need to always consider the possibility of hATTR in patients with neurological/cardiological symptomatology.

**References:**
No

**References 1:**

**References 2:**

**References 3:**

**References 4:**

**Grant Support:**

**Keywords:** hereditary TTR-mediated amyloidosis, screening, care
TRPV4 mutations causing mixed neuropathy and skeletal phenotypes result in severe gain of ion channel function

Poster No:
25b

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Introduction:
Distinct dominant, gain-of-function mutations in the calcium-permeable ion channel TRPV4 (transient receptor potential vanilloid 4) typically cause non-overlapping diseases of either the neuromuscular or skeletal systems. Neuromuscular diseases include Charcot-Marie-Tooth disease 2C and forms of spinal muscular atrophy, and skeletal diseases include a spectrum of skeletal dysplasias. Although a strict separation between neuromuscular and skeletal disease was initially presumed, accumulating evidence suggests that some patients develop mixed phenotypes that include manifestations of both conditions. However, there is limited understanding of the genetic and clinical features of these patients.

Methods:
We report a 2-year-old with a novel R616G mutation in TRPV4 with a severe neuropathy phenotype and bilateral vocal cord paralysis. Interestingly, a different substitution at the same residue, R616Q, has been reported in families with isolated skeletal dysplasia. To gain insight into clinical features and potential genetic determinants of mixed phenotypes, we perform in-depth analysis of previously reported patients. Based on this analysis, we then perform comparative functional and structural assessment of selected TRPV4 mutations.

Results:
We describe a wide range of neuromuscular and skeletal manifestations in patients with mixed phenotypes. We find that some specific mutations that are more frequently associated with overlap syndromes and that mixed phenotypes have an earlier age of onset. Functional analysis of mutations that cause severe, mixed phenotypes demonstrates more marked elevations of calcium, increased cytotoxicity, and reduced sensitivity to TRPV4 antagonism. Structural analysis of the two mutations with the most dramatic gain of ion channel function suggests that these mutants likely cause constitutive channel opening through disruption of the TRPV4 S5 transmembrane domain.

Conclusions:
These findings demonstrate that the degree of baseline calcium elevation correlates with development of mixed phenotypes, age of disease onset, and sensitivity to pharmacologic channel inhibition, observations that will be critical for the design of future clinical trials for TRPV4 channelopathies.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support: NIH/NINDS K08 NS102509 American Academy of Neurology Neuroscience Research Training Fellowship NIH/NINDS R35 NS122306 Muscular Dystrophy Association 629305

Keywords: Charcot-Marie-Tooth Disease, Spinal muscular atrophy, TRPV4, Natural history, hereditary neuropathy
A Role for Calpain in Secondary Loss of Axonal Integrity in Experimental Models of Paranodal Demyelination

Poster No:
26b

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Introduction:
Axon degeneration accounts for poor recovery in patients with Guillain-Barré syndrome. The mechanism underlying axon loss in the acute motor axonal neuropathy (AMAN) variant is predicted to involve anti-ganglioside antibody (AGAb) binding and activation of the complement cascade. Uncontrolled influx of water and ions, including calcium, through complement pores results in structural disruption through activation of the calcium-dependent cleavage enzyme calpain. However, the mechanisms of secondary bystander axon loss in demyelinating variants are less clear. We have recently generated 'Glial' Tg-mice that exclusively express complex gangliosides on their glial membranes, allowing selective targeting with an AGAb. Using these mice we developed acute(4h) and extended(20h) experimental models in which we observed an early disturbance in the localisation of key paranodal junction proteins, followed by a delayed loss of axonal integrity. Herein, we assessed the role of calpain in both paranodal disruption and secondary axon loss using the exogenous inhibitor AK295 (provided by J.Glass), and transgenic mice that over-express the endogenous calpain inhibitor calpastatin (hCAST, provided by K.Saatman) in their axons (Glial x hCAST).

Methods:
Paranodal and axonal integrity were compared in our established acute and extended ex vivo injury models, respectively. Immune-mediated injury was induced at distal axons by administering AGAb and complement. Immunostaining for AnkyrinB was performed to assess cleavage of this known calpain substrate as it is a critical glial cytoskeletal anchor for neurofascin155 at the paranode. Additionally, neurofilament, also a known calpain substrate, was used as a marker of axonal structural integrity.

Results:
Both AnkyrinB and neurofilament integrity are protected by AK295 treatment, while only axon integrity is protected by endogenous axonal hCAST.

Conclusions:
In summary, calpain has a role in both paranodal disruption and secondary bystander axon loss. These studies provide proof of principle that calpain inhibition can protect axons in either variant and lays the foundation for further study.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support: Wellcome Trust

Keywords: paranodal demyelination, secondary bystander axon degeneration, calpain, node of Ranvier
Kinome dysregulation in a CMT2E iPSC-derived motor neuron system

**Poster No:**
27b

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**Introduction:**
Missense variants in the neurofilament light chain gene (NEFL), an integral protein in the axonal cytoskeleton, cause Charcot-Marie-Tooth disease type 2E. Molecular pathomechanisms have yet to be described for CMT2E. The NEFL protein (NFL) is dynamically shifting between states of assembly/disassembly as the axonal cytoskeleton is continuously remodeled, driven by phosphorylation of the NFL head domain at certain serine residues. A causal variant of CMT2E substitutes asparagine for a serine in the rod domain adjacent to the known head domain phosphoserines. We hypothesize that aberrant phosphorylation is created at this residue, catalyzing NFL misdistribution and NFL-positive deposits observed in iPSC-derived motor neurons.

**Methods:**
To identify candidate kinases involved in the phosphorylation at the serine substitution, we performed a network absorption analysis using RNA sequencing data from iPSC-derived patient and control motor neurons. A curated list of 54 kinases able to recognize the binding motif surrounding the serine substitution was generated using the software Group Based Prediction Systems. Protein-protein interactions were determined through the Reactome and KEGG databases. Changes in gene expression from the iPSC-derived motor neuron RNA sequencing were used to model patterns of information flow through protein-protein interactions using a network propagation approach.

**Results:**
This approach determined the probability of protein-protein interactions as a function of the gene's expression, denoting the interactions within the network that significantly differ between affected and controls. Significantly altered interactions were explored using co-localization immunocytochemistry. Candidate kinases were compared for co-localization with NFL-positive deposits and quantified in a HSC platform.

**Conclusions:**
Computational approaches based on expression profiles have shed light on potential pathomechanistic outcomes in CMT2E. Ongoing experiments include solubilization/isolation of NFL (p.N98S) for HPLC/MS as well as exploration of top kinase candidates in co-precipitation with NFL. Identification of key kinases involved in observed molecular pathology is imperative to development of small molecule treatment strategies for a disorder currently without treatment.

**References:**
No

**References 1:**
Keywords: Axonal neuropathy, RNA sequencing, Network Analysis, Kinase, Neurofilament
INChase: a Global CIDP Registry

Poster No:
28b

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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) is a remarkably heterogeneous disease with many unanswered questions. INChase is a global web-based registry, with the collective aim of gathering large-scale uniform, high quality prospective data on CIDP patients. Objectives include development of a prognostic model to predict treatment response and discovery of novel biomarkers for diagnosis, disease activity and prognosis, and to elucidate unknown pathophysiological aspects of CIDP.

Methods:
INChase is a modular registry, accessible by researchers worldwide, with which extensive longitudinal data on CIDP patients can be obtained. All modules include the collection of comprehensive baseline data, with follow-up varying from a minimal clinical dataset each 6 months (core module) to extensive data collection and extra visits (extended module). Collection of biomaterials is optional. Supplementary modules capture data on plasma-exchange and subcutaneous immunoglobulins. The database is subject to ongoing improvements, including adjustments to the EAN/PNS diagnostic criteria. Additionally, a new module on biomarkers of disease activity is in production, which will include home-measurements by patients and additional collection of biomaterials to identify novel biomarkers.

Results:
Many centers have expressed interest in participation. Currently, 12 centers from 5 countries are operational, with 40 patients total included. Another 20-30 centers are expected to complete local regulatory procedure in the near future, including facilities in United Kingdom, Belgium, Denmark, Germany, Russia, Australia, Malaysia, and Taiwan. The biomarker of disease activity module is expected to be operational by June 2022.

Conclusions:
Collection of large-scale standardized prospective data on CIDP patients is feasible using INChase. Further enrollment of centers worldwide is anticipated. Centers are invited to contact us for participation. Collected data will be used to answer vital unresolved questions in CIDP and may lead to more patient tailored treatment. INChase is supported by the GBS/CIDP foundation, CSL Behring, Grifols, Takeda, Kedrion and Terumo BCT.

References:
No

References 1:

References 2:

References 3:
References 4:

**Grant Support**: INCbase is supported by the GBS/CIDP foundation, CSL Behring, Grifols, Takeda, Kedrion and Terumo BCT.

**Keywords**: Chronic inflammatory demyelinating polyneuropathy, CIDP, INCbase, Biomarker
Changes in the expression of TRP channels induced by oxaliplatin in lumbar dorsal root ganglia and spinal cord of male and female rats

Poster No:
29b

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Introduction:
Transient receptor potential (TRP), cation channels involved in the detection of different types of stimuli, play a crucial role in pain neurotransmission. TRPA1 can be activated by chemical, thermal (cold) and mechanical stimuli; TRPV1 by capsaicin, noxious heat and low pH; TRPM8 by cool temperatures and cooling compounds. Interestingly, TRP expression and activity have been proposed to be regulated by sex hormones. In addition, sex differences have been observed in the expression of clinical and experimental pain. However, they have not yet been evaluated in oxaliplatin-induced pain.

Methods:
The objective of our work was to evaluate the development of mechanical and cold allodynia in animals exposed to oxaliplatin, analyzing the existence of sex-related differences. We also analyzed the expression of TRPV1, TRPM8 and TRPA1 in lumbar dorsal root ganglia (DRGs) and spinal cord (SC) of control and oxaliplatin-treated animals. Adult male and female rats were injected with oxaliplatin or saline. Mechanical and cold allodynia were assessed using von Frey and Choi tests, and TRPs mRNA levels were evaluated by real time RT-PCR.

Results:
Oxaliplatin administration induced the development of mechanical and cold hypersensitivity and allodynia in both male and female animals. No significant sex-related differences were observed. Oxaliplatin also induced a significant increase in the expression of TRPV1, TRPM8 and TRPA1 in the DRGs of male and female rats. Interestingly, while TRPV1 and TRPA1 upregulation showed no sex difference, the increase in TRPM8 mRNA levels was more pronounced in female ganglia. TRPV1 and TRPM8 were also found to be upregulated in the SC of both male and female rats.

Conclusions:
Our results show that the upregulation of TRPV1, TRPM8 and TRPA1 may contribute to oxaliplatin-induced mechanical and cold allodynia in males and females.

References:
No

References 1: 

References 2: 

References 3: 

References 4: 
Grant Support:

**Keywords:** Chemotherapy-induced neuropathic pain, Transient receptor potential channels, Sex-differences, allodynia, Dorsal root ganglia
Development of Chemotherapy-induced Peripheral Neuropathy is Reduced in MRL Mice Strain

Poster No: 30b

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Introduction: Chemotherapy induced peripheral neuropathy (CIPN) is an impactful clinical entity affecting 30-70% of patients that often determines the length and dosage of cancer treatment. While an effective treatment against cancer cells, it also has an affinity for peripheral nerve fibers leading to dysfunction or degeneration in 50-70% of patients acutely and 30% of patients chronically. The Murphy Roths Large (MRL/MpJ) strain of mice have demonstrated superior wound healing and peripheral nerve regeneration through resisting the degradation of myelin. This study aims to examine whether the same principles can prevent the development CIPN.

Methods: A validated model of CIPN was used to compare, MRL/MpJ (experimental) and C57/BL6 (control) mice. Animals received paclitaxel (PTX) at a total dose of 8mg/kg administered at 2mg/kg for four doses on alternate days (low-dose) or a single 35mg/kg dose (high-dose). Evaluation of allodynia, thermal sensitivity, gait analysis, and electrophysiology was completed. At the 4-week end point sciatic nerves were harvested from both groups for analysis.

Results: Low-dose animals failed to develop clinical signs of CIPN. In the high dose experiments, C57/BL6 developed significant gait disturbances and thermal sensitivity compared to the MRL/MpJ strain. In both high- and low-doses, the MRL/MpJ demonstrated no significant change in nerve conduction analysis whereas the C57/BL6 had a significantly decreased velocity and increased latency. Histologically, the MRL/MpJ strain demonstrated no significant change in myelination or axon irregularity whereas the C57/BL6 demonstrated significantly decreased myelination and increased irregularity.

Conclusions: This study suggests that future animal models for CIPN should focus in clinically translatable doses. The MRL/MpJ strain has demonstrated a resistance to developing CIPN that is likely due to the prevention of axonal demyelination. Future long-term studies are required to determine whether this is long-lasting. Encouragingly, this strain may open novel mechanistic opportunities that target the prevention of CIPN.

References: No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: chemotherapy, neuropathy
Skin biopsy parameter-driven phenotyping of autoimmune neuropathies

Poster No:
31b

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Introduction:
A sector/antigen-based classification system has been suggested to systemize autoimmune neuropathies and avoid taxonomic confusion. In this study, we attempted to phenotype autoimmune neuropathies based on the morphology of dermal myelinated fibers.

Methods:
Twenty-five patients with autoimmune neuropathies underwent skin biopsy. We labeled the sections with antibodies targeting major domains of myelinated fibers: axon (PGP9.5), myelin (MBP), paranode (Caspr), and node (Nav). Several quantitative parameters were calculated from Z-serial confocal images. Data-driven clustering partitioned patients into subgroups with similar myelinated fiber morphologies.

Results:
Each of the three clusters showed distinct clinico-pathological profiles. Cluster 3 showed internodal alterations with sparing of the nodo-paranodal structure. This group could be referred to as demyelinating internodopathy. Complete loss or extensive dispersion of the Caspr bands was distinct in cluster 2; we suggest paranodopathy for this group, which can be further divided into paranodo-internodopathy or nodo-paranodopathy. Cluster 1 showed pathologic alterations restricted to the nodal domain and several clinical clues for nodopathy; therefore, nodopathy explains this cluster better than the classical axonopathy.

Conclusions:
Skin biopsy may aid systematic classification and provide mechanistic insights into individuals with autoimmune neuropathies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:
**Keywords:** Autoimmune neuropathy, Skin biopsy, Data-driven clustering, Neuropathology
A hiPS-derived cellular model of motor neurons to investigate impaired mechanisms in GDAP1-associated Charcot-Marie-Tooth disease.

Poster No:
32b

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Institutions:
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Introduction:
Charcot-Marie-Tooth (CM) disease is the most common inherited peripheral neuropathy in humans. Nevertheless, pathophysiological mechanisms of CMT are not always known, because of its wide genetic and phenotypic heterogeneity. In our study, we have focused on GDAP1 gene, coding for a mitochondrial protein, and responsible for axonal, dominant and recessive, CMT forms. In previous works, some GDAP1-associated mechanisms have been suggested by functional analysis conducted on animal models, or cellular models, like cell lines and human fibroblasts. However, GDAP1 seems mostly expressed in neural cells.

Methods:
Starting from dermal fibroblasts of a CMT2H patient and two control subjects, we developed a cellular model of human induced-pluripotent stem cells (hiPSCs)-derived motor neurons (MNs). First of all, we evaluated neural cells' proliferation and viability. Then, morphological analyses were conducted by electron microscopy, focusing on mitochondrial inner organization, and cytoplasmatic structures. At functional level, oxidative stress and energetic production were analyzed by specific tests.

Results:
Our analyses have shown that CMT2H patient's neural cells, carrying the p.Ser194* GDAP1 mutation, presented reduced cell proliferation and a significant lower cell viability, compared to controls. At morphological level, we observed, in cytoplasm of patient's MNs, the accumulation of lipid droplets, which are often considered as markers of cellular stress, or bioenergetic disorders. Moreover, their mitochondria displayed a general disorganization of the inner structure, and swollen cristae. These morphological alterations were not associated with reduction of ATP synthesis. Finally, we have demonstrated that patient's cells were characterized by a most important mitochondrial oxidative stress in basal conditions.

Conclusions:
In conclusion, our study, presenting the first functional analysis on human GDAP1-mutated MNs, has allowed to highlight some impaired mechanisms in this CMT axonal form. In the near future, it will be interesting to better explore GDAP1-associated oxidative stress and metabolic networks, to identify new potential targets for innovative CMT-therapeutic strategies.

References:
No
References 1:
References 2:
References 3:
References 4:

Grant Support:

Keywords: CMT, Motor neurons, hiPSC, GDAP1
Injury-associated IL-6 and ephrin B2 Drive Both Somatic and Axonal Protein Synthesis in a Subset of Human DRG Neurons and Spinal Nociceptive Circuits

Poster No:
33b

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Institutions:
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Introduction:
Current chronic pain therapies remain largely ineffective forcing millions of individuals across the globe to overcome their often, persistent and debilitating symptoms without adequate relief. A major obstacle to improving the poor outcomes of these patients is that few findings from pre-clinical rodent models are successfully transferred to the clinic. This underscores the variation in chronic pain mechanisms between rodents and humans. Therefore, we need to interrogate the basic biology of injury-induced signaling in human nociceptive circuit function and regulation. A wealth of work in rodent models has shown that chronic pain states arise from long-term, maladaptive plasticity in primary nociceptors and spinal circuits that drives abnormal pain pathway activity. This extreme shift in function requires activity-dependent protein synthesis in both DRG and spinal neurons. In mice, injury-associated signals such as IL-6 and ephrin B2 are critical drivers of this process and engage nociceptive circuitry through distinct mechanisms. In humans, a significant gap in our understanding of chronic pain pathophysiology is whether these signals drive protein synthesis in subsets of DRG and spinal cord neurons.

Methods:
To approach this question, we assayed IL-6 and/or ephrin B2 driven protein synthesis in DRG and spinal cord acute slice preparations from organ donors using Fluorescent Noncanonical Amino Acid Tagging (FUNCAT).

Results:
Here, we show that these injury-associated signals drive increased protein synthesis in TRPV1-expressing DRG somata and in a subset of lamina I/II and IV/V spinal neurons. We further found that these signals drive local translation in the dorsal root and spinal compartments of TRPV1-expressing nociceptors.

Conclusions:
Overall, these findings are consistent with nociceptor and spinal circuit-specific roles for IL-6 and ephrin B2 driven protein synthesis in the development and maintenance of chronic pain in human patients.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support: NIH NINDS R01, 2019 - 2024- Project #: 5R01NS115441-02

Keywords: Protein Synthesis, Nociceptor, Translation, Spinal Cord, FUNCAT
Characterization Of Axonal Degeneration Mechanisms in Bortezomib-Treated Sensory Neurons

Poster No:
34b

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Introduction:
Bortezomib (BTZ) is a proteasome inhibitor used for the treatment of multiple myeloma. BTZ treatment results in axonal degeneration, producing a disabling painful toxic peripheral neuropathy in approximately 50% of patients. In the current study, we examined whether treatment with BTZ for 24 hours would affect microtubule (MTs) stability as well as axonal transport and oxidative phosphorylation in primary cultured dorsal root ganglion (DRG) sensory neurons.

Methods:
MT stability was indirectly measured by western blotting and quantitative confocal microscopy of delta2-tubulin and tubulin acetylation, while axonal mitochondrial trafficking was evaluated by time-lapse confocal microscopy and kymograph analysis. To evaluate the effects of BTZ on the generation and regulation of cellular bioenergetics, mitochondrial oxidative phosphorylation (OXPHOS) was assessed via western blot analysis of key molecular markers.

Results:
BTZ treatment of cultured DRG sensory neurons induced an approximately 2.5-fold increase of delta2 and acetylated tubulin levels, which occurred at the onset of axonal degeneration. Furthermore, DRG axonal mitochondrial motility and trafficking were decreased by BTZ; these changes occurred independently of the direction of mitochondrial trafficking. Finally, BTZ treated DRG neurons had differential protein expression of OXPHOS subunits compared to untreated DRG neurons.

Conclusions:
In summary, our results demonstrate that BTZ affects both MT stability and mitochondrial function in DRG neurons, supporting the idea that both loss of normal tubulin and mitochondria function together promote the development of BTZ mediated neuropathy. This work is supported by Fondazione Cariplo, Grant # 2019-1482

References:
No

References 1:

References 2:
Grant Support: This work is supported by Fondazione Cariplo, Grant # 2019-1482

Keywords: Bortezomib, peripheral neuropathy, microtubule stability, tubulin, mitochondria
Investigating the Activation and Modulation of YAP/TAZ in a Mouse Model of CMT1A

Poster No:
35b

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Introduction:
Charcot-Marie-Tooth 1A (CMT1A) is caused by duplication of the peripheral myelin protein 22 (PMP22) gene leading to its overexpression. There is no cure for this debilitating peripheral neuropathy and the pathological mechanisms involved in the observed demyelination are poorly understood.

Methods:
The transcriptional coactivators Yes-associated protein 1 (YAP), and transcriptional coactivator with PDZ-binding motif (TAZ) are critical for the proper myelination of peripheral nerves (PNs) (Poitelon et al., 2016). The complex regulation of their activity includes inhibition via the mechanosensitive HIPPO kinase cascade. The differing mechanical environment of PNs in CMT1A may lead to altered regulation of YAP/TAZ, amplifying the pathology in Schwann cells (SCs). To investigate YAP/TAZ activation, their nuclear enrichment and protein phosphorylation were assessed in the C3-PMP22 overexpressing mouse model of CMT1A (CMT1A mice). Furthermore, YAP/TAZ associate with the transcription factor TEA domain 1 (TEAD1) which directly positively regulates PMP22 expression (Fernando et al., 2016; Lopez-Anido et al., 2016). This indicates an exciting novel potential therapeutic target in CMT1A. To begin to investigate the therapeutic potential of YAP/TAZ modulation, CMT1A mice with heterozygous ablation of YAP or TAZ alleles were assessed for phenotypic rescue.

Results:
Preliminary findings reveal a decrease in YAP SC nuclear enrichment in PNs of CMT1A mice during developmental and early symptomatic timepoints. Interestingly, protein levels of phosphorylated and total YAP and TAZ do not appear altered at symptomatic timepoints in these mice. Analysis of Cre lox mediated heterozygous deletion of YAP or TAZ alleles in SCs of CMT1A mice is ongoing.

Conclusions:
Further studies and analysis will both confirm and elucidate the significance of decreased YAP SC nuclear enrichment, and assess the potential of YAP/TAZ modulation to ameliorate disease phenotypes in CMT1A.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT1A, PMP22, YAP/TAZ, Schwann Cells
Hereditary Neuropathy With Liability To Pressure Palsies: A Case Series With Early-Onset

Poster No:
36b

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Introduction:
Hereditary neuropathy with liability to pressure palsies (HNPP) is a rare autosomal dominant peripheral neuropathy, caused by a 17p11.2 deletion encompassing the PMP22 gene or mutations in the same gene. Onset is typically in the second or third decade; at present literature on early onset large case series are scarce.

Methods:
We retrospectively reviewed clinical, electrophysiological, and genetic findings of 22 patients with early-onset HNPP referred to our Institute.

Results:
Age of onset ranged between 5 and 16 years. Family history was negative in 17 cases. A wide phenotypic heterogeneity was highlighted, ranging from acute (46%) to subacute (27%) motor and sensory deficits or brief transient and recurrent sensory symptoms (27%). The most affected site was the peroneal nerve (9 patients), followed by ulnar (5), median (4), brachial (3) and radial (1) nerves. Provocative factors were reported in 16 cases. Neurophysiological studies were available in 15 patients, showing multifocal conduction velocity slowing across entrapment sites in 12, associated with signs of diffuse demyelinating polyneuropathy in 7 of them. Two patients showed only generalized sensory-motor polyneuropathy; one patient had a normal study performed after clinical remission. Evidence of entrapment of median nerve at the wrist was nearly constant but rarely symptomatic. Most patients experienced complete recovery (87%). We verified a wide range of time to diagnosis (few months - 3 years) preceded by several invasive investigations in 10 patients before coming to our observation. 19 patients carried the 17p11.2 deletion and 3 PMP22 point mutations.

Conclusions:
We suggest that HNPP should be suspected in presence of acute, subacute, transient or recurrent motor and sensory deficits even in absence of family history and precipitating factors. Nerve conduction studies should include a minimum set with bilateral median, ulnar, and peroneal nerves examination. Early diagnosis is crucial to expedite appropriate molecular studies, care and familial genetic counseling.

References:

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: CHILDHOOD, HNPP, EARLY ONSET, MONONEUROPATHY
Preclinical Development of a Curcumin-Based Nanoparticle Treatment for Charcot-Marie-Tooth-1A Disease

Poster No:
37b

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Introduction:
Curcumin has been shown to display antioxidant properties and promyelinating effects in low concentration upon local delivery to the injury site in a sciatic nerve crush rat model. However, given the unfavourable pharmacokinetic of curcumin, we opted for delivering curcumin using a nanoparticle vector. Therefore, curcumin loaded-cyclodextrin (CD)/cellulose (CNC) nanocrystals (Nano-Cur) were synthesized and tested in a rat model of Charcot-Marie-Tooth disease type 1A (CMT1A), the most common hereditary peripheral neuropathy. The first results showed that Nano-Cur was effective in improving sensorimotor symptoms, in increasing myelination and decreasing oxidative stress. Furthermore, Nano-Cur markedly improved curcumin bioavailability, bio-distribution and intracellular delivery.

Methods:
In our current study, we aim at investigating the toxicity and confirming the potency of Nano-Cur both in vitro and in preclinical models of the disease.

Results:
Preliminary data suggest a low toxicity of both CD and CNC in different cell lines (Schwann cells, fibroblasts, cancer cell line). As a matter of fact, the addition of curcumin into the nanoparticles decreased cellular viability at very high concentrations (30 µM) but not at low concentration (0.15 µM), a concentration that was previously shown to be effective in the enhancement of the disease phenotype in primary CMT1A Schwann cells. In vivo, the potential effects on reversibility of the lesions after a long-term treatment is under investigation in 3-months-old CMT1A rats, and another CMT1A model (i.e. C22 mice) will be used to confirm Nano-Cur efficacy. For this sake, electrophysiological, sensory and motor behavioural measurement are being carried out as well as histopathological examinations in target organs.

Conclusions:
Taken together, this project aims at producing Nano-Cur in GLP and later GMP grades, testing its safety, elucidating its mechanisms of action, confirming its efficacy in two CMT1A animal models, while aiming at a translational application for patients with CMT1A and other forms of peripheral neuropathies.

References:
Yes

References 1:
References 2:

References 3:

References 4:

Grant Support: AFM-Téléthon

Keywords: Charcot-Marie-Tooth 1A, Peripheral Neuropathies, Nanoparticles Treatment, Curcumin, Pre-clinical studies
Clustering Peripheral Neuropathy Models with Transcriptomic Data to Identify Shared Pathways, Predictive Signatures, and Therapeutic Targets

Poster No: 38b

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Institutions: 1The Jackson Laboratory, Bar Harbor, ME, 2The University Of Maine Graduate School of Biomedical Science and Engineering, Orono, ME

Introduction: Charcot-Marie-Tooth disease (CMT) is a heterogenous group of inherited peripheral neuropathies that affect approximately 1 in 2,500 people. Clinical presentations include foot deformities, progressive muscular weakness, and loss of sensation in the distal limbs. Causal variants in more than 100 genes cause CMT implying the existence of a similar number of causal mechanisms; however, it is also known that in some CMT variants in different genes affect the same biological pathways producing convergent cellular pathophysiology, i.e. multiple forms of neuropathy involve pathological activation or disruption of cellular stress responses, cholesterol metabolism, lipid synthesis, myelination, lysosomal trafficking, etc.

Methods: The degree to which different kinds of CMT exhibit overlapping gene expression patterns and consistent dysregulation of cellular mechanisms has not been characterized in a systematic way. Here we integrate novel RNA sequencing data with public datasets from the Gene Expression Omnibus for differential expression, pathway, and enrichment analyses to compare the transcriptomic signatures of disease across multiple mouse models of CMT neuropathy and several human cell-based models.

Results: We find that mouse models of Gars and Yars aminoacyl tRNA-synthetase neuropathies exhibit converging gene expression signatures with activation of the integrated stress response, and that mouse models of CMT1A have higher Jaccard similarity to human cell-based models of CMT1A than to mouse models of other forms of CMT, suggesting consistent disease-associated gene expression programs in mice and humans. We describe the biological processes and pathways that underlie these similarities and their relative enrichment as a preliminary framework for transcriptomic categorization and clustering of CMT models, which we will expand to include several additional CMT subtypes.

Conclusions: We propose that clustering additional CMT models by shared gene expression signatures may identify novel molecular subtypes of CMT with diagnostic relevance to help improve CMT patient counseling and expand the applicability of putative treatments between CMT forms in the same transcriptomic subtype.

References: No

References 1: No

References 2:
References 3:

References 4:

**Grant Support:** 2 R37 NS054154-14 1 R21NS116936-01A1

**Keywords:** Charcot-Marie-Tooth disease, Mouse models of neuropathy, Transcriptomic subtyping, Clustering, Disease associated expression signatures
Real time imaging of mitochondrial dynamics in the dorsal root ganglion following nerve injury

Poster No:
39b

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Introduction:
Mitochondria are dynamic and motile organelles that respond rapidly to oxidative stress and cellular energy demands. Their morphological changes, as determined by fission and fusion, have been linked to the progression of neuropathic pain. However, little is known about specific pathology underlying mitochondrial dysfunction after peripheral nerve injury or how pharmacological interventions affect these changes. Our goal is to evaluate mitochondrial dynamics following peripheral nerve injury by characterizing axonal mitochondrial density, movement in axons and fusion-fission events.

Methods:
We dissociated dorsal root ganglia (DRG) from mice with spare nerve injury (SNI) and selectively labelled mitochondria with a live-cell fluorescent dye. Time lapse videos were then captured using a spinning disk confocal microscope.

Results:
We observed a significant increase in axonal mitochondrial density in DRG cultures obtained from SNI mice when compared to naïve cultures. Representative kymograph images depict a larger proportion of mitochondria moving anterogradely in axons of DRG neurons from SNI mice. Interestingly, we found that the SNI-mitochondria are trafficked at lower velocities. Previous studies have shown that calcium overload in damaged mitochondria may contribute to decreased mitochondrial motility. Additionally, we observe a decrease in perinuclear clustering within the SNI group which may indicate a disruption in mitochondrial networking or a failure to regulate fission events in DRG neurons after injury.

Conclusions:
Collectively, our findings highlight the benefit of real time imaging of DRG neurons to gain greater insight into specific aspects of mitochondrial dysfunction after nerve injury. Our findings likely have important implications for therapeutic approaches to neuropathic pain.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Supported by NIH grant NS065926
Keywords: Mitochondria, Live-cell Imaging, Spare Nerve Injury
No association between RFC1 repeat expansion and inflammatory neuropathies

Poster No:
40b

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Introduction:
Biallelic expansion of the AAGGG repeat in the replication factor C subunit 1 (RFC1) on chromosome 4 has recently been described to be responsible for the neurologic condition CANVAS characterized by cerebellar ataxia, peripheral sensory neuropathy and vestibular areflexia. This genetic alteration has also been shown in one third of patients having idiopathic sensory neuropathy; however, its frequency in inflammatory neuropathies is unknown. Therefore, we aimed to screen patients with acute inflammatory demyelinating polyneuropathy (AIDP), chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) for RFC1 repeat expansions.

Methods:
We screened 21 patients with AIDP, 152 patients with CIDP (including 5 patients with sensory variant), 63 patients with MMN and further 94 controls without neuropathy for the pentanucleotide AAGGG repeat expansion using short-range flanking PCR and repeat-primed PCR. Cases without amplifiable PCR product on flanking PCR and positive repeat-primed PCR were also tested for the non-pathogenic expansions of AAAGG and AAAAG repeat units.

Results:
None of the 236 patients showed biallelic AAGGG expansion of RFC1. The frequency of AAGGG carrier status in the heterozygous state was 4.8% in AIDP, 4.9% in CIDP and 5.5% in MMN patients, respectively. The carrier frequency for AAGGG and AAAGG expansions were comparable to controls without any statistically significant difference.

Conclusions:
Data suggests that pathologic expansion of AAGGG repeats does not contribute to the development of inflammatory neuropathies. We could not identify any patients with CANVAS misdiagnosed as immune-mediated peripheral nerve disease. Accordingly, genetic screening for RFC1 repeat expansion is not indicated in this patient group. Our results also reinforce the understanding that RFC1 is specific to sensory but not to sensory-motor or motor neuropathy. Further, the data highlights the true frequency of AAGGG expansion of ~ 5% being one of the most common pathogenic alleles in the population.

References:
No

References 1:
Keywords: Inflammatory neuropathy, RFC1, CANVAS, CIDP, MMN
Allele-specific inactivation of dominant negative FUS mutations

Poster No:
41b

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Introduction:
Mutations in the nuclear RNA-binding protein 'fused in sarcoma' (FUS) cause approximately 5% of all genetic cases of ALS and FTD and result in incurable early-onset dementia and rapid motor neuron degeneration. Over 60 dominant pathologic FUS mutations have been reported, but strong genetic and experimental evidence demonstrate that FUS is haplosufficient. We have identified spCRISPR-Cas9 gRNAs that target two naturally occurring, non-pathogenic single nucleotide polymorphisms (SNPs) in exons 3 and 4 of FUS. Editing either of these SNPs allows for specific inactivation of any mutant FUS allele while leaving the normal allele intact. Due to the high incidence of these SNPs in human populations, optimization of just 4 different gRNAs could treat up to 64% of FUS-FTD/ALS patients.

Methods:
To study FUS pathology in a clinically-relevant system, we generated a panel of human iPSC lines and iPSC-derived motor neurons (iMN) consisting of an isogenic series of FUS mutations (Prion-like domain, C-terminal truncation, and NLS) engineered into the KOLF control background (which is heterozygous at both SNP loci), two independent patient lines harboring FUS mutations, and wild-type controls.

Results:
Under arsenic-induced cell stress, all cell lines display cytoplasmic stress granules, but only lines with a mutation affecting the C-terminal NLS demonstrate mislocalization of FUS to these granules. Independent editing of each allele of each SNP in iPSCs demonstrates high editing efficiency and specificity of gRNA targeting SNP3-C, SNP3-A, and SNP4-C alleles, but poor editing of SNP4-T. Subsequent differentiation of iMNs of each edited mutant allele shows complete resolution of FUS mislocalization.

Conclusions:
These studies demonstrate a potential therapeutic approach for FUS-FTD/ALS via SNP-targeted editing. We are now exploring alternate gRNA and Cas enzymes (SaCas9, Cas12a) for improved specificity. We are also deep phenotyping our isogenic panel to explore how distinct FUS mutations lead to different cellular pathologies, which may help explain differing clinical presentations.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** iPSC, CRISPR, ALS, FTD, Fused in Sarcoma
A Comprehensive Update of the 3Gene Study

Poster No:
42b

Authors:
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Introduction:
Natural history studies of CMT1B, CMT2A, and CMT1X (the three genes) utilizing the CMT Neuropathy, and Exam Scores (CMTNS/CMTES) have been performed. However, evaluations with more recent clinical outcome assessments (COA) such as CMT Functional Outcome Measure (CMT-FOM) and CMT Health Index (CMT-HI) have not been performed nor have biomarkers or imaging studies with the three genes been completed. Potential therapies are being developed for all three disorders and 'clinical trial readiness' must be completed to permit clinical trial performance to be performed over time periods that are reasonable for industrial partners.

Methods:
The objective is to prospectively measure the natural history of patients with CMT1B, CMT2A, and CMT1X correlating functional, and patient reported COA with plasma, skin, and imaging biomarkers over a 12-month period. CMTES/CMTNS, CMT-HI, CMT-FOM, thigh and calf MRI, and biomarkers are performed at a baseline and 12-month follow-up visit. Clinical information from each visit is electronically submitted and maintained in a database housed at the Rare Disease Clinical Research Network (RDCRN) at the Data Management and Coordinating Center at Cincinnati Children's Hospital.

Results:
76 patients have been enrolled overall, with 14 CMT2A, 35 CMT1B, and 27 CMTX subjects. The lead site has enrolled 2 CMT2A, 17 CMT1B, 11 CMTX patients. There are two other sites in the U.S. One has enrolled 1 CMT2A patient, 0 CMT1B, 3 CMTX patients, and the other U.S. site has enrolled 3 CMT2A, 5 CMT1B, 3 CMTX patients. There are two sites outside of the U.S. One has enrolled 8 CMT2A, 13 CMT1B, 10 CMTX patients, and the other has begun the recruitment process.

Conclusions:
Study recruitment is ongoing and will facilitate clinical trial readiness for CMT1B, CMT2A, and CMT1X. With 76 patients enrolled, we continue to work towards our goal of 120 enrolled patients.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support: Funding for this research is provided by the CMTA.

Keywords: CMT, Charcot-Marie-Tooth, Neuropathy
Italian Database on Multifocal Motor Neuropathy: lesson from the first 100 included patients

Poster No:
43b

Authors:
EDUARDO NOBILE-ORAZIO, Pietro Doneddu, Dario Cocito, Anna Mazzeo, Luana Benedetti, Raffaella Fazio, Chiara Briani, Marco Luigetti, Gabriele Siciliano, Sabrina Matà, Giovanni Antonini, Girolama Marfia, Massimiliano Filosto, Giuseppe Cosentino, Fiore Manganelli, Maurizio Inghilleri, Vincenzo Di Stefano, Marinella Carpo, Luca Gentile, Erdita Peci, Marta Campagnolo, Erika Schirinzi, Angelo Schenone, Federica Moret, Giuseppe Liberatore

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Introduction:
Multifocal motor neuropathy (MMN) is a purely motor asymmetric neuropathy characterized by the presence of conduction blocks (CB) on motor nerves, frequent association with IgM anti-GM1 antibodies and response to intravenous immunoglobulin (IVIg). CB is the main diagnostic feature of MMN even if there are patients with clinically typical MMN responding to IVIg without detectable CB.

Methods:
We included in an electronic database data from patients followed by Italian Centres with expertise on immune mediated neuropathies to analyze the adopted diagnostic criteria and response to therapy. We reviewed data from the first 100 included patients (69 men, 31 women) with a mean age at onset of 41.5 years (range 14-78).

Results:
An initial selective involvement of upper limbs was reported by 68% of the patients, of the lower limbs in 22%, while 10% had concomitant upper and lower limbs impairment. At the time of inclusion, patients had a mean disease duration of 12.0 years (range 0.5-35 years) with a mean ONLS score of 3.2, and MRC sumscore of 54/60. A persistent selective upper limb involvement was present in 43% of the patients, of lower limb in 3% and of both upper and lower limbs in 54%. Nerve conduction studies were available in 90 patients. A definite or probable motor CB according to EFNS/PNS criteria (area reduction) was
reported in 32 (36%) patients, while 36 (40%) patients had >50% CMAP amplitude reduction including 24 with more than 60% reduction. There was no evidence of CB in 22 (24%). Increased anti-GM1 IgM antibodies were found in 26/72 (36%) patients. Treatment with IVIg was effective in 80% of treated patients.

Conclusions:
The initial review of the data revealed only a partial compliance with the EFNS/PNS criteria leading to a shared revision of the data and criteria leading to a more adequate subsequent application by the Centers.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: “Investigator-Initiated Research grant (no. IISR-2017-104226) from Baxalta US Inc, a Takeda company”

Keywords: Multifocal Motor Neuropathy, Database, Conduction Block, Diagnosis
Cellular communication of Schwann cell subtypes in Metabolic syndrome-associated neuropathy

Poster No:
44b

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Introduction:
The prevalence of the metabolic syndrome (MetS) is increasing worldwide due in part to the increased consumption of a Western diet. MetS is associated with peripheral neuropathy (PN). PN develops in a cell non-autonomous manner with involvement of axons, Schwann cells (SC) and nerve tissue infiltrating macrophages (TIM). SC are divided into subtypes with different roles in nerve injury. In the current study, we aimed at investigating how gene expression of different types of SC and macrophages are affected in MetS and how these cells communicate with one another.

Methods:
C57BL6/j male mice (6-weeks old) were fed either a standard diet (SD, 10% fat) or high fat diet (HFD, 60%) for 17 weeks. Metabolic and PN phenotyping were performed for all mice and SC were extracted from sciatic nerves for single cell RNA sequencing (scRNA-seq). Cellular communication was determined using the CellChat tool.

Results:
Mice on HFD had higher fasting blood glucose (FBG), glycated hemoglobin (HbA1c) and decreased nerve conduction velocities and intraepidermal nerve fiber densities consistent with PN compared to mice on SD. Analysis of SC scRNA-seq data revealed unique RNA expression signatures for TIM and 4 subpopulations of SC denoted as myelinating SC (mySC), non-myelinating SC (nmSC), SC precursors (SCP) and regenerating SC. Inflammatory genes such as Ptprc and Il1b were significantly more expressed in both TIM and mySC in HFD mice compared to SD mice. CellChat analysis of cellular communication revealed more crosstalk between TIM and various types of SC in HFD animals and identified multiple metabolic and inflammatory pathways that were activated in HFD compared to SD mice.

Conclusions:
In conclusion, our study shows that there are many subtypes of SC that behave differently in MetS. Their communication with each other and with TIM strongly implicates these two cell types in the pathogenesis of MetS-associated PN.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support: Funding was provided by the National Institutes of Health (NIH) (1R24082841 to ELF), Novo Nordisk Foundation (NNF14OC0011633 to ELF), the Nathan and Rose Milstein Research Fund (to SAE), NeuroNetwork for Emerging Therapies at the University of Michigan (t

Keywords: Schwann cells, single cell RNA seq, Peripheral neuropathy, Diabetes
Peripheral neuropathy evaluations of patients with Long-COVID

Poster No:
45b

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Introduction:
SARS-CoV-2 recovery is exponential, leaving a tail of patients with prolonged unexplained symptoms including fatigue/exertional intolerance, dysautonomic and sensory concerns. ‘Long-COVID’ is caused by multiple types of tissue/organ damage. Reported neuropathies include Guillain-Barré syndrome, mononeuritis multiplex, brachial plexitis and cranial neuropathies. Various long-COVID symptoms overlap with symptoms of small-fiber neuropathy.

Methods:
To better characterize long-COVID neuropathies, this 10-state study analyzed WHO-defined long-COVID patients without pre-existing neuropathy or risks referred for neuropathy evaluations. We captured patient-reported symptoms using the Small-fiber Symptom Survey, standardized neuropathy examinations, objective neurodiagnostic tests, and outcomes.

Results:
Among 17 patients (43.3 ±3.3y, 69% female, 94% Caucasian, 19% Latino), 59% had ≥1 test interpreted as confirming neuropathy—63% (10/16) of skin biopsies, 50% (4/8) of autonomic function tests, and 17% (2/12) of electrodiagnostic results. Initial SFN symptom scores were 40.7% of ideal; pain averaged 4.8/10. Initial exams averaged 77.0% of ideal, with reduced/abnormal distal pin and vibration and absent Achilles reflexes most prevalent. Only two patients—one with critical-care neuropathy (after severe COVID-19 with prolonged intubation) and another with multifocal motor neuropathy (after mild COVID)—had distal weakness and muscle atrophy. ≥10 received small-fiber neuropathy diagnoses, all after mild COVID. During >1y post-COVID, symptom improvement averaged 52% without complete remissions. 65% (11/17) received immunotherapies (corticosteroids and/or IVIg).

Conclusions:
The most common neuropathy was prolonged, often disabling, small-fiber neuropathy starting within 1 month of mild COVID-19. This first reported case of multifocal motor neuropathy increases types of COVID-associated neuropathies. Evidence suggested infection-triggered immune dysregulation as the most prevalent pathogenesis. Some human DRG neurons express SARS-CoV-2-associated receptor ACE2. Virus/spike protein attachment might promote antibodies cross-reacting with adjacent neural epitopes. Patients' slightly delayed onsets, prolonged post-infectious courses and apparent responses to immunotherapy support dysimmune causality. Case series cannot confirm causality. However, identifying small-fiber and multifocal motor neuropathy in this long-COVID series provides preliminary data for larger study.

References:
No
**Grant Support:** Supported in part by the National Institutes of Health; R01NS093653 (ALO). Division of Intramural Research, NINDS (AN) and the Department of Neurology of Thomas Jefferson University (MCD)

**Keywords:** SARS-CoV-2, post-infectious neuropathy, small-fiber neuropathy, multifocal motor neuropathy
A Cross-sectional Analysis Of Spinal MRI Findings In UK hATTR

Poster No:
46b

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Introduction:
As well as peripheral neuropathy, hereditary transthyretin amyloidosis (hATTR) is known to be associated with spinal stenosis. Gene silencing therapy including patisiran and inotersen are now standard treatment in the UK. This study aimed to analyse the extent of spinal MRI changes in a cohort of hATTR patients some of whom were subsequently treated with gene silencing therapy.

Methods:
Data was obtained from 139 patients on gene silencing therapy, 61 of whom had been assessed between March 2009 and September 2021. Using electronic patient records, we performed a cross sectional analysis of 18 patients who had an MRI scan of their spinal cord.

Results:
Ligamentum flavum (LF) hypertrophy was demonstrated in 13 patients, 3 of whom had definitive symptoms of spinal claudication. LF hypertrophy was present across most TTR variants with the highest proportion in the T60A and V122I variants. Ten patients had LF hypertrophy with associated spinal stenosis, 3 of which were classified as severe. Three patients had repeat spinal imaging post gene silencing therapy (range 9-26 months) and had no significant radiological change and did not require surgery. Of the patients not on treatment at the time of repeat imaging, one required spinal surgery and one patient developed new LF hypertrophy and neural foraminal stenosis.

Conclusions:
Significant spinal MRI findings are present in hATTR patients and occur across different genetic variants. Further longitudinal studies examining this will be of future benefit.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: hATTR, Spinal stenosis
Muscle MRI Findings In Patients With SORD Neuropathy

Poster No:
47b

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Institutions:
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Introduction:
Recently biallelic mutations in the sorbitol dehydrogenase (SORD) gene were identified as the most frequent cause of autosomal recessive Charcot-Marie-Tooth (CMT) disease. MRI quantification of intramuscular fat accumulation is a highly responsive biomarker for disease progression in other hereditary neuropathies such as CMT1A. We aimed to define the pattern of abnormality on muscle MRI in SORD neuropathy in order to assess its potential role as a disease biomarker in clinical trials.

Methods:
We retrospectively identified patients with a confirmed pathogenic variant in the SORD gene in whom an MRI scan of lower limb muscles had been performed. Clinical data was retrieved within 3 months of the MRI scan. T1-weighted and STIR MRI sequences of thigh and lower leg muscles were retrospectively analysed using semi-quantitative scales for: fat infiltration (Mercuri grade), atrophy and oedema (STIR extent and intensity).

Results:
Six patients were identified (5 male, mean age 33; range 21-44). Mean Mercuri and atrophy grades were higher in calf than thigh muscles, however all patients had abnormal fat infiltration in the thigh, most commonly distally within vastus lateralis and intermedius. There was calf muscle atrophy in all patients and STIR hyperintensity was present on all scans, most markedly in tibialis anterior. There was correlation with MRI Mercuri and atrophy grades with age, CMTES (CMT Examination Score) and disease duration with the highest correlation observed with CMTES (r 0.74). One patient had a second MRI scan after a 4 year interval which demonstrated progression in Mercuri and atrophy grades without change in CMTES.

Conclusions:
This is the first semi-quantitative MRI study in SORD neuropathy and demonstrates longitudinal MRI changes. MRI has potential as a sensitive outcome measure in clinical trials for SORD neuropathy and larger prospective studies using 3-point-Dixon fat-fraction should be considered for further validation.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: SORD, MRI
Cutaneous Neuropathic Features in Prurigo Nodularis

Poster No:
48b

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Introduction:
Prurigo nodularis (PN) is a chronic inflammatory skin disease characterized by hyperkeratonic nodules. It affects about 0.1% of the population (majority are middle aged females). General symptoms include intense pruritis, burning pain, stinging in the affected skin, which result in limiting patients' activity and can dramatically reduce their quality of life. Previous research focused mainly on immune dysregulation hypothesis involving cytokines, inflammatory mediators and immune cells.

Methods:
In the current study, we compared intraepidermal nerve fiber density (IENFD), mechanoreceptors and blood vessels from affected and unaffected skin from patients with PN and control subjects. Three mm punch skin biopsies were obtained from 10 prurigo nodularis patients at the distal leg of both affected skin and adjacent unaffected areas and were compared to biopsies from distal leg site in 10 healthy control subjects. Samples were processed for immunohistochemistry using several markers including PGP9.5 (a general neuronal marker), cytokeratin 20 (CK20, for Merkel cells), CD31 (an endothelial cell marker to label blood vessels) and mast cell tryptase (a mast cells marker). Subsets of IENF were further stained for CGRP, SP and NFH. Structures were quantified using stereology or validated quantification methods in accordance with established guidelines.

Results:
We observed that affected skin from PN patients had a thickened epidermis compared to PN-unaffected or matched control subjects. PN-affected skin had significantly lower IENFD than PN-unaffected or anatomically matched control skin in the epidermis. In contrast, the number of Merkel cells, a cutaneous mechanoreceptor, was found more numerous in the PN-affected compared to PN-unaffected skin (p < 0.05). Moreover, the density of blood vessels and mast cell counts were increased significantly in PN-affected skin compared to either control or PN-unaffected skin.

Conclusions:
These findings imply that alterations in prurigo nodularis patients extend beyond keratinocytes and may provide insight into the neuropathic itch these patients experience.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: neuropathy, itch, intraepidermal nerve fiber, prurigo nodularis, skin biopsy
Validation of Modified Erasmus GBS Outcome Score in Low and Middle Income Countries

**Poster No:**
49b

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**Introduction:**
The modified Erasmus GBS Outcome Score (mEGOS) is one of the most commonly used models to predict the outcome of patients with Guillain-Barré syndrome (GBS) after six months of disease onset. The model was developed and validated in developed counties and the model performance is unknown for low and middle income countries. The aim of this current study was to assess and improve the performance of the mEGOS among patients with GBS from Bangladesh.

**Methods:**
We prospectively enrolled GBS patients from two cohort studies in Bangladesh. Poor outcome was defined as being unable to walk independently at week 4 and week 26. We excluded patients able to walk independently, patients who died within the first week, or with missing GBS disability scores. The performance of the mEGOS at entry and week 1 was determined based on the discriminative ability (ability to differentiate between patients able and unable to walk independently; measured using area under receiver operating characteristic curves [AUC]) and calibration (observed probability versus predicted probability of poor outcome).

**Results:**
A total of 506 patients aged ≥6-years-old were enrolled, with 471 and 366 patients included in mEGOS validation analysis at entry and week 1, respectively. The AUC values for predicting poor outcome (1) at week 4 were 0.69 (mEGOS entry) and 0.78 (mEGOS week 1) and (2) at week 26 were 0.67 (mEGOS entry) and 0.70 (mEGOS week 1). Mean predicted probabilities of poor outcome corresponded with observed outcomes except for the probability of poor outcome at week 4 which was overestimated by mEGOS week 1. This was resolved by updating the model intercept.

**Conclusions:**
The mEGOS shows valid outcome predictions among GBS patients from Bangladesh. The model can aid identification of patients at high risk of poor outcome and help to adequately allocate healthcare resources in low-resource settings.

**References:**
No

**References 1:**
References 2:

References 3:

References 4:

Grant Support:

Keywords: Modified Erasmus GBS Outcome Score, Guillain-Barré syndrome, Low and Middle Income Countries
AUTOANTIBODY SCREENING IN IDIOPATHIC SMALL-FIBER NEUROPATHY

Poster No:
50b

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Introduction:
Small-fiber neuropathies (SFN) are a heterogeneous group of disorders of thinly myelinated Aδ-fibers and unmyelinated C-fibers. Multiple causes of SFN have been reported, including genetic mutations and immune-mediated systemic disorders, but the cause remains unknown in up to 50% of cases (idiopathic SFN=iSFN). Recently, autoantibodies to plexin-D1 were detected by ELISA in SFN patients. ELISA had 75% sensitivity and 100% specificity using DRG sections as the gold standard for anti-Plexin-D1 detection. We aimed to screen for autoantibodies reacting against neural structures and Plexin-D1 in a well-defined cohort of iSFN.

Methods:
We tested baseline sera from 60 skin biopsy-proven iSFN patients enrolled in a clinical trial assessing IVIG effectiveness for iSFN. Sera from HC, ALS, CMT and MS were used as controls. IgG against neural structures were tested by (1) ICC using primary cultures of rat DRG neurons; (2) ICC using human neuroblastoma-derived neurons; (3) IHC using macaque peripheral nerve sections; (4) ELISA using RH Plexin-D1 Protein (R&D).

Results:
iSFN sera reacted against DRG neurons significantly more frequently than controls [16/60 (27%) vs 6/90 (7%) (p <0.001)]. No differences were observed in the proportion of patients reacting against neuroblastoma-derived neurons [4/60 (7%) vs 10/90 (11%) (p=0.36)]. In macaque peripheral nerve sections we identified a significantly higher frequency of IgG reactivity to NCAM+ unmyelinated Schwann cells in iSFN patients vs controls [13/60 (22%) vs 3/56 (5%) (p=0.01)]. Anti-Plexin-D1 antibodies were detected by ELISA in 3/60 (5%) of patients but not in controls. All 3 anti-PlexinD1+ sera showed IgG reactivity to DRG neurons.

Conclusions:
iSFN patients showed a heterogeneous repertoire of autoantibodies against neural structures. Anti-Plexin-D1 IgG were detected in 5% of iSFN. Another subset of patients showed IgG reactivity to unmyelinated Schwann cells. The specific antigens and clinical implications of these autoantibodies are yet to be determined.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: Small-fiber neuropathy, Autoantibodies, Plexin-D1
Nerve Regeneration Following Ablation of Monocarboxylate Transporters 1, 2 and 4 from Schwann Cells

Poster No:
51b

Authors:
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Institutions:
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Introduction:
Monocarboxylate transporter 1 (MCT1) has been found to contribute to the support of axons and peripheral nerve regeneration. Schwann cells play a critical role in nerve regeneration and thus it was surprising in our recent publication that selective ablation of MCT1 from Schwann cells did not impact nerve regeneration. In addition to MCT1, Schwann cells also express MCT4 and MCT2.

Methods:
Given the potential for these other transporters to compensate for the loss of MCT1, we obtained and evaluated peripheral nerve regeneration in mice with selective ablation of MCT1, MCT2, and MCT4 from Schwann cells, termed P0-Cre:MCT Triple Flox mice.

Results:
Knockdown of these transporters was validated by real time RT PCR of Schwann cell primary cultures. P0-Cre:MCT Triple Flox mice have no clear behavioral or electrophysiologic abnormalities, at least during young adulthood. P0-Cre:MCT Triple Flox mice and WT:MCT Triple Flox mice underwent sciatic nerve crush and recovery was followed for six weeks by electrophysiology, behavior studies, and histology. By electrophysiology there was incomplete recovery of conduction velocity, with the maximum recovered conduction velocity (CV) being 45.2% of pre-crush values in P0-Cre:MCT Triple Flox mice, as compared to 76.7% in WT:MCT Triple Flox mice (t-test, p<0.05). In contrast, there was no significant difference in the recovery of compound motor action potential (CMAP) in P0-Cre:MCT Triple Flox mice when compared to WT:MCT Triple Flox mice (22.2 mV versus 25.6 mV). Impaired recovery was also seen by behavior, with significantly impaired toe spread index (TSI), but not by ladder walk or hindlimb grip strength in P0-Cre:MCT Triple Flox mice. Further analysis is ongoing, including quantification of axon counts, myelination, and neuromuscular junction innervation in regenerating nerves.

Conclusions:
Our findings suggest that knockout of all Schwann cell MCTs impairs the capacity to remyelinate regenerating axons without playing a role in the regeneration of axons themselves.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support: RO1NS086818

Keywords: Regeneration, metabolism, Monocarboxylate Transporters, Animal Models
Diagnosing neuropathy in patients with alcohol abuse: when bias influences clinicians

Poster No:
52b

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Introduction:
With the lack of any distinctive features or diagnostic biomarkers, patients are often misdiagnosed with alcohol-related neuropathy, influenced by underlying implicit and explicit bias against patients with alcohol use disorders (AUD). Patients often experience devaluation and stigma, affecting adherence to medical advice and social reclusion.

Methods:
We describe two illustrative cases and provide a literature review.

Results:
A 65-year-old male presented with a 3-year-history of progressive ascending numbness, weakness, gait difficulty, and tremor attributed to AUD, and treated with thiamine supplementation. However, his symptoms worsened, and he became socially withdrawn and wheelchair dependent. On evaluation, the EMG showed a severe axonal and demyelinating sensorimotor polyradiculoneuropathy and elevated CSF protein. Neurofascin-155-IgG-antibodies were positive confirming an autoimmune neuropathy. The patient had a marked response to IVIG, regaining ability to walk independently. The second patient, a 51-year-old male with AUD, presented with rapidly progressive numbness, weakness, and gait ataxia, necessitating a wheelchair. The length-dependent sensorimotor neuropathy was attributed to AUD, leading to abrupt cessation of alcohol consumption and severe withdrawal. Workup at our institution, 6 months after initial symptoms, revealed ANNA1-IgG and CRMP5-IgG seropositivity confirming a paraneoplastic syndrome, which led to diagnosis of small-cell lung cancer. Following high-dose steroids and chemotherapy for his cancer he regained ambulation. Alcohol-related neuropathy is described in the literature mostly as mild but painful, predominantly affecting small fibers, and may be indistinguishable from idiopathic sensory neuropathies. The exact pathogenic mechanisms are unknown; however, direct alcohol toxicity and nutritional deficiencies have been proposed. Alternative diagnoses should be strongly considered, especially in cases with more severe involvement.

Conclusions:
Misdiagnosis is common among patients with AUD, partly reflecting bias by healthcare workers, and may lead to stigmatization and suboptimal medical care. If true alcohol-related neuropathy exists, it remains rare.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: Alcohol related neuropathy, Bias, Immune mediated neuropathy
AT-007 Significantly Lowers Blood Sorbitol Levels in Patients with Hereditary Neuropathy Resulting from Sorbitol Dehydrogenase (SORD) Deficiency

Poster No:
53b

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Institutions:
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Introduction:
Sorbitol Dehydrogenase Deficiency (SORD Deficiency) is a hereditary neuropathy affecting approximately 3,000 patients in the US, and 4,000 patients in Europe. Prior to the identification of the specific gene defect, patients with SORD Deficiency were classified symptomatically into the broader neurological diseases Charcot-Marie-Tooth Type 2 or distal Hereditary Motor Neuropathy (dHMN). SORD is the second enzyme in the two-step polyol pathway, an alternative glucose metabolism pathway. Patients with SORD Deficiency are unable to process sorbitol, leading to accumulation of this toxic metabolite in blood and tissues. In vitro and in vivo studies have recently demonstrated that treatment with AT-007 prevents accumulation of sorbitol in a SORD deficient animal model of disease and in cultured human fibroblasts from SORD Deficiency patients.

Methods:
The present open label pilot study was designed to evaluate the effect of AT-007 treatment on blood sorbitol levels in a cohort of patients with SORD Deficiency. There was no placebo treatment arm in this study. Eight patients (19-55 yrs; 4M/4F) with a genetic diagnosis of SORD Deficiency were enrolled in the study and treated with AT-007 liquid suspension at 20mg/kg for 30 days.

Results:
The mean circulating sorbitol level at baseline was approximately 38,000ng/ml - a near 100-fold increase compared to healthy individuals. AT-007 oral treatment once daily reduced blood sorbitol levels by a mean of 66% from baseline over the 30 day treatment period with a range of 55-74% reduction.

Conclusions:
In summary, SORD Deficiency is a severe and progressive neuropathy caused by abnormally elevated levels of sorbitol. AT-007 treatment reduced sorbitol levels substantially from baseline and was safe and well tolerated. An ongoing placebo-controlled Phase 2/3 study is evaluating AT-007 treatment and impact on clinical outcomes in SORD Deficient patients.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** SORD Deficiency, AT-007, Charcot-Marie-Tooth Type 2, distal Hereditary Motor Neuropathy, Aldose Reductase Inhibitors
Deep-learning based cellular profiling to enable patient-specific genetic and pharmacological perturbation screens in inherited neuromuscular diseases

Poster No:
54b

Authors:
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Institutions:
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Introduction:
The functional evaluation of the causes and potential therapeutic interventions for genetic diseases requires robust disease-associated phenotypes that are amenable to experimental perturbation. Especially in genetically heterogeneous conditions such as inherited neuropathies, the lack of such phenotypes, and the technologies to identify them, severely delays genetic diagnoses and translational research. Enabled by a custom deep-learning framework, we establish an integrated, high-content single-cell morphological profiling platform to screen primary patient-derived cells for specific, sub-cellular phenotypes associated by their condition that can be leveraged in downstream perturbation screens.

Methods:
We employ a custom high-throughput morphological profiling platform consisting of (a) an automated, single-cell resolution, multiplexed image-acquisition protocol, and (b) a suite of cutting-edge deep-learning methods including a novel computational method for phenotype-preserving batch-effect correction. We combine these methods to collect and mine a large image-dataset for robust, disease-associated phenotypes in patient cells across a range of neuromuscular disease subtypes.

Results:
We find evidence of an abundance of complex cell-morphological phenotypes that remain hidden to conventional analytical methods, and which distinguish an array of genetically and clinically distinct inherited neuromuscular conditions including major axonal subtypes of Charcot-Marie-Tooth disease. We demonstrate how the discovered phenotypes can be leveraged to conduct unbiased and scalable perturbations screens.

Conclusions:
We establish a rapid and unbiased cellular profiling approach to identify latent disease-associated phenotypes in primary patient-derived cells that enables downstream applications including high-content genetic or pharmacological screens. We propose that our approach could significantly accelerate both gene-discovery and translational research in inherited neuromuscular diseases.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: AI, CMT, High-throughput, Genetics, Drug Screen
Comprehensive and comparative protein binding screen reveals new interactions of the MPZ(P0) cytosolic tail.

Poster No:
55b

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Introduction:
Myelin Protein Zero is the major myelin protein expressed by Schwann cells. Mutations in the cytosolic tail of MPZ can cause defects in myelin compaction or lead to axonal degeneration. However, the protein interaction(s) MPZ uses to mediate its functions are poorly characterized.

Methods:
To identify interactors of the MPZ tail we used DEEPN, (Dynamic Enrichment for Evaluation of Protein Networks), a yeast 2-hybrid workflow that we developed that uses next-generation sequencing on a population of yeast undergoing selective pressure over time as 'bait' and 'prey' protein fusions interact. The custom 'prey' library we used was composed of fragments of the human ORFeome.

Results:
Among the interactors are regulators of the actin cytoskeleton, which plays a critical role in the early differentiation of Schwann cells and their ability to wrap myelin. Specifically, the dynamics of actin assembly, and activation of myosin light chain kinase have been found pivotal for myelination. DEEPN recovered a myosin light chain kinase (MLCK3), FHL3 and FAM13B as interactors with MPZ tail. MLCK3, is homologous to MLCK that is required for myelin compaction and undergoes increased phosphorylation and relocation to the cell surface during Schwann cell differentiation. FHL3 binds actin, regulates assembly of actin stress fibers, and also binds SMADs, which can regulate a number of cellular differentiation events including Schwann cell development. FAM13B is a Rho GAP (GTPase accelerating protein), implicating it in the control of the cytoskeleton. The finding that MPZ may interact with a regulator of Rho is particularly relevant since Rho kinase (ROCK) can regulate myosin light chain phosphorylation during myelination and defects in the Rho guanine-nucleotide exchange protein FGD4 result in an autosomal recessive form of CMT.

Conclusions:
Some interactors were sensitive to disease-causing mutations in the MPZ tail, suggesting that loss of these interactions contribute to CMT pathogenesis.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: MPZ, Schwann cell, Myelin, Interaction
Phenotypical and Genotypical Variability in Hereditary Transthyretin Amyloidosis – A Register Study in Germany

Poster No:
56b

Authors:
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Introduction:
Systemic transthyretin amyloidosis can be acquired (ATTRwt) or hereditary (ATTRv) and is characterized by deposition of transthyretin (TTR) fibrils primarily in the peripheral and autonomic nervous system and the heart. The clinical spectrum is heterogeneous and the age of onset variable even within the same genotype of ATTRv. With the availability of promising therapies like TTR stabilizers and gene silencing agents it is important to understand the clinical spectrum. However, most data on clinical presentation of ATTRv relies on characterization of a few most frequent endemic mutations. Therefore, a better understanding of phenotype and genotype variability in ATTRv is needed.

Methods:
Within the Amyloidosis Center Charité Berlin (ACCB) we developed an algorithm for longitudinal clinical characterization and evaluation of disease progress and therapy effectiveness. Extensive clinical characterization included neurological examination, questionnaires, histology, electrophysiology, DPD-scintigraphy, magnetic resonance imaging, echocardiography, and laboratory examinations in a longitudinal setting.

Results:
We collected clinical data of 33 ATTRv patients, including 15 patients with the most common variant p.Val50Met. Patients with p.Val142Ile, and p.Thr60Ala variants presented with cardiomyopathy, while severe autonomic neuropathy was seen in a family with p.Leu75Arg ATTRv. Interestingly, in a family with p.Thr80Ala ATTR we detected significant interindividual alterations in phenotype ranging from cardiomyopathy to neuropathy. Furthermore, we identified several patients with variants of unknown significance within the TTR gene and typical ATTR phenotype, including p.Cys30Arg, p.Glu27Lys, p.Ala129Val, and p.Thr126Asn.

Conclusions:
TTR Amyloidosis is a clinically diverse disorder ranging from cardiomyopathy to neuropathy dominant phenotypes. Interestingly, phenotypes can vary even within the same mutation. These results reveal a new diversity in clinical presentation of ATTRv amyloidosis. Further research is needed to unravel the pathophysiology for phenotypical variations and to define therapeutic options for patients that do not meet current treatment requirements.

References:
No

References 1:

References 2:
References 3:

References 4:

**Grant Support:** Helena Pernice: Alnylam Pharmaceuticals Inc. Katrin Hahn: Akcea Therapeutics Inc., Alnylam Pharmaceuticals Inc., Takeda Pharmaceutical Inc., Pfizer Pharmaceuticals Inc. and Swedish Orphan Biovitrum Inc.. KH further received research funding by the found

**Keywords:** Transthyretin amyloidosis, ATTR, phenotype variance, register study, clinical characterization
Herpes Zoster may be a trigger for Lumbosacral Radiculoplexus Neuropathy

Poster No: 57b

Authors: Marcus Pinto¹, Catarina Aragon Pinto², P. James B. Dyck¹

Institutions: ¹Mayo Clinic, Rochester, MN, ²Mayo Clinic, Rochester, MN

Introduction: Lumbosacral Radiculoplexus Neuropathy (LRPN) is an immune mediated neuropathy that may have a trigger in approximately 1/3 of cases. The most common triggers are surgery, rapid glycemic changes, vaccines and infection. Varicella-zoster virus (VZV) is known to cause central and peripheral nervous system complications but the association of VZV and LRPN has never been systematically studied.

Methods: We performed an electronic chart review to identify patients who developed LRPN up to 4 weeks after the appearance of VZV infection rash at our institution between 1/1/2000 to 12/31/2017. We only included patients who had classic herpes zoster diagnosed by a physician.

Results: Seven patients were identified. 5 (71.4%) had diabetes. Median age-at-onset was 68 years (range 48-76), 5 (71.4%) were female and median time to LRPN diagnosis was 6 (2-16) months. Median time from rash onset to LRPN onset was 3 (1-4) weeks, and median time from LRPN onset to nadir was 6 (2-12) months. The rash location was in the trunk region in 3 (42.9%) patients, face in 2(28.5%), groin in 1 (14.3%) and arm in 1(14.3%). No patient had diffuse VZV infection. All patients had weakness and pain in roots and nerves distributions outside of the rash location. At diagnosis, 3 (42.8%) patients had more than 10 lbs of weight loss, 5 (71.4%) had bilateral lower extremity involvement, 3 (42.9%) had panplexus involvement, and the median modified Rankin scale was 3 (2-4). In 3 patients, herpes zoster anteceded a recurrence of patient's previous episode of LRPN. One patient was immunosuppressed (liver transplant).

Conclusions: Herpes zoster can be associated with LRPN. Even though VZV might cause direct peripheral nerve injury, the protracted progression of LRPN, neuropathic symptoms far away from the rash location and recurrence of LRPN may suggest that VZV is rather a trigger for LRPN.

References: No

References 1:

References 2:

References 3:

References 4:

Grant Support:
Keywords: Lumbosacral Radiculoplexus Neuropathy, VZV, Herpes zoster
Diabetic Lumbosacral Radiculoplexus Neuropathy after COVID-19

Poster No:
58b

Authors:
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Introduction:
Lumbosacral Radiculoplexus Neuropathy (LRPN) is a subacute, painful, asymmetric immune mediated lower-limb neuropathy that is associated with weight loss and diabetes mellitus (DM) (DLRPN). Approximately one-third of LRPN cases may have a trigger.

Methods:
The purpose of this report is to raise awareness that DLRPN can be triggered by COVID-19.

Results:
55-year-old man with diabetes mellitus type 2 who presented with acute sinusitis and loss of smell in early October 2020. Nasopharynx Sars-Cov-2 PCR was positive. He became fatigued, weak and had 30 pounds unintentional weight loss. Four weeks after his COVID-19 infection symptom onset, the patient developed progressive severe neuropathic pain in his lower extremities with allodynia and weakness. He started to require a wheelchair for ambulation. Neurological exam showed severe proximal and distal lower extremities weakness, absent tendon reflexes, and pan-modality sensation loss in his distal legs. NCS/EMG demonstrated an axonal and asymmetric lumbosacral plexopathy with right thoracic radiculopathies. CSF analysis was normal, excepting for elevated protein at 138 mg/dl. Right sural nerve biopsy was diagnostic of nerve microvasculitis. He was diagnosed with DLRPN and treated with IV methylprednisolone 1 g weekly for 12 weeks. The patient had marked improvement and at 3 month-follow up visit was walking unassisted.

Conclusions:
COVID-19 can trigger post-infectious inflammatory neuropathies including DLRPN.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Diabetic Lumbosacral Radiculoplexus Neuropathy, COVID-19
VCMTES: a validated virtual evaluation for Charcot-Marie-Tooth patients

Poster No:
59b

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Introduction:
COVID-19 pandemic highlighted the need for reliable scales for remote evaluations of Charcot Marie Tooth (CMT) disease patients unable to travel to clinics because of their disabilities, distance, financial concerns or other reasons. This is also important to enable evaluation of patients with very rare forms of CMT for which there are only a few families worldwide. The CMT Examination Score (CMTES) has been used in clinical and research practice for many years to measure disease severity and progression over time.

Methods:
We modified the CMTESv2 replacing the pinprick and vibration items with light touch and position sense, which can be performed by the patient on his own or with assistance remotely. We developed a standardized protocol to be used on a video platform, a training and certification program and enabled the vCMTES data to be housed in the Inherited Neuropathy Consortium databases. We then evaluated patients in person and remotely and performed inter and intra-examiner validation studies.

Results:
Sixty-four patients with genetically confirmed CMT were evaluated with CMTESv2 and vCMTES in person. Fifty three (83%) of these have been evaluated virtually three weeks after their initial examination. Ten patients were assessed with vCMTES by two different examiners five days apart. CMTESv2 correlates strongly with the vCMTES in person and virtually (p<0.0001) and there was also a strong correlation between the vCMTES performed in person and virtually (p<0.0001). Similar results were obtained comparing symptoms items, sensory items and the motor items. Considering the test-retest reliability, interclass correlation coefficients showed good results (≥0.92).

Conclusions:
All the statistical analyses showed that the vCMTES is valid and reliable as a clinical outcome assessment for CMT. Further studies are needed to test responsiveness to change and progression in different subtypes. vCMTES may also offer the potential to reach a large number of patients who do not have access to specialized CMT centers.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: Virtual outcome measures, CMT, Virtual evaluations
A C. elegans model of neuropathy-associated GARS1 mutations

Poster No:
60b

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Institutions:
\textsuperscript{1}University of Michigan, Ann Arbor, MI

Introduction:
Charcot-Marie-Tooth disease (CMT) is a heritable peripheral neuropathy that is characterized by motor and sensory defects in the distal extremities. Mutations in five genes encoding aminoacyl-tRNA synthetases (ARSs)—a family of enzymes that ligate amino acids to cognate tRNA molecules during the beginning stages of protein translation—have been implicated in dominantly inherited CMT. One of these implicated enzymes is glycyl-tRNA synthetase (GARS1), the enzyme responsible for ligating glycine to cognate tRNA molecules. It has been demonstrated that there is wide allelic and clinical heterogeneity of GARS1-mediated neuropathy.

Methods:
We recently reported a 12-base-pair, in-frame deletion in GARS1, (E245_Q248; or ΔETAQ) in a patient with a severe form of peripheral neuropathy that is similar to infantile-onset spinal muscular atrophy. The ΔETAQ mutation ablates enzyme activity in vitro, reduces viability in yeast complementation assays, and is dominantly toxic to mouse neurons. To further determine the pathological significance of the ΔETAQ mutation and to establish a pipeline by which disease-causing ARS mutations may be systematically studied in a robust model organism, we employed a CRISPR/Cas9 method to generate a C. elegans model of GARS-mediated disease.

Results:
Here, we provide characterization of the first C. elegans GARS1-mediated neuropathy model, which supports a loss-of-function effect of the patient variant. Heterozygosity for ΔETAQ gars-1 produces a robust motility defect and fluorescent imaging of axons reveals neurotoxicity in the motor neurons. Pharmacological characterization of the neuromuscular junction of mutant worms indicates a degenerative defect in synaptic transmission, consistent with the patient phenotype.

Conclusions:
Here, I will present our unpublished data and plans to improve the phenotype observed in worm toward developing patient therapeutics. This work contributes to our understanding of the role of GARS1 in peripheral neuropathy and establishes a framework for studying the pathogenicity of other ARS mutations of interest.

References:
Yes

References 1:

References 2:
References 3:

References 4:

Grant Support: A.A. is supported by a grant from the National Institute of General Medical Sciences (GM136441)

Keywords: Neuropathy, Aminoacyl-tRNA Synthetase, Model organism, Mendelian Disease
PMP22 Overexpression Causes Lipid Recycling Defects That Alters The Plasma Membrane In CMT1A

Poster No:
61b

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Introduction:
Duplication of the peripheral myelin protein 22 (PMP22) causes Charcot-Marie-Tooth disease 1A (CMT1A) and is known to dysregulate lipid metabolism. However, a lack of knowledge persists in the underlying mechanisms that lead to lipid metabolic defects that ultimately give rise to the CMT1A phenotype.

Methods:
We performed bulk RNA-sequencing on sciatic nerves of the C3 and C22 CMT1A mouse models (3-12 weeks of age) and on CMT1A patient derived Schwann cell precursors differentiated from induced pluripotent stem cells (iPS-SCPs). LC-MS/MS lipidomic analysis was also performed on 5-week-old C3 mice and on CMT1A iPS-SCPs. The lipidomic phenotypes were further analysed via electron microscopy, flow cytometry, high-content confocal immunofluorescence imaging and western blot.

Results:
Bulk RNA-sequencing data demonstrated that cholesterol metabolism is the most dysregulated pathway throughout CMT1A mice development. PMP22 overexpression suppressed cholesterol metabolism in a dose-dependent manner. Lipidomics analysis revealed dysregulated relative expression of lipids regulating lipid storage/droplet homeostasis, plasma membrane composition, and very-long-chain polyunsaturated fatty acids, which were similarly altered in CMT1A patient-derived iPS-SCPs. Moreover, bulk RNA-sequencing revealed dysregulated expression of plasma membrane-associated genes in the CMT1A iPS-SCPs versus their isogenic control. Lipid accumulations and membrane alterations in CMT1A iPS-SCPs were identified via electron microscopy and di-4-ANEPPDHQ flow cytometry analysis demonstrated increased membrane disorder in CMT1A iPS-SCPs compared to their isogenic iPS-SCPs. Using high-content confocal imaging we observed that CMT1A iPS-SCPs have reduced membrane cholesterol and upon oleic acid stimulation generate a larger size and quantity of lipid droplets and lysosomes. This lipid droplet/storage phenotype was confirmed using western blot analysis which showed alterations in DGAT1, perilipin-2, seipin, LAMP1, and NPC1. As a proof-of-concept, we showed that forskolin treatment can modulate and improve the deficits in lipolysis/autophagy and increase the release of free cholesterol in CMT1A iPS-SCPs.

Conclusions:
The current work shows that lipolysis/autophagy modulation in CMT1A iPS-SCPs attenuates lipid recycling homeostasis and restores their membranes' cholesterol content.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT1A, Inherited neuropathies, Lipid metabolism, PMP22, Schwann cells
Solution structure studies of the Ig domain of the MPZ(P0) myelin adhesion protein

Poster No:
62b

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Introduction:
Mutations in Myelin Protein Zero (MPZ) account for 5% of CMT cases overall and can cause demyelinating or axonal phenotypes, reflecting the diverse roles of MPZ in Schwann cells. MPZ holds the apposing membranes of the myelin sheath together, with the adhesion role fulfilled by the extracellular Immunoglobulin-like domain (IgMPZ), which can oligomerize.

Methods:
Most of what we know for how the IgMPZ might form oligomeric assemblies has been extrapolated from a protein crystal structure in which individual rat IgMPZ subunits are packed together under artificial conditions. The current molecular model for how IgMPZ oligomerizes involves 3 potential weakly-interacting interfaces. These include an interface that organizes the IgMPZ into tetramers, a 'dimer' interface that could link tetramers together, and a third hydrophobic interface that could mediate binding to lipid bilayers or the same hydrophobic surface on another IgMPZ domain. Currently, there are no data confirming whether the proposed IgMPZ interfaces actually mediate oligomerization in solution, whether they are required for the adhesion activity of MPZ, whether they are important for myelination, and whether their loss results in disease. Analysis of the IgMPZ molecular structure reveals that axonal late-onset disease phenotypes (CMT2) mostly map to surface residues of IgMPZ whereas early-onset severe demyelinating mutations (CMT1) map to the IgMPZ interior core. The correlation of surface mutations to CMT2 suggests the dysfunction of protein interaction interfaces as a possible cause of this disease phenotype.

Results:
To better understand how IgMPZ works as an adhesion protein, we have used NMR and small-angle X-ray scattering in combination with mutation analysis to learn how IgMPZ oligomerizes in solution.

Conclusions:
Our studies aim to determine the precise role of IgMPZ self-interactions required for adhesion and myelin formation and maintenance and to inform future functional experiments in animal disease models.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: Myelin, Adhesion, neuropathy, CMT, MPZ
The first two large deletions of KIF5A responsible for Charcot-Marie-Tooth disease, detected using CovCopCan software.

Poster No:
63b

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Introduction:
Charcot-Marie-Tooth disease (CMT) is the most common hereditary peripheral neuropathy, affecting both sensory and motor peripheral nerves. PMP22 was the first gene described to be involved in CMT via a Structural Variation (SV) of duplication-type, explaining about 15% of the overall CMT cases in our cohort. To date, more than 90 genes are known to be involved in CMT, on which mainly Single Nucleotide Variants (SNVs) and short insertions or deletions have been described, while SVs are often underdiagnosed.

Methods:
In our study, we used targeted NGS and the CovCopCan bioinformatics tool to analyze NGS data from two unrelated families with CMT symptoms associated with a pyramidal syndrome.

Results:
We then discovered two large SVs in the KIF5A gene, a gene associated with axonal forms of CMT (CMT2), in which no SVs have yet been described. In the first family, the patient had a large 12 kb deletion in KIF5A including exons 2-15. In the second family, two cases had a large 3 kb deletion in KIF5A including exons 24-28. In addition, bioinformatics analysis of the breakpoint region sequence revealed that the NAHR (Non-Allelic-Homologous-Recombination) mechanism, similar to that involved in PMP22-duplication, may be responsible for one of these KIF5A SVs and could potentially be present in several other patients.

Conclusions:
This study establishes a new concept of mechanism involved in neurological diseases, since large deletions of KIF5A can cause CMT2. Furthermore, we emphasize the importance of analyzing not only SNVs but also SVs when diagnosing neuropathies, as they might be involved in peripheral neuropathies more frequently than currently suspected.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: Structural Variants, Charcot-Marie-Tooth, KIF5A, NGS, CovCopCan
Single-exon-deletions responsible for peripheral neuropathies. Are you able to detect them?

**Poster No:**
64b

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**Introduction:**
Next-Generation-Sequencing (NGS) allows the detection of a large number of mutations increasing the rate of patients getting a positive diagnosis. However, while Single-Nucleotide-Variants (SNVs) or small indels were easily detected, we had to wait for additional software such as CovCop and CovCopCan to detect also Structural-Variations (SVs) such as Copy-Number-Variants (CNVs). In addition to the known PMP22-duplication responsible for Charcot-Marie-Tooth disease (CMT), large deletions of several exons in KIF5A, for instance, have been identified recently thanks to these software to also be responsible for CMT. However, to our knowledge, no single-exon deletions and/or duplications inducing peripheral neuropathies have been detected.

**Methods:**
We present here how we modified our bioinformatics analyses to detect them more efficiently. This approach is illustrated here by the presentation of two distinct cases of peripheral neuropathies. Targeted-amplicons NGS has been performed in both cases. First, the NGS data were aligned to the human reference sequence. In addition to the routine diagnosis, we particularly paid attention to supposed homozygous mutations and single heterozygous mutations in genes transmitted in a recessive manner. Then, we completed our NGS bioinformatics analyses by modifying slightly the use of the CNVs detection bioinformatics tools.

**Results:**
This strategy allowed detecting single-exon-deletions in these two distinct cases, increasing then the number of CNVs responsible for peripheral neuropathies.

**Conclusions:**
Our study points out that CNVs are certainly underdiagnosed and more notably CNVs affecting a single exon. Thus, we suggest searching systematically SVs in all peripheral neuropathies genes in order to improve diagnosis.

**References:**
No

**References 1:**
Keywords: Structural Variants, single-exon-deletion, Charcot-Marie-Tooth, NGS, CovCopCan
Autoantibody studies in the CIDP01 /CIDP04 clinical trials

Poster No:
65b

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Introduction:
Autoantibodies play a pathogenic role in a proportion of patients fulfilling chronic inflammatory demyelinating polyneuropathy (CIDP) criteria. These autoantibodies are not usually considered when designing clinical trials in CIDP. We performed a systematic screening of autoantibodies against known peripheral nerve antigens, neural tissue, and neural cells in patients with CIDP included in the CIDP01/04 clinical trials (NCT03861481 and NCT04051944), assessing efficacy, safety and tolerability of the anti-FcRn mAb, rozanolixizumab.

Methods:
Autoantibody screening was performed in serum samples from the 34 patients with CIDP included in the CIDP01/04 clinical trials. Anti-ganglioside, anti-nodo/paranodal, anti-CRMP5 and anti-MAG autoantibody titers, immunocytochemistry on neuroblastoma-derived human motor neurons and murine dorsal-root ganglia (DRG) neurons, and immunohistochemistry on monkey peripheral nerve sections were used to screen for the presence of nerve-specific autoantibodies. We analyzed autoantibody titers before treatment and at last follow-up.

Results:
One patient (2.9%) was positive for anti-NF155 antibodies, 2 patients (5.8%) had IgM anti-MAG antibodies and 3 (8.8%) had anti-ganglioside antibodies (1 had low IgG titers against GQ1b, and 2 had high IgM titers against the Gal(beta 1-3)GalNAc epitope and the disialosyl plus NeuNacGal epitopes respectively). IgG from 2 patients and IgM from 3 patients reacted strongly against DRG neurons. IgG and IgM reactivity against monkey nerve tissue was detected in 7 and 9 CIDP patients, respectively. IgG from 3 patients and IgM from 2 patients reacted strongly against neuroblastoma-derived human motor neurons. Autoantibody titers before and after the treatment did not change.

Conclusions:
Almost 40% of patients included in the CIDP01/04 clinical trial displayed nerve-specific autoantibodies, of which half are of the IgM isotype. Autoantibody titers remained stable during the trial. Taking autoantibody profiles into account in the inclusion criteria could help optimize the outcome of future clinical trials addressing humoral immunity in CIDP.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support:

**Keywords:** rozanolixizumab, chronic inflammatory demyelinating polyneuropathy, autoantibodies
Rozanolixizumab in Chronic Inflammatory Demyelinating Polyradiculoneuropathy: Randomized Subject-/Investigator-Blind Placebo-Controlled Phase 2a Trial

Poster No:
66b

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Introduction:
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated peripheral nerve disorder characterized by weakness and sensation loss. Rozanolixizumab, a fully humanized IgG4 mAb, inhibits the neonatal Fc receptor, reducing serum IgG. The efficacy and safety of rozanolixizumab for CIDP were evaluated.

Methods:
CIDP01 (NCT03861481) was a randomized (1:1), subject- and investigator-blind, placebo-controlled, Phase 2a study. Patients had definite/probable CIDP (EFNS/PNS criteria 2010), were Ig-dependent (based on clinical examination during therapy/interruption within 18 months pre-screening) and received a stable dose of SC lg/IV lg for ≥4 months before entry into the study. At study start patients switched from their previous Ig treatment to 12 weekly subcutaneous infusions of rozanolixizumab 10mg/kg or placebo. The primary endpoint was change from baseline (CFB) to Week 13 in inflammatory Rasch-built Overall Disability Scale (iRODS) score. Secondary outcomes included CFB to Week 13 in Inflammatory Neuropathy Cause and Treatment (INCAT) and grip strength, CIDP relapse and safety.

Results:
Overall, 34 patients were randomized. There were no differences between rozanolixizumab and placebo in mean CFB at Week 13 for iRODS (difference [90% CI] –0.052 [–0.892,0.788]), INCAT (–0.4 [–0.9,0.0]) or grip strength (–2.41 [–11.09,6.28]). iRODS CIDP relapse was 43.8% with rozanolixizumab vs 35.3% with placebo (proportion difference 0.085 [90% CI –0.195,0.364]; HR 1.363 [0.546,3.404]). Rozanolixizumab reduced mean IgG by >80% to approximately 2g/L. Treatment-emergent adverse event (TEAE) profiles were similar between rozanolixizumab and placebo (any TEAE: 14 [82.4%] vs 13 [76.5%]; serious TEAE: two [11.8%] vs none).

Conclusions:
The primary endpoint was not met in the patient population of the Phase 2a study CIDP01, despite an IgG reduction >80% in the treatment arm. Two-thirds of patients on placebo remained stable suggesting that not all patients were Ig-dependent, which might have skewed results. The TEAE profile was similar to placebo, with no concerning safety signals. Funded by UCB Pharma.
References:
Yes

References 1:

References 2:

References 3:

References 4:


Keywords: CIDP, rozanolixizumab, clinical trial
Assessment timing and choice of outcome measure in determining treatment response in CIDP: a post-hoc analysis of the PRISM trial

Poster No:
67b

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Introduction:
Treatment response and its timing is variable in chronic inflammatory demyelinating polyneuropathy (CIDP). We here aimed to study this variability with multiple outcome measures.

Methods:
We performed a post-hoc analysis of the PRISM trial, a 24-week prospective, multicentre, single-arm, open-label phase 3 study of IqYmune, a 10% intravenous immunoglobulin preparation, for CIDP. We ascertained timing of response with primary/secondary outcome measures.

Results:
At 6 weeks post-treatment initiation, 13/40 subjects (32.5%) were defined as responders on the primary outcome measure, the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) scale. This increased to 20/41 (48.8%) at 12 weeks and to 32/42 (76.2%) at 24 weeks. Use of minimal important difference (MID)-determined amelioration of the inflammatory Rasch-built Overall Disability Scale (I-RODS), or of the Medical Research Council Sum Score (MRCSS), or of dominant hand grip strength, in addition to the adjusted INCAT, offered a sensitivity of 41.7% in identifying adjusted INCAT non-responders at week 12 who subsequently responded at week 24. Specificity was of 60% versus INCAT non-responders at week 24. Consideration of amelioration of any amplitude on any secondary outcome measure offered a 75% sensitivity but only 30% specificity versus adjusted INCAT nonresponders at week 24.

Conclusions:
Immunoglobulin treatment continuation may be justified for up to 24 weeks in CIDP. Additional outcome measures may help in early treatment stages to predict delayed response on the adjusted INCAT. However, their use is limited by high false-positive rates. More robust, reliable and relevant outcome measures are needed to detect early improvement in CIDP.

References:
Yes

References 1:

References 2:

References 3:
References 4:

Grant Support:

**Keywords:** Chronic Inflammatory Demyelinating Polyneuropathy, , immunoglobulins, , outcome measures, , response to treatment
An inflammatory lumbar radiculoplexopathy pos severe covid-19 infection associated with heterotopic ossification

Poster No:
68b

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Introduction:
Neurological complications due to covid-19 infection have been linked to severe cases of COVID-19 infection since the onset of the pandemic. However, the clinical and pathophysiological characterization of peripheral nervous system involvement is still unclear.

Methods:
We describe a case report of a 57 years old man, previously healthy, who presented an assimetric lumbar radiculoplexitis after a severe presentation of COVID-19 infection responsive to corticotherapy.

Results:
In December of 2020 the patient was admitted to the hospital with a respiratory failure related to covid-19 infection. He was intubated and placed on ECHMO for 26 days. During this time, the patient had 3 secondary infections, multiple blood transfusions, and drug-induced hepatitis. He was tracheostomized and in February of 2021, after sedation was removed, the patient was quadriplegic and arreflex, and the diagnosis of critical ill polyneuropathy was made. In the following months, the patient was under rehabilitation, but no motor improve was noted on the left foot. In september 2021 came to our peripheral neuropathy center. At physical examination the patient presented a plegia on the left foot with areflexia on left Achilles tendon. The nerve conduction study and the EMG showed an important partial axonal involvement of the left tibial and peroneal nerves with few functioning motor units. Partial axonal involvement of the right peroneal nerve Lumbosacral MRI with neurography showed signs of inflammation in the roots of L4 to S1 and hyperintensity in T2 STIR with gadolin enhancement bilaterally, but more intensive on the left, with extension to left ciatic nerve. A heterotopic ossification was identified between the left gluteus minimus muscle.

Conclusions:
Severe cases of COVI-19 infection can lead to an inflammatory presentation of the peripheral nervous system as a radiculoplexitis. Clinicians should be aware about this possibility that can respond to corticotherapy and have a better prognosis.

References:
Yes

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: Inflammatory radiculoplexopathy, COVID-19, Neurography
Co-designing a strategy to engage people with rare neurological diseases from racially minoritized backgrounds in research

Poster No:
69b

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Introduction:
There is evidence of poor representation people from racially minoritized backgrounds in clinical research. People with rare diseases are considered 'hard to reach' and the intersection of both characteristics compounds the issue. People with rare diseases can be dispersed geographically, so common engagement strategies, such as local community groups, may not be appropriate. The people who can help us to develop the best strategies for engagement are people with this lived experience. The aims are to explore the experiences of people living with rare neurological diseases from ethnic minority backgrounds on awareness and engagement with research activities for their condition.

Methods:
Through a process of reflection on these experiences, and their deep understanding of their community, culture and accessibility issues, we will facilitate development of ideas to formulate a strategy for involvement, engagement and inclusion. We are creating a panel of up to 6 people living with rare neurological diseases from Black, Asian & Minority Ethnic backgrounds. There will be three workshops for this project that will be conducted using video conferencing, to limit travel for a group of people that live with physical disability. Workshop 1: Exchange of experiences and ideas; Workshop 2: Bringing ideas together as a strategy with action points; Workshop 3: Agreeing the final strategy and identifying training needs

Results:
We will present the finalised, co-produced engagement strategy.

Conclusions:
This will be a long-term partnership with the panel. We will launch the strategy to research colleagues so they can involve the panel in grant applications to secure funding for future time and training, ensuring sustainability longer term.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** Patient engagement, Equality, diversity and inclusion, Engagement in research, Co-production
Programming Injury-induced Enhancers in Schwann Cells

Poster No:
70b

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Introduction:
Schwann cells play a critical role after peripheral nerve injury by clearing myelin debris, forming axon-guiding Bands of Bungner, and re-myelinating regenerating axons. Schwann cells undergo epigenomic remodeling to differentiate into a repair state that expresses unique genes, some of which are not expressed at other stages of Schwann cell development. For example, the Sonic Hedgehog (Shh) gene is only upregulated in repair Schwann cells compared to other stages of Schwann cell development.

Methods:
We determined if injury-induced enhancers are pre-programmed into the Schwann cell epigenome as poised enhancers prior to injury. Poised enhancers share many attributes of active enhancers, such as open chromatin, but are marked by repressive H3K27 trimethylation (H3K27me3) rather than H3K27ac. The JUN subunit of AP-1 is required for Schwann cell injury responses, and we determined if JUN-binding enhancers are required for Sonic Hedgehog induction.

Results:
Most injury-induced enhancers are not marked as poised enhancers prior to injury. Injury-induced enhancers are enriched with AP-1 binding motifs, and in vivo ChIP-seq analysis of the JUN subunit of AP-1 after injury revealed that it binds to a subset of injury-induced enhancers. We confirm that JUN regulates these enhancers and also show for the first time that injury-induced enhancers are required for robust induction of the Sonic Hedgehog gene after injury.

Conclusions:
The pro-regenerative actions of Schwann cells after nerve injury depends upon profound reprogramming of the epigenome, and our studies suggest that pioneer factors like AP-1 are required to activate injury-induced enhancers in Schwann cells. While many long range enhancers drive expression of Sonic hedgehog at different developmental stages of specific tissues, these studies identify an entirely new set of enhancers that are required for Sonic hedgehog induction in Schwann cells after injury.

References:
No

References 1:

References 2:

References 3:

References 4:
**Grant Support:** NIH: R01 NS100510 and P50 HD105353

**Keywords:** injury, Schwann, transcription, regeneration
Minigene designs for pre-clinical studies in the ultra-rare SBF1/MTMR5-related neuropathy

Poster No:
71b

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Introduction:
CMT4B3 is an ultra-rare recessive form of complex Charcot-Marie-Tooth disease (CMT) with fewer than 10 cases reported thus far. The phenotypic expression ranges from demyelinating neuropathy (1 case) to axonal neuropathy with cranial nerve involvement and microcephaly, short stature, and syndactyly. The underlying gene is SBF1 (MTMR5). Considering a presumed loss-of-function mechanism of action, a gene replacement strategy for treatment appears appropriate. The primary challenge with this approach is the size limit of the adeno-associated virus (AAV) being ~4,700 bp and the cDNA of SBF1 is 5,679bp. Given the success of AAV Micro-dystrophin gene therapy, we sought to rationally design a functional SBF1 minigene that may be appropriate for future treatment trials.

Methods:
To inform the design of minigene candidates, we have analyzed the protein structure using comparative protein family, cross species, and cross domain investigations. In addition, we explored the tertiary protein models in detail.

Results:
Our efforts thus far have yielded the design of three minigene candidates following proteomic considerations and taking into account published functional studies and knowledge on the MTMR family of proteins. We also have created HEK293 SBF1 CRISPR knockout cell lines that are currently undergoing single colony selection and expansion. These cells appear to show deficits in their endosomal structure and long-term survival impairments, potentially revealing additional insight into the normal function of SBF1. The cells will be valuable as a rescue model using WT and minigene constructs.

Conclusions:
In conclusion, gene replacement therapy of large genes remains a challenge. Minigene construction is a potential pathway for drug development. As our studies evolve, we will gain more insight into the potential of this strategy for CMT4B3.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: Charcot-Marie-Tooth disease, CMT, gene therapy, minigene, neuropathy
The effect of surgical weight loss on neuropathy in the severely obese

Poster No:
72b

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Introduction:
The aim of this study was to determine the effect of surgical weight loss on neuropathy outcomes in people with severe obesity.

Methods:
We completed a prospective cohort study of participants with severe obesity who underwent bariatric surgery. At baseline and at 2 years following bariatric surgery, participants had outcome measurements and underwent metabolic phenotyping. The updated National Cholesterol Education Program (NCEP) criteria were used to define the metabolic syndrome (MetS) and its individual components. The co-primary outcomes were changes in intraepidermal nerve fiber density (IENFD, units=fibers/mm) at the distal leg and proximal thigh. Secondary outcomes included nerve conduction studies, Michigan Neuropathy Screening Instrument questionnaire and examination, Neuro-QOL, and quantitative sensory testing.

Results:
Among 138 baseline participants, 80 (mean (standard deviation) age: 45.6 (11.2) years, 72.5% female) completed 2 years of follow-up. Participants lost 31.9 (17.5) kg. All metabolic syndrome components improved with the exception of blood pressure. IENFD in the distal leg improved (baseline: 8.5 (6.8), 2-year: 11.7 (8.3), p<0.01) and IENFD in the proximal thigh (baseline: 14.9 (7.8), 2-year: 15.0 (7.7), p=0.51) did not significantly change. Greater reduction in waist circumference was associated with significant improvements to IENFD of the distal leg (point estimate: -0.15, 95% Confidence Interval: -0.27, -0.03), after adjusting for age, sex, and baseline BMI. Improvements were observed on the Michigan Neuropathy Screening Instrument questionnaire, Neuro-QOL, and quantitative sensory testing vibration threshold.

Conclusions:
Surgical weight loss was associated with improvements in all metabolic parameters except blood pressure, and IENFD of the distal leg improved after 2 years. Metabolic and neuropathy specific outcome improvements were more robust than a previous comparable study of medical weight loss.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support: The project described was supported by Grant Number P30DK020572 (MDRC) from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Dr. Callaghan is currently funded by a NIH NIDDK R-01 award (DK115687). Dr. Reynolds was supported b

Keywords: peripheral neuropathy, obesity, surgical weight loss, metabolic syndrome
The Genetic Spectrum And Diagnostic Rates Of CMT In A Single Large Specialist Centre

Poster No:
73b

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Introduction:
Charcot-Marie-Tooth disease (CMT) is the most common form of inherited neurological disease. As diagnostic science has evolved, methods for genetic testing in CMT have shifted from single gene tests to targeted gene panels, whole exome (WES) and whole genome sequencing (WGS). New genes are frequently being discovered through research. We present a large single centre cohort, with an up-to-date breakdown of genetic diagnosis, diagnostic rates, and how the diagnosis was obtained.

Methods:
A retrospective analysis of patients referred to the inherited neuropathy clinic between 2009 and 2021 was performed. Patient exclusion criteria included: patient refused genetic testing, no neuromuscular disorder identified and disease more likely to be acquired.

Results:
1496 patients met inclusion criteria. 88 were diagnosed with hereditary TTR amyloidosis, leaving 1408 patients with CMT and related disorders. A genetic diagnosis was obtained in 75.4% (1062/1408). In the 'solved' cases, the most frequent diagnoses were CMT1A 44% (465/1062), GJB1 13% (143/1062), MFN2 4% (44/1062), MPZ 4% (39/1062) and SPTLC1 4% (39/1062). Biallelic RFC1 repeat expansions were seen in 24/1062 (2%), SORD in 11/1062 (1%) and HNPP in 6% (65/1062). The method of diagnosis was known in 93.7% (995/1062). This was a single gene test (mainly either the PMP22 duplication or known family mutation screening) in 76% (753/995), a diagnostic panel in 11% (109/995) and research finding (including single gene testing, WES, and WGS) in 13% (133/995). Diagnosis is confirmed in 97% (553/573) of CMT1, with 100% (513/513) in autosomal dominant CMT1. Diagnostic rates are 48% (128/268) in CMT2, 79% (154/194) in CMTi, 59% (61/103) in HSN and 44% (61/139) in HMN.

Conclusions:
75.4% of our CMT patients receive a genetic diagnosis. Next generation sequencing has revolutionised diagnosis with much improved diagnostic rates, and WGS is currently being integrated into routine clinical practice.

References:
Yes

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: CMT, Genetics, Diagnosis, WGS
An International Longitudinal Study Of X-linked CMT Due To GJB1 Mutations

Poster No:
74b

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Introduction:
CMTX1, due to variants in gap junction protein beta-1 (GJB1), is the second most common form of CMT. We present a large cohort of CMTX1 patients with longitudinal clinical data up to 8 years.

Methods:
CMTX1 patients were recruited from one of 21 international sites from 2009 to 2021. Baseline and longitudinal clinical data were prospectively collected and analysed including the CMT Examination Score (CMTESv2) and CMT Neuropathy Score (CMTNSv2).

Results:
404 patients were identified, with complete GJB1 variant information (141 variants) available for 341 cases (84.4%). 51.2% were male (174/340). Initial analysis showed significant differences in the mean age at recruitment (37.7 vs 44.3 years, p=0.0002) and mean age at onset of lower limb symptoms (18.3 vs 27.1 years, p=0.00005) between men and women. Men were clinically more affected than women at baseline; CMTESv2 = 10.7 vs 8.6 (p=0.00002) and CMTNSv2 = 15.9 vs 11.4 (p=0.000005). Longitudinal analysis of CMTESv2 showed no significant difference between mean values at baseline and one- or two-year follow up. However mean CMTESv2 significantly increased from baseline to three years (10.3 vs 11.3; n=76, p=0.001), four years (10.2 vs 10.8; n=83, p=0.021), five years (10.6 vs 11.4; n=62, p=0.039), seven years (9.9 vs 11.0; n=46, p=0.04) and eight years (9.6 vs 11.1; n=24, p=0.02). The Rasch-modified CMTESv2 (CMTESv2-R) performed very similarly with maximum change at eight years (13.3 vs 15.1; n=24, p=0.043). Males did not significantly influence any changes seen in CMTESv2.

Conclusions:
In CMTX1, statistically significant differences from baseline CMTESv2 and CMTESv2-R are seen only from three years onwards but even at eight years, the difference is less than two points, limiting the use of these outcome measures in clinical trials. Ongoing studies comparing CMTESv2 and CMTNSv2 with biomarkers, including lower limb muscle MRI and neurofilament light chain, will be of interest.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: CMTX1, X-linked CMT, GJB1, Natural history, CMTES
Patisiran-Responsive Val50Met Hereditary Transthyretin Amyloidosis Mimicking CIDP with Persistent Conduction Blocks

Poster No:
75b

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Introduction:
Hereditary transthyretin amyloidosis (hATTR) is an autosomal dominant disease leading to severe polyneuropathy and cardiomyopathy. Accumulating data on hATTR polyneuropathy support the possibility of a demyelinating component, fulfilling European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria, raising the question of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) misdiagnosis in hATTR. Interestingly, conduction blocks (CB) were described only in one hATTR patient. Describing a patient with hATTR polyneuropathy who met CIDP EFNS/PNS electrodiagnostic criteria including several CB, we aim to raise awareness of this peculiar electrodiagnostic presentation.

Methods:
We describe a 64-year-old male complaining of distal four limbs paresthesias from the age of 54. Progressively, he developed gait unsteadiness, walking disability and limitations to climb stairs. His past medical history consisted in cardiac arrhythmia with left ventricle hypertrophy, cataract, bilateral carpal tunnel syndrome and narrow lumbar canal. His father was known to have 'feet paralysis' at the age of 84. Clinical examination showed lower limbs distal amyotrophy, positive Romberg's sign, diminished distal pallesthesia but preserved reflexes.

Results:
Blood tests were unremarkable. During the evolution, electroneuromyography showed a sensory-motor neuropathy fulfilling EFNS/PNS CIDP criteria and including definite partial CB out of usual compression sites on both median and right ulnar nerves (1999 American Association of Electrodiagnostic Medicine criteria). TTR gene sequencing identified the c.148G>A (p.Val50Met) mutation. TTR silencing RNA (Patisiran) therapy conducted during two years led to an improvement of walking ability, balance and the release of using banister to climb stairs. However, demyelinating electrodiagnostic features remained including unexpected CB.

Conclusions:
Our case underlines the need, in evolving polyneuropathies meeting CIDP EFNS/PNS criteria, even with CB, to rule out hATTR especially when red flags are present such as CIDP resistant to treatment. In addition, the persistence of demyelinating features including CB does not exclude a positive clinical response to Patisiran in hATTR polyneuropathies.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, Amyloidosis, Conduction Blocks
Peculiar Phenotypical Findings in Intermediate-Charcot–Marie–Tooth Type C Associated With a Novel YARS1 Probably Pathogenic Variant

Poster No:
76b

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Introduction:
Monoallelic Tyrosyl-tRNA synthetase gene (YARS1) mutation may lead to autosomal dominant intermediate-Charcot–Marie–Tooth disease Type C (CMTDIC) (#MIM 608323). Intermediate CMT is characterized by motor median nerve conduction velocities between 25 and 45 m/s with several mode of inheritance. YARS1-related CMTDIC were very rarely worldwide described (<10 families). We aim to report a case of CMTDIC harboring a novel YARS1 probable pathogenic variant and to identify additional phenotypical findings to enlarge phenotype-genotype knowledge of that disease.

Methods:
We describe a 48-year-old male patient presenting initially isolated fasciculations calves from the age of 20 years. At the age of 40, he developed difficulties to remain durably in standing position and reported exercise-related cramps, fatigue, hearing loss and fecal incontinence. The past medical and family histories were unremarkable. Clinical examination showed lower limbs distal amyotrophy, preserved reflexes and mild sensory impairment.

Results:
Routine blood tests for excluding acquired peripheral neuropathy etiologies were normal. Conduction velocity study showed a dramatic decrease of distal compound muscle action potential and sensory nerve action potentials on the lower limbs. Motor and sensory nerve conduction velocities were preserved at lower and upper limbs. Needle electromyography (EMG) demonstrated giant motor unit action potentials in tibialis anterior muscles. Audiometry showed a loss of perception in high frequencies and external anal sphincter EMG revealed neurogenic signs. Clinical exome sequencing identified the heterozygous c.145C>T (p.His49Thr) variant. Its absence form control database GnomeAD, in silico analyses (prediction sites, Deogen score) and strong amino-acid conservation thorough species supported its pathogenic nature. The variant was not found in the father (mother being unavailable).

Conclusions:
Describing a case of CMTDIC associated with a probable pathogenic variant of YARS1 and undescribed phenotypical findings being hearing loss, fecal incontinence and preserved nerve conduction velocities, we enlarge the phenotype-genotype comprehension of this very rare entity.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: CMTDIC, YARS1, incontinence, hearing loss
**Introduction:**

Over 50 million Americans suffer from chronic pain, with opioids being the primary drug used to treat pain. In order to develop non-opioid drugs for treating chronic pain, molecular mechanisms of chronic pain need to be understood and putative drug targets identified. Our goal is to quantify whole transcriptome RNA abundances using RNA-seq in pain-associated human DRGs from vertebrectomy patients, and to comprehensively identify molecular changes in these samples by contrasting them with non-pain associated DRGs.

**Methods:**

RNA was extracted from the excised DRGs, and cDNA library prepared using stranded, single-end library preparation kit from Illumina, mapped to the reference transcriptome using STAR, and relative abundances quantified using Stringtie. Comparing gene expression distributions across pain-associated and non-pain-associated DRGs in a sex-specific manner identify pain-associated genes for males and females. Gene co-expression modules for these differentially expressed genes are identified. Ligand–receptor signaling based on the set of differentially expressed genes reveal a clear picture of sex differential neuro-immune signaling.

**Results:**

We have currently sequenced over 80 human DRGs, with 50 having neuronal mRNA enriched libraries. Differential expression analysis revealed a sex dimorphic set of genes in males (including IL1B, TNF, CXCL14, OSM) and females (including CCL1, CCL21, IL2RA, PENK and TRPA1), and a small set common to both. A subset of these findings have been validated using RNAscope. Co-expression analysis suggests roles of TNF and OSM signaling in male samples, and interferon signaling in female samples. Neuroimmune signaling pathways reveal multiple cytokine signaling pathways in males (OSM, LIF, SOCS1) and females (CCL21, IL2RA).

**Conclusions:**

Sex differential molecular pathology for chronic pain in males and females suggest the need to sex specific pain therapies. Identification of distinct T cell, B cell and macrophage signature reveals the need for immune cell profiling in chronic pain associated tissues.

**References:**

No
References 3:

References 4:

Grant Support: Funding: NS111929 (to PMD and TJP), NS102161 (to TJP)

Keywords: neuropathic pain, human transcriptomics, association study, chronic pain, RNA-seq
Neurovascular interactions in skin regeneration: from a compartmentalized model to a 3D tissue-engineered skin

Poster No:
78b

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Introduction:
Skin integrity is required for maintaining homeostasis of the human body. Recent studies have demonstrated that interactions between sensory nerves and vascular networks play an important role under physiological and pathological conditions, notably in the context of peripheral neuropathies. Vascular networks directly support neuron outgrowth and neuronal network development by efficient distribution of oxygen and nutrients. Nowadays, the generation of fully human innervated tissue-engineered skin can be achieved using patient-derived cells, with prospective applications in skin disease models for personalized medicine approaches.

Methods:
Here, we propose to study neurovascular interactions in both a microfluidic device and a 3D macro-scale culture using human induced pluripotent stem cell-derived sensory neurons and Schwann cells along with human endothelial cells. We intent to identify the molecular determinants promoting synaptic connectivity and to study the influence of sensory neurons on vascular network formation.

Results:
Initial data reported here intend to present our cell models, the functionality of the obtained sensory neurons, evaluated notably by extracellular electrophysiology. We also show the setup of our co-culture model in microfluidic chamber and the resulting neurovascular contacts visualized by immunostaining. Then, preliminary results show the effect of the neuronal compartment on the morphological organization of the endothelial compartment. Finally, we propose our on-going study of an innovative compartmentalized 3D model of a vascularized and innervated skin.

Conclusions:
We expect that our vascular and neuronal networks modeled could promote a better understanding of their interactions in skin physiology and in critical processes.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

**Keywords:** neurovascular interplay, skin, peripheral neuropathy, sensory neurons, tissue-engineering
Two new MORC2 gene mutations are associated with distinctive features: from axonal neuropathy to late adult-onset SMA like phenotype.

Poster No: 79b

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Introduction: MORC2 gene encodes a nuclear protein, ubiquitously expressed, playing a role in chromatin remodeling, DNA repair, transcriptional regulation. Heterozygous mutations in MORC2 have been associated with disorders affecting the peripheral nervous system such as Charcot-Marie-Tooth (CMT2Z), spinal muscular atrophy-like (SMA-like) with or without cerebellar involvement and a developmental syndrome including impaired growth, dysmorphic facies, and axonal neuropathy (DIGFAN syndrome). Such variability in clinical manifestations associated with the increasing number of variants of unknown significance detected by next generation sequencing poses a real diagnostic challenge. We report the characterization of an in vitro model to evaluate the pathogenicity of MORC2 variants.

Methods:  
2 MORC2 variants of unknown significance found in CMT2 and SMA-like patients, and known pathogenic MORC2 mutations were overexpressed in neurblastoma SH-EP cell lines and in cortical neurons. Cell survival rate and apoptosis induction were quantified using Immunofluorescence staining. Neurite outgrowth was measured using the Metamorph software on confocal images of the eGFP reporter gene.

Results:  
MORC2 mutants affect survival and trigger apoptosis over time in SH-EP cell line. Overexpression in primary cortical neurons is also associated with survival loss, decreased neurite outgrowth and apoptosis induction. Altogether, these experiments establish the pathogenicity of two new variants p.G444R and p.H446Q in three patients from two families. These new mutations are associated with an autosomal dominant CMT and with an adult late onset SMA-like phenotype, increasing the spectrum of clinical manifestation.

Conclusions:  
We propose a simple cellular model to assess the pathogenicity of MORC2 variants, which is easily transposable to hospital facilities with a diagnosis purpose. MORC2 should be included not only in the panel of genes involved in CMT but also in proximal SMA and to some extend to other panels, considering the broad range of phenotypes induced by its mutations.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth, Spinal muscular atrophy, cell culture, unknown significance variants
Metrologic characteristics of the Motor Function Measure (MFM): a systematic review

Poster No:
80b

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Introduction:
The Motor Function Measure (MFM) is a quantitative scale designed to monitor the severity and progression of motor function in neuromuscular disease. It applies to patients from 2 to 60 years old, whatever the severity of the disease. It assesses the symptomatology and the evolution of neuromuscular diseases, the impact of therapeutic measures, and helps caregivers to communicate and define rehabilitation interventions. This study aims to review the different studies assessing MFM's metrological characteristics.

Methods:
MEDLINE, SCOPUS and Web of Science were searched in April 2021 for articles dealing with validation studies of the MFM, MFM responsiveness or use of the MFM as an outcome measure in interventional and non-interventional studies. Measurement properties and studies quality were evaluated according to the COSMIN manual for systematic reviews.

Results:
We extracted 423 cases, 40 being retained in our study. 16 were related to validation or metrological studies, 27 related to responsiveness and natural history study (3 to both). 4526 patients of various neuromuscular diseases were involved in the studies. MFM structural validity, internal consistency, reliability, criterion validity, construct validity and responsiveness were rated as sufficient with a high quality of evidence. Structural validity was rated sufficient with a moderate quality of evidence.

Conclusions:
MFM’s reliability, sensitivity to change, construct validity, and criterion validity have been verified through validation studies. MFM is effective for a wide range of neuromuscular diseases. The increasing number interventional study requires the use of a solid, standardized tool such as MFM to assess clinically relevant outcomes like motor function.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** Motor Function Measure, Outcome measure, Neuromuscular diseases, Systematic review
Biallelic variants in COQ7 leading to coenzyme Q10 deficiency cause Charcot-Marie-Tooth disease

Poster No: 81b

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Introduction: COQ7 encodes a hydroxylase responsible for the penultimate step of coenzyme Q10 (CoQ10) biosynthesis in mitochondria. CoQ10 is a redox-lipid essential for multiple cellular functions, including mitochondrial oxidative phosphorylation. Mutations in COQ7 have been previously associated with primary coenzyme Q10 deficiency, a clinically heterogeneous multisystemic mitochondrial disorder. We identified COQ7 biallelic variants in seven families diagnosed with Charcot-Marie-Tooth disease (CMT) or distal hereditary motor neuropathy (dHMN), expanding the phenotype associated with defects in this gene.

Methods: Whole exome sequencing data from CMT patients was analyzed by the GENESIS platform in order to identify novel candidate disease genes. A strict filtering approaches was used to select variants with low allele frequency (MAFgnomad<0.001), high conservation and functional scores. Functional studies were performed on fibroblasts from patients harboring recessive COQ7 variants to evaluate the pathological effects of the mutations on protein function. Cells were assessed for CoQ10 levels by HPLC assay, while mitochondrial function was analyzed by cell respiration. We are also currently generating iPSCs-derived motor neurons as a disease modeling tool for biochemical analysis.

Results: We identified COQ7 biallelic variants in seven sporadic CMT patients. The following variants predicted to be pathogenic were identified in homozygosity or compound heterozygosity (Met1Ile, Arg54Gln, Ile66Asn, Arg107Trp, Tyr149Cys). Western blot analysis from two patient fibroblasts revealed a substantial depletion of COQ7 protein levels indicating protein instability leading to loss-of-function. HPLC assay showed that fibroblasts from patients have reduced levels of CoQ10 leading to abnormal accumulation of the biosynthetic precursor 6-DMQ. Accordingly, fibroblasts showed significant decreased oxygen consumption rate in patients, suggesting mitochondrial respiration deficiency.

Conclusions: Our findings substantially expand the phenotype of COQ7 recessive mutations. Our functional studies demonstrated COQ7 loss-of-function leading to CoQ10 biosynthesis deficiency, confirming mitochondrial dysfunction as a relevant player in the pathogenesis of CMT. Importantly, CoQ10 supplementation provides a potential treatment and should be evaluated in (pre-) clinical studies.
Keywords: Novel CMT gene, COQ7, Coenzyme Q10 (CoQ10), mitochondria, genetics
Measurement of Elevated Sorbitol Levels in CMT Patients with SORD Mutations Using High Pressure Liquid Chromatography-Tandem Mass Spectrometry

Poster No:
82b

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Introduction:
We have reported that biallelic loss-of-function mutations in SORD, the gene coding for sorbitol dehydrogenase (SORD), is the most common recessive form of hereditary neuropathies. We have demonstrated that patients lacking the SORD protein develop elevated levels of sorbitol in blood serum. Sorbitol level is, therefore, an important biomarker and diagnostic tool for CMT. However, the number of laboratories which offer sorbitol measurements is limited.

Methods:
The biochemical and molecular genetics diagnostic laboratory at our institution has developed a test to measure sorbitol levels in patient samples. We studied material from patient-derived cells and serum. High pressure liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) was performed on human samples, including fibroblasts and serum (from fasting patients) to determine sorbitol levels. Lysate samples underwent protein precipitation with acetonitrile (1:2), protonation with 4% phosphoric acid (1:2) and clean up on Oasis HLB cartridges (10 mg/1ml), before injection in HPLC (1μl). Linearity of the method was assessed between 2.5-64 uM MS/MS conditions. We are currently refining the method on different sources of material and begin to screen human controls and cases for sorbitol levels.

Results:
Sorbitol levels in serum from fasting patients as well as patient-derived cell lines, homozygous for the SORD mutation pAla253GlnfsTer27, was over 19 times higher compared to control individuals. These results confirm the lack of SORD enzymatic activity and accumulation of sorbitol as the pathological mechanism of the disease.

Conclusions:
Our developed methodology to measure sorbitol from patient serum and cells has demonstrated increased levels of sorbitol as an important diagnostic biomarker for SORD-associated CMT, a tool to assess pathogenicity of variants, and will allow to monitor clinical responses to therapeutic interventions.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: CMT, Sorbitol, HPLC, Neuropathy, SORD
Characterizing fatigue in patients with hereditary neuropathy with liability to pressure palsies

Poster No:
83b

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Introduction:
Hereditary Neuropathy with Liability to Pressure Palsies (HNPP) is an autosomal dominant peripheral neuropathy caused by a heterozygous deletion of peripheral myelin protein-22 (PMP22). As we demonstrated earlier, action potential propagation is impaired in HNPP due to the disruption of junctions and thereby excessive increase in myelin permeability through a mechanism called functional demyelination. This mechanism expects to cause fatigue in these patients. In this study we aimed at evaluating fatigue in HNPP and investigate the relationship between fatigue, nerve pathology, disability, and quality of life in these patients.

Methods:
Nine females with HNPP were included in this study. Genotypes, nerve conduction studies, neurological exam, quantitative magnetic resonance imaging, and a physical therapy exam incorporating upper and lower extremity function and survey measures of fatigue were collected from these patients in a single study visit. Ecological momentary assessment was done using a wrist-worn device to capture fatigue ratings five times per day for 2 weeks following their first visit.

Results:
Neuropathy scores of patients in this study showed a mild neurological impairment (CMTNS: 5.7 ± 2.8), However, they were experiencing very high fatigue levels with average fatigue intensity of 5.9 out of 10 in 2 weeks. Higher fatigue levels were associated with poorer quality of life and more pain. Peripheral nerve MRI also demonstrated a direct association between fatigue and distal nerve proton density. The higher proton density likely relates to the increased myelin hyper-permeability in HNPP.

Conclusions:
Fatigue is a very common feature in HNPP and patients who show minimal disability through conventional outcome measures experience severe fatigue. Therefore, fatigue may potentially serve as a robust outcome measure in patients with HNPP in clinical trials.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support: NIH (R01NS066927), VA BLR&D (IBX003385A), and Detroit Medical Center Foundation (2018-3328)

Keywords: HNPP, Outcome measure
Comparison of combined morphological and quantitative biomarkers obtained with high-field MRI in sciatic nerves of CMT1A patients and healthy controls

Poster No:
84b

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Introduction:
Patients with peripheral nerve disease such as Charcot-Marie-Tooth (CMT) syndrome are thought to exhibit various anatomic differences from healthy controls. Some of these differences are morphological, such as nerve cross-sectional areas, while others reflect microscopic differences. With high-resolution magnetic resonance imaging (MRI), morphological changes can be visualized, but imaging of microstructural tissue changes often requires specialized quantitative MRI. Here, we combine morphological and quantitative MRI in one imaging method. We compare the results in CMT1A patients and healthy controls.

Methods:
Using a version of the Double-Echo in Steady-State (DESS) MRI sequence that allowed quantification of the MRI parameters of T2 relaxation, apparent diffusion coefficient (ADC), and fat fraction (FF), in addition to morphology, axial images were acquired in the lower right thigh of 6 CMT1A subjects and 6 age- and sex-matched healthy controls. Imaging was performed in a 7 Tesla MRI scanner, allowing a resolution below 0.15 mm and clear visualization of nerve fascicles. Quantitative parameter maps were produced at the same resolution. A slice was selected at the sciatic nerve bifurcation. By drawing regions of interest (ROIs) around individual fascicles, the fascicle cross-sectional area (CSA), T2, ADC, and FF were measured. This was repeated for the tibial and fibular nerves, 1 cm below the bifurcation slice. The results were compared between patients and controls. Statistical significance was determined using a two-sided t-test with α = 0.05.

Results:
Images clearly displaying individual nerve fascicles and their quantitative measurements were obtained. The results indicated a larger CSA, T2, and ADC in CMT1A patients compared to controls, but only the difference in CSA was statistically significant.

Conclusions:
Using simultaneous morphological and quantitative MRI at high resolution, we were able to obtain several measurements in peripheral nerve fascicles, some showing differences between patients and controls. This could contribute to establishing imaging biomarkers for peripheral nerve disease.

References:
No

References 1:

References 2:

References 3:
References 4:

**Grant Support:** NIH K99AG066815; Research scholarship grant from the American Academy of Neurology (AAN)

**Keywords:** CMT1A, MRI, Biomarkers, Imaging, Quantitative
Autoimmune Nodopathy With Antibodies To CNTN1/CASPR1 Complex In A Patient With Cystic Fibrosis.

Poster No:
85b

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Institutions:
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Introduction:
Nodo- and paranodopathies are autoimmune neuropathies associated with antibodies to nodal-paranodal antigens (neurofascin, contactin-1, caspr1) characterized by poor response to intravenous immunoglobulins (IVIg) and benefit from anti-CD20 monoclonal antibody (rituximab) therapy. The forms with antibodies to caspr1/contactin-1 complex are rare, rapidly progressive, sometimes associated with pain and cranial nerves involvement.

Methods:
We report on a 26-year-old woman, affected by cystic fibrosis, who developed a disabling anti-CNTN1/CASPR1-mediated polyneuropathy.

Results:
She presented with subacute onset of sensory symptoms at 4 limbs, followed two weeks later by motor (distal>proximal) weakness. For neurophysiological evidence of demyelinating neuropathy, she was diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy and treated with IVIg without benefit. The symptoms rapidly worsened, the patient was forced to discontinue her job and lost autonomy in daily activities. Three months after symptoms onset she was admitted to our Hospital. Neurological evaluation showed ataxic-stepping gait, severe (distal>proximal) motor weakness at four limbs, upper limbs low frequency postural tremor, sensory loss up to the trunk, loss of vibration sense at four limbs, areflexia. Electrodiagnostic evaluation confirmed a severe demyelinating polyradiculoneuropathy with sensory and motor conduction blocks. MRI with 3D Neurographic sequences showed diffuse, symmetrical, homogenous hypertrophy and marked T2-STIR signal hyperintensity of roots and main divisions of brachial and lumbosacral plexi. Brain MRI was unremarkable. Extensive immunological and microbiological workup resulted negative. Cerebrospinal fluid analysis showed 710 mg% protein, 13 WBC/µL, severe blood–spinal nerve root barrier damage.

Conclusions:
Despite intravenous methylprednisolone and physical therapy, the patient progressively worsened, sensory loss spread to chin and tongue, distal strength was abolished distally and severely reduced proximally, she became unable to stand independently being restricted to wheelchair. Antibodies to nodal-paranodal antigens were searched for by ELISA and cell-based assay. Anti CNTN1/CASPR1 IgG antibodies resulted positive, and diagnosis of CNTN1/CASPR1-mediated neuropathy was made. The patient is currently undergoing therapy with rituximab.
References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Nodopathy, CNTN1/CASPR1 Complex
Magnetic Resonance Neurography and Diffusion Tensor Imaging of the sciatic nerve in hereditary transthyretin amyloidosis polyneuropathy

Poster No:
86b

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

Methods:
19 subjects with a TTR gene mutation (mean age 62.32), including 13 patients affected by axonal or predominantly axonal polyneuropathy (ATTR-FAP) and 6 pre-symptomatic carriers (ATTR-carriers) were prospectively evaluated with Magnetic Resonance imaging at 3 Tesla and compared with 19 healthy controls (mean age 61.42). 2D MRN and DTI sequences were conducted at the right thigh from the ischiatic foramen to the popliteal fossa. Cross-section area (CSA), normalized signal intensity (NSI), DTI metrics, including fractional anisotropy (FA), mean (MD), axial (AD) and radial diffusivity (RD) were measured at proximal, mid and distal thigh. Neurologic and electrophysiologic examinations were conducted in ATTR-FAP and ATTR-carriers and correlated with MR parameters.

Results:
increased CSA, NSI, MD, RA and reduced FA reliably differentiated ATTR-FAP from ATTR-carriers and controls at all levels (p<0.01). NSI was able to differentiate ATTR-carriers from controls at proximal (1.50±0.28 vs 1.11±0.14 p=0.001) and midthigh (1.56±0.29 vs 1.19±0.17 p<0.05), FA at midthigh (0.52±0.02 vs 0.58±0.04 p<0.05) and RD at proximal (1.02±0.10 vs 0.86±0.12 p) and midthigh (1.08±0.11 0 vs.93±0.15 p<0.05). CSA and AD were unable to differentiate ATTR-FAP from ATTR-carriers. CSA, MD and RD positively correlated with NIS-LL (average 20.56±17.65 in ATTR-FAP) and negatively with cMAPs and NCVs. FA positively correlated with cMAPs and NCVs and negatively with NIS-LL.

Conclusions:
The combination of MRN and DTI can be reliably used to differentiate between ATTR-FAP, ATTR-carriers and healthy controls, based on quantitative structural and functional parameters information obtained from the sciatic nerves which are significantly correlated with neurophysiology. More importantly MRN-DTI is able to non-invasively identify early microstructural changes in pre-symptomatic carriers, thus representing a potential tool for monitoring disease progression.
References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: TTR, MR Neurography, Imaging
Age-Associated Gene and Gene-Pathway Alterations in Dog Peripheral Nerve

Poster No:
87b

Authors:
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Institutions:
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Introduction:
The client-owned dog population provides a unique opportunity to study aging and disease by providing a spontaneous large animal model that has a shared environment with humans. Dogs also have shorter lifespans that their human counterparts, and humane euthanasia is often elected at end of life. Alterations in gene expression profiles in a higher mammal in peripheral nerve tissues due to aging has not been described. The objective of this study was to identify alterations in gene expression and pathway signaling associated with aging in peripheral nerve in the dog.

Methods:
RNA-sequencing provides an unbiased and high-resolution genome-wide expression profile of the transcriptome, enabling assessment of differentially expressed genes and gene pathways. Tissues were collected from 8 dogs, including 4 aged dogs and 4 young dogs. All dogs in the study did not have clinical evidence of peripheral or central neuropathy with normal neurologic examinations. Tissues were collected within 45 minutes of euthanasia and stored for RNA-sequencing.

Results:
Gene expression analysis resulted in 148 differentially expressed genes. Twenty-seven gene pathways were also identified, including pathways associated with the matrisome, the SOX2 target pathway and stem-cell associated pathways.

Conclusions:
Our results support prior findings that extracellular matrix and stem cell pathways are altered with aging. These pathways are features of interest in peripheral nerve and reflect the ability for the peripheral nervous system to undergo regeneration. Alterations in stem cell regenerative capacity because of aging is likely influenced by alterations in the extracellular matrix. Taken together, this study highlights broad but targetable alterations in aged peripheral nerve, which is a consideration in treatment of peripheral nerve injury in the aged population.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support: NIH K01 FOA PA-14-044; NIH R03 OD026601-01

Keywords: Aging, Dog, RNA-seq, Gene expression, Peripheral nerve
Evaluation of Differential Gene Expression in a Canine Late-Onset Peripheral Neuropathy

Poster No:
88b

Authors:
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Introduction:
Late-onset peripheral neuropathy (LPN) is an idiopathic disease of older dogs that has a genetic basis. Clinical signs include upper respiratory obstruction due to laryngeal paralysis and paraparesis. Spontaneous diseases in dogs serve as valuable models for corresponding human conditions. Dogs have shorter lifespans than humans; humane euthanasia is often elected at end of life. This provides opportunities for fresh tissue collection from aged large animal models. The objective of this study was to identify alterations in gene expression and pathway signaling associated with LPN using peroneal nerve from a homogenous population of dogs with LPN and aged control dogs.

Methods:
RNA-sequencing provides an unbiased genome-wide expression profile of the transcriptome, enabling assessment of differentially expressed genes and altered pathway signaling. Tissues were collected from 12 dogs, including 8 LPN-affected dogs and 4 aged controls. RNA-sequencing was undertaken, and differential gene expression and pathway analyses were performed.

Results:
Eleven genes were found to be differentially expressed, although 8 of these genes were either not characterized or annotated. The remaining 3 genes included Rho family GTPase 1 (RND1), selectin-E (SELE) and dermatopontin (DTP). Altered pathways included the VEGFa-VEGFR2 pathway and the APC target pathway.

Conclusions:
RND1 has not been previously studied in the PNS, although in the CNS it is implicated in regulation of actin cytoskeleton and axonal guidance. SELE. In this study it was downregulated in LPN-affected dogs, suggesting decreased vascular presence or activation. DTP has roles in collagen regulation and fibronectin fibril formation but has not been characterized in the nervous system. This study highlights the value of using spontaneous large animal disease models, and highlights novel genes and pathways associated with peripheral nerve pathophysiology.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** Peripheral neuropathy, Dog, Gene expression, RNA-seq, Laryngeal paralysis
**RFC1 Repeat Expansions And CANVAS: Initial Experience And Perspectives From A Neuromuscular Disorders Unit.**

**Poster No:**
89b

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**Introduction:**
Introduction: Biallelic AAGGG expansions in RFC1 have been described as a cause of a spectrum of disorders including late-onset ataxia, chronic cough, and cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS). Sensory neuropathy/neuropathy appears to be a major symptom of RFC1-disorder, and RFC1 expansions are common in patients with sensory chronic idiopathic axonal neuropathy or sensory ganglionopathy. We aimed to investigate RFC1 expansions in patients with suspected RFC1-related disease followed in a Neuromuscular disease Unit, with a particular interest in the involvement of the peripheral nervous system.

**Methods:**
Methods: We recruited twenty patients based on the presence of at least two of the following features: progressive ataxia, sensory neuropathy/neuronopathy, vestibulopathy and chronic cough. Medical records were retrospectively reviewed for a detailed clinical description. More extensive phenotyping of the RFC1-positive patients and clinical comparison between RFC1-positive and negative patients were performed.

**Results:**
Results: Biallelic AAGGG repeat expansions were identified in 65% of patients. The most frequent symptoms were chronic cough and sensory disturbances in the lower extremities (92.3%). Only 31% of patients had complete CANVAS. Deep tendon reflexes in lower limbs were preserved in 46.2% of patients and H reflexes in 75%. Sensory symptoms in extremities and chronic cough was the clinical phenotype in 15%, sensory ataxia and sensory symptoms in 31% and sensory ataxia, sensory symptoms and vestibulopathy in 23%. Nerve conduction studies showed generalized sensory fibre involvement with a pattern of axonal damage in both upper and lower extremities. Motor nerve conduction parameters and autonomic testing were normal in all subjects. Chronic cough and isolated sensory neuronopathy were significantly more prevalent in RFC1-positive patients.

**Conclusions:**
Conclusions: Pathogenic RFC1 expansions are a common cause of sensory neuropathy/neuropathy and should be considered in the approach to these patients. Identification of key symptoms or detailed interpretation of nerve conduction studies may improve patient selection for genetic testing.

**References:**
No

**References 1:**
References 2:

References 3:

References 4:

Grant Support:

Keywords: CANVAS, RFC1, Sensory neuronopathy, Ganglionopathy, Ataxia
**Same Same, But Different? The Neurological Presentation Of Wildtype Transthyretin Amyloidosis.**

**Poster No:**
90b

**Authors:**
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**Institutions:**
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**Introduction:**
Wild-type transthyretin amyloidosis (ATTRwt) is an age-related disorder, caused by destabilized transthyretin (TTR) protein-monomers. ATTRwt is the non-mutated 'sister' of hereditary transthyretin amyloidosis (ATTRv). Both can be associated with neurological manifestations such as carpal tunnel syndrome (CTS) or spinal canal stenosis (SCS). In contrast to ATTRv, the appearance, severity and extent of neurological involvement have not been adequately characterized. Our goal was the neurological characterization of ATTRwt-cardiomyopathy patients and comparing the clinical picture with ATTRv.

**Methods:**
We prospectively examined 50 ATTRwt-patients between November 2019 and September 2020. Diagnosis was made by genetic examination, biopsy and/or scintigraphy. Work-up included nerve conduction studies (NCS), neurological, radiological and cardiological examinations. In addition, head-up tilt-table-test (HUTT) was used in a subgroup (n=8) to assess orthostatic intolerance (OI).

**Results:**
50 patients (4 women, 46 men; mean age of 80.6 (SD±5.0) years) were diagnosed with ATTRwt. 74% (n=37) presented a mild peripheral, symmetric, length-depended mostly sensory polyneuropathy (PNP) with mean neuropathy impairment score (NIS) of 8.4 points (SD±10.1)). Despite that, 17 patients presented an atypically severe PNP (NIS >10 points). DPD-scan showed strong uptake in this subgroup (Perugini grade 2: 29% (n=5), Perugini grade 3: 53% (n=9)). 70% (n=35) showed a unilateral (34%; n=11) or bilateral (66%; n=21) CTS and a prior history of SCS in 11% (n=5). Median COMPASS-31 was 18.4 points (IQR 32.4 points) with a slightly increased rate of the OI screening-section, which couldn't be reproduced in the HUTT.

**Conclusions:**
Distal-symmetric, mostly sensory polyneuropathy without serious mobility impairments, and to a lesser extent, severe polyneuropathy is a frequent neurological feature of ATTRwt. Neurological symptoms (e.g., CTS, SCS) preceding cardiomyopathy manifestation by 10-12 years. Autonomic symptoms don't seem to be common complications. After all, ATTRwt is an often-delayed diagnosed disease, which shouldn't be missed as differential diagnosis of sensory polyneuropathy.

**References:**
No

**References 1:**

**References 2:**
References 3:

References 4:

Grant Support:

Keywords: amyloidosis, polyneuropathy, transthyretin amyloidosis, TTR amyloidosis, wild-type transthyretin amyloidosis
Bortezomib Neuropathy: Characteristics of a cohort from a tertiary multiple myeloma treatment center

Poster No:
91b

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Introduction:
Peripheral neuropathy is a dose-limiting side effect of bortezomib therapy.

Methods:
We prospectively investigated 36 patients (22 men, median age 68 years) who received bortezomib as part of multiple myeloma treatment to describe the characteristics of their neuropathy and to identify potential risk factors.

Results:
Median age at diagnosis was 61 years, median time since diagnosis 3.7 years. All patients had received comedication with dexamethasone, most had daratumumab (28/36), doxorubicin (24/36), and melphalan (27/36) in prior lines of therapy. In 18 patients, bortezomib treatment had been terminated at the timepoint of investigation, 18 were under ongoing bortezomib treatment. The median cumulative dose was 26 mg/m² (range 1.3-120.4 mg/m²). Peripheral neuropathy with a modified Toronto Clinical Neuropathy Score (mTCNS) of >3 was present in 28/36 (80%) of the patients. Of these, 21 had a moderate to severe neuropathy. In 18 of the patients, the neuropathy was painful or had been painful at some time. Nerve conduction studies were pathological in the sural nerve in 22/36, in the tibial nerve in 17/36 patients, all with an axonal pattern. Quantitative sensory testing (QST) showed more A-delta (75%) than C-fiber (61%) and A-beta (56%) involvement. Skin innervation as measured morphologically was pathological in 10/26 participants. Brain derived neurotrophic factor (BDNF) serum levels, that had previously been shown to be associated with bortezomib neuropathy and pain, did not correlate with any measures of neuropathy or pain.

Conclusions:
The strongest predictors of neuropathy were age, BMI, and pre-existing neuropathy, while other neurotoxic drugs, bortezomib dose, and BDNF levels did not play a role.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support: Deutsche Forschungsgemeinschaft KFO 5001

Keywords: chemotherapy, bortezomib, pain, quantitative sensory testing, neurophysiology
Structural Alterations Reduce Nociception in Mice Carrying the L799P-Gain-of-Function Variant in NaV1.9 Sodium Channel

Poster No:
92b

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Introduction:
Pain protects the body from injuries while impaired nociception leads to severe mutilations and tissue damage. SCN11A encodes the voltage-gated sodium ion channel NaV1.9 primarily expressed in nociceptors. The gain-of-function variant Scn11a-L799P (orthologous to p.L811P in humans) leads to overactivity of this channel and disturbed nociceptive transmission. So far, the underlying pathomechanisms of this channelopathy have not been conclusively clarified, i.e., whether the loss of pain perception is due to neurodegeneration or to altered transmission of the corresponding neurons.

Methods:
Investigations were performed on heterozygous knock-in mice carrying the Scn11a-L799P variant and compared with wild type specimen. Electron micrographs of peripheral nerves (sciatic and sural) were analyzed regarding axon size distribution and cluster size of unmyelinated nerve fibers. Frozen sections of hindpaw glabrous skin were stained free floating using protein gene product 9.5 (PGP 9.5) antibodies to determine intraepidermal nerve fibre density (IENFD). Expression of collagen type IV alpha 3 chain (Col4a3) was analyzed by quantitative real time PCR (qPCR) as well as immunofluorescence stainings on frozen sections, as this collagen was strongly upregulated in the transcriptomes from dorsal root ganglia (DRGs) of knock-in mice.

Results:
Highly elevated Col4a3 expression levels in heterozygous knock-in animals were verified by qPCR as well as immunofluorescence stainings of DRG tissue sections. This matches findings from transcriptome analyses in DRGs. Analyses of axon number and axonal size distribution in peripheral nerves indicated distinct changes within small unmyelinated axons. Preliminary evaluation of IENFD did not show marked differences.

Conclusions:
Increased expression of Col4a3 indicates an expanded extracellular matrix production. However, this collagen subtype has previously not been allocated to nervous tissue but points towards compensatory structural alterations in heterozygous animals. A different axon size distribution in peripheral nerves implies additional compensation mechanisms. Further analyses of DRGs by single cell sequencing will provide additional insights in this pain-related channelopathy.

References:
Yes

References 1:
References 2:

References 3:

References 4:

Grant Support: This project was funded by grants of the Deutsche Forschungsgemeinschaft (DFG) to Prof. Ingo Kurth.

Keywords: NaV1.9, Scn11a, channelopathy, electron microscopy, Col4a3
Molecular characterization of human dorsal root ganglion using spatial RNA sequencing and RNAscope in situ hybridization

Poster No:
93b

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Institutions:
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Introduction:
Nociceptive sensory neurons found in the dorsal root ganglia (DRG) transmit information about harmful stimuli to the central nervous system leading to the sensation of pain. In chronic pain conditions, these neurons become spontaneously active in the absence of noxious stimuli, making them enticing targets for pain treatment. While next-generation sequencing technologies (single-cell, bulk) and histology-based approaches have elucidated mechanistic drivers of pathological pain in rodents, few such studies have been conducted in human. Part of the problem is the limited availability of high-quality human tissues and technical challenges associated with the large size of human sensory neurons.

Methods:
To overcome this gap in knowledge, we conducted spatial RNA sequencing with near-single cell resolution in combination with RNAscope in situ hybridization to molecularly characterize human sensory neurons from 8 organ donors (4 male, 4 female).

Results:
We identified 12 subpopulations of human sensory neurons with distinct expression profiles including 5 C-nociceptors, 1 A-Beta nociceptor, 1 C-LTMR, 2 Aδ, 2 A-Beta and 1 proprioceptor subtypes. Comparing these populations to rodent, we find many similarities but also many differences such as the expression of TRPV1 which is robustly expressed in all human nociceptor subpopulations but is more limited in rodent. We also observed sex differences in the expression of some genes, such as CALCA (CGRP) which is more enriched in female pruritogenic nociceptors.

Conclusions:
This comprehensive spatial dataset of human nociceptors offers an invaluable means to gauge species homology, sex differences, and human-specific drug targets which will help guide preclinical pain studies and predict clinical translatability and therapeutic outcomes.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: human, dorsal root ganglion, nociceptors, pain
Neuron-macrophage interactions in models of chemotherapy-induced peripheral neuropathy

Poster No:
94b

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Introduction:
The pathological mechanisms underlying chemotherapy-induced peripheral neuropathy (CIPN) remain unclear, and treatment and prevention strategies are currently not available in the clinic. It affects over 3 million people in the US alone and symptoms include chronic and debilitating pain accompanied by pro-inflammatory changes. Hence, we investigated peripheral interactions between macrophages, the most abundant immune cell type residing in the skin, and nociceptive nerve terminals in CIPN models. Molecular profiles of macrophages change continuously depending on their extracellular environment, allowing them to transition into many intermediate forms with different inflammatory states. However, how these transitions are linked to pathological progression of nerve terminals in CIPN is still poorly understood.

Methods:
To fill this gap, we used a Drosophila model of paclitaxel-induced peripheral neuropathy to understand in vivo interactions between macrophage transition and the pathogenesis of nociceptive neurons. Building from our previous study, we examined early, intermediate, and late pathological stages (24-48-72h following paclitaxel administration) in our model to determine the time course of macrophage transition and how they are correlated with neurodegeneration and hypersensitivity phenotypes. Furthermore, to quantify in vivo changes in macrophage states throughout pathological progression, we used two complementary approaches: 1) spatially mapping molecular profiles of macrophages surrounding neurons at a single-cell-level and 2) transcriptional analysis of candidate immune pathway genes.

Results:
We found a marked proliferation of resident macrophages starting from the early pathological stage. Furthermore, levels of molecular markers for macrophage activation (protein kinase misshapen and ITGB1) increased from the intermediate stage, before morphological changes in neuron terminals.

Conclusions:
Our study revealed activation of pro-inflammatory macrophages before neuron degeneration, supporting that neuron-immune interactions may be critical in the development of CIPN pathology at the early and intermediate pathological stage. Future studies will investigate whether modulation of macrophage activation may promote neuronal health in CIPN using Drosophila and mouse models.

References:
Yes

References 1:
Integrins protect sensory neurons in models of paclitaxel-induced peripheral sensory neuropathy Grace Ji-Eun Shin, Maria Elena Pero, Luke A Hammond, Anita Burgos, Atul Kumar, Samantha E Galindo, Tanguy Lucas, Francesca Bartofini, Wesley B Grueber. Proc Na
References 2:
Neuroinflammatory Process Involved in Different Preclinical Models of Chemotherapy-Induced Peripheral Neuropathy Giulia Fumagalli, Laura Monza, Guido Cavaletti, Roberta Rigolio, Cristina Meregalli Front Immunol, 2021 PMID: 33613570 PMCID: PMC7890072 DOI:

References 3:

References 4:

Grant Support: Thompson Family Foundation Initiative at Columbia University

Keywords: Chemotherapy-induced peripheral neuropathy, Paclitaxel, Inflammation, Macrophages, Drosophila
Creation of a Schwann cell-specific “ER stress” mouse to test the contribution of ER stress to the pathogenesis of CMT1B

Poster No:
95b

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Introduction:
ER stress has been implicated in the pathogenesis of CMT1B, caused by gain-of-function mutations in myelin protein zero (MPZ). This association was first demonstrated in the context of the MPZ Ser63² mutation, which is ER-retained and elicits markers of unfolded protein response (UPR) activation in mouse models thereof. The neuropathic phenotype is partially attenuated in Ser63² mice in which either of the UPR target genes CHOP or GADD34 has been deleted. Small molecules that inhibit GADD34 and so perpetuate global translational repression phenocopy this protection, both in Ser63² and, as we have recently shown, in R98C animals.

Methods:
In vitro, a large number of CMT1B-associated MPZ mutations are associated with UPR induction, pointing to ER stress as a pathway potentially common to many or perhaps most forms of CMT1B. Yet despite the emerging consensus that ER stress contributes to Type 1 CMT, it is not clear exactly how ER stress contributes to CMT pathology. It is not known whether CMT1B is caused by induction of a generic form of ER stress by mutant MPZ, or whether the fact that it is MPZ itself that elicits ER stress contributes to the phenotype a significant way. This is because, prior to now, the functional loss of MPZ by its mutation could not be experimentally dissociated from its effects on broader ER homeostasis and UPR signaling.

Results:
To overcome this limitation, we have created a transgenic mouse model, in its early stages of characterization, in which ER stress and UPR activation can be elicited by CRE-mediated expression of a constitutively misfolded ER client protein.

Conclusions:
This protein, an ER-retained mutant of alpha-1-antitrypsin, elicits ER stress and UPR activation in heterologous cell types, and so Schwann cell-specific expression will allow the contributions of ER stress and UPR signaling to the CMT phenotype to be definitively tested.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

**Keywords:** ER stress, unfolded protein response
HIGH RESOLUTION ULTRASSONOGRAPHY AS A DIAGNOSTIC TOOL AND THERAPEUTIC GUIDE IN NEUROMUSCULAR DISEASES: CASES FROM A BRAZILIAN CENTER

Poster No:
96b

Authors:
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Institutions:

Introduction:
Peripheral nerve High-resolution Ultrasound (HRUS) is an emerging tool in the diagnosis of neuromuscular diseases. Although increasing data on HRUS in peripheral neuropathies are becoming available, the overall contribution of HRUS to clinical practice is yet to be defined.

Methods:
We discuss the results of applying HRUS in three selected cases.

Results:
1. 60-year-old woman with CIDP had recurrent motor symptoms for the last 35 years. EMG depicted demyelination pattern and high CSF proteins. Monthly IVIg was necessary to remain asymptomatic. Nerve HRUS was performed soon after an IVIg dose and close to the next one. We found a gradual nerve enlargement prior to the next dose, correlating with the need to restart the treatment. After IVIg, CSA reduced also correlating with clinical improvement. 2. 32-years-old man reported numbness in the lower limbs two weeks after gastroenteritis that evolved to tetraparesis. CSF showed high proteins and 1 cell. He was diagnosed with Guillain Barré syndrome (GBS) and received IVIg. EMG revelled a demyelinating pattern. Five months later, he still had severe gait impairment. HRUS was normal. He started rehabilitation and had a good outcome. 3. 54-vo woman started subacute tetraparesis and dysphagia. On clinical exam: arreflexia. CSF 280 mg% protein with no cells. She evolved to orotracheal intubation. IVIG course was started in ICU and was discharged only one month later. EMG revealed demyelinating pattern with active axonal loss. HRUS showed no enlargement. As she had no inflammatory component we didn't perform the second course of IVIg. She was treated by regular physical therapy with good outcome.

Conclusions:
In the first case, HRUS seemed to predict the need and response to therapy. In the second and third cases, HRUS helped us to refrain from a second IVIG cycle in GBS patients. HRUS in neurological practice may aid in diagnosis and guide therapy, becoming a cost-effective tool for neurologists.

References:
Yes

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: High Resolution ultrasound, Inflammatory neuropathy
Identification of novel autophagy modulators for CMT2L in a cellular model with Lys141Asn mutation in HSPB8

Poster No:
97b

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Introduction:
As part of the CASA complex, the chaperone HSPB8 mediates the engulfment of ubiquitinated proteins into the autophagosome. Mutations in HSPB8 are associated with inherited peripheral neuropathies like axonal CMT. Indeed, the knock-in mouse model carrying the K141N mutation in Hspb8 reports peripheral nerve degeneration and severe muscle atrophy associated with defects in LC3 and p62/SQSTM1 degradation. This suggests that enhancing the autophagy activity might represent a valid strategy to counteract the neurodegeneration.

Methods:
We performed a drug screening of FDA/EMA-approved compounds on mouse embryonic fibroblasts (MEFs) bearing the Hspb8 mutation and stably expressing GFP-LC3. After compound treatment for 24h, the autophagic activity was assessed by the quantification of GFP-LC3 autophagosomes under mTOR inhibition with Rapamycin and lysosome inhibitor BafilomycinA1. The FDA/EMA library has been tested to determine if the compounds modulate autophagy in presence of the Hspb8 mutation.

Results:
The assay quality control verified the replicability and the phenotypical difference in the number of puncta. The wild-type line shows duplication of the LC3 puncta under Rapamycin/Bafilomycin, whereas the mutant line remains at the basal level. To assess the suitability of the cellular model, we first tested known autophagy inducers and inhibitors. The pilot screening revealed 3 hits, which have been evaluated for their dose-response curve. The bet hit was selected as positive control and Z’ factor was calculated. The screening highlighted putative pathways that can be exploited to improve in vitro autophagic deficits.

Conclusions:
In this study, we confirmed the autophagy impairment due to the Hspb8 K141N mutation in MEFs from the CMT2L/dHMN mouse model. The proposed methodology places greater attention on the identification of novel autophagy modulators specifically on this mutated background. Afterwards, we aim to further validate the identified pathways in CMT animal and patient-derived models to encourages the translation of our findings in a effective therapy for inherited neuropathies.

References:
Yes

References 1:
References 2:

References 3:

References 4:

Grant Support:

**Keywords:** Autophagy inducers, Phenotypical drug screening, HSPB8, CMT2
The Importance Of Segregation in the Genetic Diagnosis Of Hereditary Neuropathies

Poster No:
99b

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Introduction:
Confirming pathogenicity or non-pathogenicity of variants in known genes is vital not just for family planning but also for the emerging treatments for genetic conditions. With the next generation sequencing technologies such as disease-specific gene panels, whole-exome sequencing, whole-genome sequencing, mitochondrial sequencing and high-throughput transcriptome sequencing used in the diagnosis of Charcot Marie Tooth Disease and related disorders, a particular challenge lies in is the interpretation of variants of uncertain significance. Segregation studies with family members are critical for the assessment of variant pathogenicity. The aim of this project was to assess the impact of the segregation studies on the diagnostic rate when using family-analysis compared to proband-only analysis for patients with genetic findings.

Methods:
Blood was requested from relatives of 150 patients, in whom only the proband's DNA was initially available. Segregation of candidate variants was performed where applicable. Variants were reassessed as to the likelihood of their pathogenicity.

Results:
Of 150 patients where a blood sample was requested from a relative, 141 families have sent samples back. A pathogenic variant was confirmed in 73% of patients through analysing DNA from relatives of affected patients (43/59). Confirmation of diagnosis would only have been possible in 27% cases without parental DNA. In particular parental DNA was required in 5 of the 6 cases (83%) for the diagnosis of SORD neuropathy, which is a potentially treatable inherited neuropathy.

Conclusions:
The impact of segregation was particularly important for de novo variants and novel variants of genes such as TFG, NEFH, AIFM1, and in newer genes such as SORD. Due to the large number of rare variants in every genome, obtaining DNA samples from relatives when their affected status is known to show segregation is critical to confirm pathogenesis in complex cases of hereditary neuropathy.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: CMT, Genetic testing
Targeting muscle to rescue impaired axonal transport in Charcot-Marie-Tooth disease

Poster No:
100b

Authors:
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Institutions:
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Introduction:
Gain-of-function mutations in the housekeeping gene GARS1, which lead to the expression of toxic versions of glycyyl-tRNA synthetase (GlyRS), cause the selective motor and sensory neurodegeneration characterising Charcot-Marie-Tooth disease (CMT). Aberrant interactions between GlyRS mutants and different proteins, including neurotrophin receptor TrkB, underlie CMT type 2D (CMT2D); however, pathomechanistic understanding of this family of untreatable diseases remains incomplete.

Methods:
Injection of a well-characterised fluorescent fragment of tetanus neurotoxin (HCT-555) into leg muscles permits in vivo imaging and tracking of HCT-containing signalling endosomes within intact sciatic nerve axons of live, anaesthetised mice. This approach was used to characterise the in vivo axonal transport dysfunction in mice modelling CMT2D and determine the molecular cause for this impairment. Live imaging was coupled with western blotting of muscles and nerves, as well as immunohistochemical assessment of spinal cords and neuromuscular junctions, to determine how disturbed BDNF-TrkB signalling underpins genetic neuropathy.

Results:
Through intravital imaging, we show that CMT2D mice display early and persistent disturbances in axonal transport of neurotrophin-containing signalling endosomes in vivo. This occurs in hindlimb-innervating sciatic nerve axons, but not forelimb-innervating neurons; thus, transport disruption strictly correlates with all the pathological phenotypes in mutant Gars mice. Intramuscular injection of human mutant, but not wild-type, GlyRS into wild-type muscles non-cell autonomously impairs endosome transport in otherwise healthy axons. Similarly, inhibition of BDNF-TrkB signalling at the nerve-muscle interface also perturbs signalling endosome trafficking in wild-type neurons. Finally, we show that boosting levels of BDNF, but not other neurotrophic factors, in CMT2D muscles is able to restore physiological axonal transport.

Conclusions:
These findings demonstrate the importance of BDNF-TrkB signalling to regulating endosome axonal transport in vivo. Furthermore, they reveal how impairments in this pathway contribute to neuropathy and hint at possible future gene therapy strategies for CMT.

References:
No

References 1:

References 2:
Grant Support: This work was funded by the Medical Research Council award MR/S006990/1 (JNS); Wellcome Trust fellowship 103191/A/13/Z (JNS); Human Frontier Science Program long-term fellowship LT000220/2017-L (SS); Wellcome Trust award 107116/Z/15/Z (GS); Rosetrees Trus

Keywords: neurotrophin signalling, signalling endosome, neuromuscular junction, BDNF, Trk receptors
How Often is Peripheral Neuropathy Diagnosed in Patients Referred to an Academic Neuromuscular Clinic?

Poster No:
101b

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Institutions:
1Mayo Clinic, Scottsdale, AZ

Introduction:
Purpose: To describe the spectrum of disorders seen in a tertiary academic neuromuscular (NM) clinic over a 5-6 year period. Neurologists focusing on NM disorders see a wide variety of patients. Some have NM disorders including peripheral neuropathy. Some have non-NM neurologic disease. Others have no neurologic diagnosis when all is said and done.

Methods:
Retrospective analysis of 1001 consecutive patients seen by a single neurologist (BES). Patients were referred to the institutional NM Clinic over a 5-6 year period (2015-2020). Patients were divided into 3 cohorts based on final diagnosis. Cohort 1: NM diagnoses (n=680), age 60.5, M:F 1.7:1. Cohort 2: non-NM neurologic disorders (n=95), age 60, M:F 1.6:1. Cohort 3: non-neurologic conditions (n=257), age 50, F:M 1.8:1. Note: numbers do not summate to 1001 in that some subjects appear in both cohorts 1 and 2, having both NM disorders and additional non-NM diagnoses (n=1032).

Results:
In cohorts 1/2/3 the most common referring symptoms/indications were paresthesia/imbalance (62.8/69.5/15.2%), pain (52.1/34.7/44.4%) and weakness/fatigue (35.4/28.4/22.6%), while the major final diagnoses of non-focal peripheral neuropathy were polyneuropathy (50.6/28.4/0.0%), small fiber neuropathy (13.7/0.0/0.0%), sensory neuropathy (5.0/2.1/0.0%), polyradiculoneuropathy (7.9/0.0/0.0%) and multifocal motor neuropathy (0.3/0.0/0.0%).

Conclusions:
1) Some 52.6% of 1001 Neuromuscular clinic referrals were found to have a form of non-focal peripheral neuropathy. 2) Some 68.0% of referrals were diagnosed with neuromuscular diagnoses. 3) Some 9.5% ended up with non-neuromuscular neurologic diagnoses. 4) Some 29.1% of the referrals were thought to have somatic symptom disorder (this condition was present in all three cohorts).

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: None
Keywords: peripheral neuropathy, neuromuscular disorders, case Series, epidemiology, clinical practice
The use of blood biomarkers to predict chemotherapy-induced peripheral neuropathy

Poster No:
102b

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Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) is a common and sometimes disabling complication of neurotoxic chemotherapy, occurring in approximately 30-40%. Currently, the presence of CIPN is usually determined by the onset of neuropathic symptoms, by which time an irreversible neuropathy may already have developed, and thus there is a need for better methods to predict the onset of CIPN. We aimed to determine whether blood levels of neurofilament light chain (NFL) and two novel peripheral nerve biomarkers could predict the onset and severity of CIPN.

Methods:
We prospectively recruited adult patients prescribed at least four cycles of chemotherapy containing oxaliplatin, cisplatin, docetaxel or paclitaxel. Patients were clinically assessed at baseline and prior to each cycle, for the duration of their chemotherapy course. Clinical outcomes included the Total Neuropathy Score Clinical Version (TNSc), National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) for motor and sensory peripheral neuropathy, and CIPN-Rasch-built Overall Disability Scale (CIPN-RODS). We used latent class analysis to determine whether patients with a high risk of neuropathy could be distinguished from those at lower risk. Blood was taken at baseline and prior to each cycle of chemotherapy, and will be tested for NFL and two novel peripheral nerve biomarkers, the levels of which will be compared to the clinical measures of neuropathy.

Results:
Forty-three patients completed the study, the majority of whom (81.4%) received oxaliplatin. Four patients (9.3%) developed NCI-CTCAE grade 2 sensory neuropathy, with the remainder being grade 0 or 1. We present the results of the biomarker analysis, and the comparison with the clinical outcomes.

Conclusions:
There is potential for blood biomarkers to be used to predict and monitor CIPN, which in the future may help clinicians mitigate the risk of neuropathy from neurotoxic chemotherapy.

References:
No

References 1:

References 2:

References 3:
**References 4:**

**Grant Support:** DS is supported by a grant from the New Zealand Neurological Foundation.

**Keywords:** chemotherapy-induced peripheral neuropathy, axonal damage, biomarkers, neurofilament light chain, toxic neuropathy
Immunoglobulin use for neuromuscular conditions: updated provincial guidelines for British Columbia, Canada

Poster No:
103b

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Introduction:
Immune-mediated neuromuscular disorders (NMDs) often require treatment with Intravenous Immunoglobulins (IVIg). In British Columbia (BC), Canada, IVIg use has increased by 48% in the last 5 years; last year, expenditure exceeded $57 million, 37% for neurological disease. IVIg is increasingly used for atypical indications where strong evidence of efficacy is lacking. With increased use and risk of IVIg shortages due to the pandemic, updated guidelines for IVIg use in NMDs are needed to optimize patient care and ensure appropriate resource utilization.

Methods:
Data for the last five years of IVIg requests in BC were reviewed to determine the frequency of IVIg requests for each condition. A focused literature review was conducted to examine available evidence for the use of IVIg in each condition. Guidelines from other jurisdictions were also reviewed. Based on the review, NMDs were categorized as approved, conditionally approved, approved only in exceptional circumstances, or not indicated.

Results:
Over 90% of IVIg use in NMDs across BC was for approved indications (CIDP, MMN, GBS, MG) where there is strong evidence for efficacy. IVIg may be beneficial as monotherapy in conditionally approved conditions such as sensory ganglionopathy, autoimmune autonomic neuropathy, and complex regional pain syndrome and as adjunctive therapy in others such as PNS vasculitis and immune-mediated necrotizing myopathy. Objective improvement must be established to continue treatment beyond the first 3 months.

Conclusions:
The majority of IVIg in BC is used for neuromuscular conditions with strong evidence of benefit. For conditions classified as conditionally approved or approved only in exceptional circumstances, improvements must be identified using objective outcome measures to continue IVIg treatment after the initial trial period. More quality evidence is needed on the effectiveness of IVIg for many NMDs. The updated BC guidelines proposed in this review emphasize using established diagnostic criteria, objective outcome measures, and minimum effective IVIg doses for NMDs.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: IVIg, Guidelines, Inflammatory Neuromuscular Disorders, Objective Outcome Measures
A Distinctive Pattern of Pathological Findings in Amyloid-like IgM Deposition Neuropathy

Poster No:
104b

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Institutions:
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Introduction:
Amyloid-like IgM deposition neuropathy is a rare complication of IgM monoclonal gammopathy largely described in Waldenström's macroglobulinemia. This IgM non-congophilic material has been found in the endoneurium mainly in the perivascular areas and are found as amorphous deposits but has never previously been described in this periaxonal deposits.

Methods:
To demonstrate a case of amyloid-like deposition neuropathy with distinct encapsulated deposits around nerve axons.

Results:
A 69-year-old man with a more than 30-year history of slowly progressive asymmetric sensory neuropathy in his feet, developed new onset progressive foot pain, asymmetric leg weakness, weight loss and autonomic symptoms. Electrodiagnostic studies showed distal demyelination, lumbar magnetic resonance imaging (MRI) showed cauda equina thickening and enhancement and autonomic reflex screen showed cardiovascular adrenergic impairment. Hematologic work-up revealed IgM monoclonal gammopathy without hematology malignancy. A nerve biopsy revealed amorphous material surrounding individual nerve fibers on semithin epoxy sections and electron microscopy involving most fibers but in a somewhat multifocal pattern (Some fascicles were more involved than others). This material was identified by mass spectrometry to be IgM kappa protein.

Conclusions:
Amyloid-like IgM protein can form around individual axons and nerve fibers and not in discrete deposits demonstrating a unique pathologic presentation of IgM deposition neuropathy as seen in our patient. These microdeposits surrounding individual fibers are hard to recognize and, in our case, required electron microscopy and mass spectrometry to diagnose.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: IgM, amyloid-like, deposition neuropathy
**Long-term effects of AAV9-microRNA-mediated gene silencing in a CMT1A mouse model**

**Poster No:**
105b

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**Institutions:**
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**Introduction:**
Charcot-Marie-Tooth type 1A (CMT1A) is the commonest inherited demyelinating peripheral neuropathy, caused by duplication of peripheral myelin protein 22 (PMP22) gene. This gene dosage effect destabilizes the myelin sheath structure leading to demyelination and ultimately to secondary axonal loss and disability. We have developed and validated an AAV9-miR-driven gene silencing approach, which targets PMP22 and improves myelination in a CMT1A mouse model after intrathecal injection.

**Methods:**
Our goal is to examine the long-term effects of our CMT1A gene therapy approach. Hence, we analyzed AAV9-miR-treated CMT1A mice by vector genome copy number (VGCN), RT-qPCR, western blot, and plasma neurofilament light (NFL, axonal degeneration marker) levels at 4 months post-injection. In addition, we examined systemic and PNS inflammatory reactions 6 weeks and 4 months after vector injection by immunohistochemistry.

**Results:**
VGCN analysis showed sufficient transduction of PNS and non-PNS tissues at 4-months after lumbar intrathecal vector injection. At the mRNA level, AAV9-miR silenced PMP22 and increased the levels of other myelin-related genes. At the protein level, our treatment reduced PMP22 levels, while MPZ protein levels were increased in roots and femoral nerves. The elevated plasma NFL and PNS inflammatory cells levels of CMT1A mice were improved after AAV9-miR treatment. A transient immune reaction observed in the liver at 6 weeks post-injection subsided by 4 months.

**Conclusions:**
Taken together, AAV9-miR-driven silencing of PMP22 achieves long-term transduction of PNS and non-PNS cells. It also provides stable silencing of PMP22 mRNA and protein levels accompanied by increased levels of other myelin related genes/proteins. In addition, treatment ameliorated NFL levels and inflammatory status in the CMT1A model without causing toxicity. Thus, intrathecally delivered AAV9-miR represents a clinically translatable and relevant approach to treat CMT1A.

**References:**
No

**References 1:**

**References 2:**
References 3:

References 4:

Grant Support: CMT Research Foundation, The UK Dementia Research Institute; Wellcome Trust

Keywords: Gene Therapy, Charcot Marie Tooth, AAV, microRNA, Biomarkers
The State of the INC: A Comprehensive Update of the Inherited Neuropathy Consortium of the Rare Diseases Clinical Research Network

Poster No:
106b

Authors:
Sydney Stork, Shawna Feely, Nidia Villalpando, Michael Shy, members of the Inherited Neuropathy Consortium

Institutions:
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Introduction:
The Inherited Neuropathy Consortium (INC) is composed of 20 sites that evaluate patients with Charcot-Marie-Tooth disease (CMT) and maintain data pulled from clinical visits in a standardized manner.

Methods:
Clinical information from patient visits is electronically maintained in a database housed under control of a centralized data management center. All sites are actively seeing patients, and DNA samples from INC sites are tested for identification of potential new forms of CMT and genetic modifiers of CMT1A. Current projects include: Natural History Evaluation of Charcot-Marie-Tooth disease (with particular emphasis on CMT1B, CMT2A, CMT4A, and CMT4C); Genetics of CMT; Development of CMT Peds Scale for Children with CMT; Charcot-Marie-Tooth Disease Infant Scale (CMTInfS); and Digital Measures of Physical Activity, Gait and Balance in CMT.

Results:
These projects have helped create validated outcome measures to use in clinical trials. Additionally, over the past 10 years, the INC has identified over half of all genes currently known to cause CMT. The INC has evaluated 6,728 patients for the Natural History Evaluation of CMT; 2,714 of these patients also participate in the Genetics of CMT, 1,031 participate in the Pediatric study, 63 participate in the Infant study, and 157 participate in the Digital Measures study. All these studies are actively recruiting. The INC also partners with patient advocacy groups (PAGs) to enhance patient knowledge and establish connections between patients, researchers, and physicians. These groups include the Muscular Dystrophy Association, the Charcot Marie Tooth Association, CMTUK, ACMT-Rete, Hereditary Neuropathy Foundation, CMT Research Foundation, CMTA Australia, and Telethon from Italy.

Conclusions:
Through development of validated outcome measures, curation of an extensive longitudinal CMT database, and investigation into new genetic factors of CMT, the INC has contributed to the current understanding of the causes and outlook of CMT for medical and patient communities alike.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support: The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01)

Keywords: Charcot-Marie-Tooth, CMT, Neuropathy
Controlled Drug Release From Peptide Based Bio-conduits Accelerate Recovery After Peripheral Nerve Injury And Repair

Poster No: 107b

Authors: An-Jey Su¹, Ning Jiang², Bing Li¹, Yong Wang¹, W Ryan Williamson¹, Charles Owens¹, Nicholas Busquet¹, Neil Khatter³, Alkesh Jani¹, Christene Huang¹, Wei-Fang Su², Kia Washington¹

Institutions: ¹University of Colorado Anschutz Medical Campus, Aurora, CO, ²National Taiwan University, Department of Materials Science and Engineering, Taipei, Taiwan, ³Oakland University William Beaumont School of Medicine, Auburn Hills, MI

Introduction: Clinical use of Polycaprolactone (PCL) elastomers to treat peripheral nerve injury is limited by its drug release properties. Polybenzyl glutamate (PBG) is a peptide-based polyelectrolyte that we functionalized with the neuroprotective antibiotic Minocycline hydrochloride (MH). PBG and PBG-MH were evaluated as nerve-wraps in a sciatic nerve injury (SNI) model.

Methods: Release of MH loaded 4% (w/v) from PCL-MH and PBG-MH was assessed over 168h by UV-Vis spectrophotometry. PBG or PBG-MH versus naïve (contralateral leg), sham-surgery, or transect/no-repair animals were examined in a rat SNI model (12-16 week-old male LEW rats, n=3/group). After sciatic nerve transection, 21mm² wraps were sutured in place, between stumps, leaving a 10mm gap. Recovery was compared by measuring sciatic function index (SFI) at 2-week intervals over 12-weeks, electromyography (EMG) at 4 and 12-weeks and gastrocnemius weight at 12-weeks.

Results: MH release from PCL exceeded 80% of total within 24h, while PBG released 42.55% after 168h. At 4-weeks, EMG peak-to-trough for sham animals measured ~60mV, while no-repair, PBG and PBG-MH measured ~11mV, ~11mV and ~13mV. At 12-weeks, sham and no-repair EMG peak-to-trough remained unchanged, but PBG and PBG-MH EMG increased >50% (median=16mV, 19mV; P=0.0063, 0.0131). Final gastrocnemius weights of naïve and sham groups were equivalent (2.62±0.12g, 2.80±0.22g; P>0.01), while no-repair, PBG and PBG-MH measured 0.75±0.25g, 0.77±0.14g, 1.04±0.38g). Pre-surgery, SFI ranged from (-0.25±3.96 to -13.26±10.61). Over 12-weeks, sham SFI was ~10.6±7.72 at each time point; at 2-weeks, no-repair, PBG and PBG-MH was -77.33±3.16, -79.25±5.68, and -72.75±2.85 respectively. At 10-weeks, SFI of PBG-MH, PBG and no-repair was -71.4±5.15, -73.52±3.16, and -84.13±5.49 respectively.

Conclusions: We demonstrated better sustained release of MH from PBG versus PCL. PBG and PBG-MH could repair 10mm nerve gaps with PBG-MH outperforming PBG in accelerated functional recovery as measured by SFI. EMG and final muscle weight showed improved neuro-regeneration in both wrap groups over 12-weeks recovery.

References: No

References 1:
References 2:

References 3:

References 4:

Grant Support: University of Colorado Department of Surgery AEF Seed Grant #63503960

Keywords: Tissue engineering, Sciatic nerve, Nerve wrap
Probing the Mechanism of FUS-ALS/FTD pathogenesis

Poster No:
108b

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Institutions:
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Introduction:
'Fused in Sarcoma' (FUS) is an RNA and DNA-binding protein that shuttles continuously between the nucleus and cytoplasm for mRNA export and stress granule formation. Pathological mutations in FUS have recently been identified as genetic causes for frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). Mutations causing FUS-FTD/ALS frequently occur in the N-terminal prion-like domain and the C-terminal nuclear localization signal (NLS). However, the mechanism regarding how FUS mutations cause FUS-FTD/ALS remains widely debated. I hypothesize that aberrant translocation of mutant FUS and its subsequent retention in RNA granules is the underlying mechanism for FUS-induced disease. Interestingly, mutations leading to FUS-FTD/ALS are dominant, while FUS is also haplosufficient. This raises the question about the molecular mechanism that allows the pathogenic FUS protein to cause FUS-ALS/FTD in the presence of the normal FUS protein. I hypothesize 3 potential mechanisms: 1) loss of nuclear function of wildtype FUS due to trapping by mutant FUS in stress granules, 2) gain of toxic function by mutant FUS sequestering other RNA-binding mutant FUS through sequestering other RNA-binding proteins (RBPs) or mRNA in the stress granules, or 3) gain of toxic function by mutant FUS interfering with normal stress granule function.

Methods:
I am dissecting the FUS-ALS/FTD mechanism by determining the cellular localization of normal and mutant FUS protein by high-resolution fluorescence microscopy and mRNA-FUS binding events by eCLIP in the heterozygous dual-tagged iPSC-derived motor neurons.

Results:
We have generated an isogenic series of human iPSC lines with disease relevant FUS mutations engineered into the KOLF background and refined a rapid and scalable method to produce human motor neurons by doxycycline-inducible expression of 3 human transcription factors (NGN2, ISL1, and LHX3, or 'hNIL').

Conclusions:
The development of these robust assays could serve as phenotypic assays for imaging-based pool screening, using the localization of FUS proteins and mRNA spatial distribution as the outcome measures.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: iPSC, motor neuron diseases, ALS, FUS
Plasma and Skin Biomarkers for Charcot-Marie Tooth Disease

Poster No: 109b

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Introduction: While several candidate biomarkers that have been developed for CMT1A, it is important to establish if similar biomarkers apply to other common forms of Charcot Marie Tooth (CMT) disease, including CMT1B, CMT1X, and CMT2A. Since recent studies showed elevated levels of microRNA's in plasma from CMT1A, the goal of this study was to determine if microRNA's (miR) are elevated in other major forms of CMT, and to determine if Schwann cell-derived transcripts in skin can serve as biomarkers of other types of CMT.

Methods: We have collected plasma and skin samples from individuals with genetically confirmed cases of CMT1B, CMT1X, and CMT2A, and are evaluating plasma samples using microRNA profiling. We also have screened for Schwann cell-enriched transcripts using Nanostring analysis of skin biopsies with a custom gene CodeSet based on bioinformatic analysis of peripheral nerve data sets from CMT1B and CMT1Xs. Biomarker levels are correlated with other patient data to test if biomarkers levels correlate with disease severity.

Results: Screening plasma miRNA revealed that muscle-derived microRNA's (myomiRs) are elevated in CMT1B, 1X, and 2A compared to controls. While the myomiRs likely reflect the progressive muscular atrophy in CMT1A, some of the elevated miRs may reflect Schwann cell processes that underlie the pathogenesis of the disease. In addition, we have further developed a Nanostring transcript detection assay to apply to CMT1B, CMT1X, and CMT2A, and several candidate biomarkers have emerged from pilot studies of these forms of CMT.

Conclusions: Biomarkers for CMT may be subtype-specific based on the unique pathogenesis of each CMT subtype, but others may reflect common processes involved in CMT progression, and our data sets allow comparative analysis across major CMT subtypes. The elevation of muscle-derived myomiR's likely reflects ongoing muscular atrophy in individuals with CMT, and it is possible that this could provide a complementary biomarker in clinical trial design for CMT.

References: No
References 1:

References 2:

References 3:

References 4:

Grant Support: NIH R21TR003034 and Charcot-Marie-Tooth Association

Keywords: Biomarker, Schwann, microRNA, CMT, neuropathy
Sulforaphane enhances proliferation and maintenance of repair Schwann cells after peripheral nerve injury via Nrf2/HO-1 signaling

Poster No:
110b

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Introduction:
Nuclear erythroid 2-related factor 2 (Nrf2) is commonly activated in response to cellular stresses such as oxidative damage and drives expression of various factors involved in cytoprotection and dampening of inflammatory processes. The activation of the Nrf2/HO-1 signaling pathway has been associated with markedly accelerated peripheral nerve regeneration by clinical, electrophysiological as well as histological measures. However, the exact mechanisms underlying these improvements have not been elucidated so far.

Methods:
To better understand the role of Nrf2 following peripheral nerve injury, we aimed to study the consequences of treatment with the Nrf2 activator sulforaphane (SFN), a naturally occurring isothiocyanate from cruciferous plants, in the murine sciatic nerve crush model. SFN was administered daily via intraperitoneal injection at a dose of 10 mg/kg, starting immediately after sciatic nerve crush injury was introduced. Animals were sacrificed and sciatic nerves were excised at 7, 14 and 21 days post-crush (dpc) for molecular, immunohistochemical and morphometric analyses. Moreover, at the respective time points clinical testing by grip strength analysis was performed.

Results:
From the end of Wallerian degeneration at 7 dpc, we noted a marked upregulation of the Nrf2/HO-1 signaling pathway under treatment with SFN, which was maintained throughout the entire regeneration phase until 21 dpc. This effect was accompanied by a significant increase in the number of repair Schwann cells as identified by positivity for Sox-2, c-Jun and p75-NTR. In these cells, we also observed elevated proliferation rates identified by Ki67 staining. Concomitantly, apoptotic/autophagic pathways were modulated. These observed changes correlated with a significant clinical improvement in the grip strength test performance as well as ameliorated histopathological measures at 21 dpc.

Conclusions:
Collectively, SFN treatment was associated with an upregulation of cytoprotective pathways, leading to increased numbers of repair Schwann cells that presumably contribute to a permissive environment for successful nerve regeneration.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: Schwann cell, Nerve regeneration, Sulforaphane
Normal Aging of the Peripheral Nervous System in the General Population: Clinical and Electrophysiological Characteristics

Poster No:
111b

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Introduction:
Neurological deficits are commonly seen in elderly persons and the prevalence of chronic axonal polyneuropathy increases with age. Several heterogenic studies or studies with small sample sizes showed that functions of the peripheral nervous system decline with age. However, information is lacking whether this should be considered pathological or is part of normal aging.

Methods:
Between June 2013 and January 2020, 4179 participants of the population-based Rotterdam Study were screened for chronic axonal polyneuropathy using a symptom questionnaire, neurological examination of the legs and nerve conduction studies. Based on the level of abnormalities in the screening and after careful discussions, participants were categorized as having no, possible, probable or definite axonal polyneuropathy.

Results:
In total, 3782 (90.5%) participants with no or possible polyneuropathy were included (mean age 63.3 years [range 41-96], 55.3% female). Abnormal neurological examination was markedly more prevalent in higher aged persons, especially absent ankle jerks, lowered vibration sense at the hallux and lowered sural sensory nerve action potential (SNAP) amplitude. Ankle jerks were absent in 6.1% of the participants aged 40-50 years up to 33.6% in participants aged >80 years. Mean vibration sense (Rydel Seiffer tuning fork) decreased from 6.6/8.0 (SD1.5) in the youngest group to 3.6/8.0 (SD3.1) in the oldest group. Median sural SNAP amplitude decreased from 12μV (IQR 9-17) to 5μV (IQR 0-7) in these age groups. Effect of age on the presence of knee jerks and pinprick abnormalities was relatively low. In persons aged >80 years, knee jerks were often present (90.8%) and pinprick test was normal in 89.6% of the participants.

Conclusions:
Normal aging of the peripheral nervous system may result in absent ankle jerks, lower vibration sense at the hallux and lower sural SNAP amplitudes. Some characteristics of polyneuropathy may yet be present in persons without this disease and likely correspond to normal aging of the peripheral nervous system.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support: Prinses Beatrix Spierfonds (W.OR17-10)

Keywords: peripheral nervous system, polyneuropathy, aging, normal aging, neurological examination
Prevalence and Risk Factor Profiles for Chronic Axonal Polyneuropathy in the General Population

Poster No:
112b

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Introduction:
Chronic axonal polyneuropathy is a disease that impacts quality of life and leads to difficulties with various activities in daily life. Yet, persons with polyneuropathy may not always seek medical care and thus the societal burden of polyneuropathy is likely underreported. Given the aging populations worldwide there is need for contemporary data on the prevalence as well as risk factor-profiles of polyneuropathy in the general population.

Methods:
Between June 2013 and January 2020, participants of the population-based Rotterdam Study underwent extensive in-person examination to diagnose polyneuropathy. Age-standardized prevalence's were calculated for populations aged ≥40 years of the Netherlands, Europe, United States and the world population. Prevalence of risk factors and co-occurrence was assessed using laboratory findings, interviews, questionnaire data and a review of medical records.

Results:
In total, 4078 participants were included (mean age 64.3 years, 55.2% females). Chronic axonal polyneuropathy was diagnosed in 164 participants of whom 48.8% had not yet received the diagnosis through regular care. Age-standardized prevalence's were 3.3% (95%CI 2.8-3.9) for the European, 2.9% (95%CI 2.5-3.5) for the U.S. and 2.3% (95%CI 1.9-2.8) for the world population. Prevalence increased with age and are overall expected to increase with a minimum of 1% in the next 20 years. The majority of polyneuropathy cases was idiopathic (37.8%). Cases with known risk factors had most frequently diabetes (31.7%) and vitamin deficiencies (14.6%). Of the polyneuropathy cases with risk factors (N=102), 30.4% had multiple known and potentially modifying risk factors, highlighting the need to determine a full risk factor-profile.

Conclusions:
Prevalence of chronic axonal polyneuropathy will increase as populations are aging and prevalence of risk factors is expected to rise. As a large proportion of polyneuropathy cases had multiple risk factors, possible cumulative effects should be taken into account. A full diagnostic work-up is important, even when one risk factor for polyneuropathy is yet known.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support: Prinses Beatrix Spierfonds (W.OR17-10)

Keywords: polyneuropathy, neuropathy, diabetes, risk factors, prevalence
Conversion to full-blown CANVAS is frequent among RFC1-neuropathy cases in a cohort-sequential study

Poster No: 113b

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Introduction: Cerebellar Ataxia with Neuropathy and Vestibular Areflexia Syndrome (CANVAS), a rare multisystem neurological disease often characterized by sensory disturbances years at onset, has recently been associated to a biallelic Replication Factor C subunit 1 AAGGG intronic repeat expansion mutation (RFC1exp). Penetrance of the full phenotype and predictors of clinical progression are currently unknown. We investigated RFC1exp in a Chronic Idiopathic Axonal Polyneuropathy (CIAP) population to assess its prevalence, characteristics and long-term disease progression.

Methods: Pathology records of neuropathy cases referred to our Center for a sural nerve biopsy procedure from 2007 to 2020 were screened to only include patients with a final diagnosis of CIAP. We identified 292 CIAP cases and included 286 subjects with an available DNA sample. We reported clinical features at the time of biopsy (T1) and pathology results in RFC1exp and non-mutated cases. RFC1exp patients were longitudinally reevaluated (T2) to assess disease progression.

Results: RFC1exp cases were common among patients with pure sensory (31/58, 53%) and predominantly sensory neuropathies (13/73, 18%) compared to sensorimotor cases (3/155, 2%) and characterized by frank signs of sensory ataxia often associated to mild autonomic disturbances. Apart from the distinct retention of deep tendon reflexes, other peculiar CANVAS features at T1 were exceptional. Pathology revealed a severe and diffuse involvement of all nerve fibers and scant regenerative changes. Clinical progression was evident at T2 (median disease duration 13 years IQR 9-16), with most patients now exhibiting at least mild features of cerebellar (19/23, 83%) and vestibular involvement (16/22, 73%). Chronic cough was universally reported. Intriguingly, age at visit was a stronger predictor of overall functional impairment than disease duration.

Conclusions: Emergence of the full-blown CANVAS phenotype is a frequent but late event in RFC1exp patients presenting with an isolate sensory neuropathy. Aging but not age at onset is a major determinant of disease progression.

References: No

References 1: 
Keywords: CANVAS, RFC1, Chronic Idiopathic Axonal Polyneuropathy
Information and communication technology devices and applications for chemotherapy-induced peripheral neurotoxicity: a systematic review

Poster No:
114b

Authors:
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Introduction:
Chemotherapy-induced peripheral neurotoxicity (CIPN) is the most common non-hematological toxicity of several widely used anticancer agents. CIPN diagnosis is largely based on the patient's subjective reporting of signs and symptoms rather than objective measures, potentially causing delays in CIPN detection. Severe treatment-emergent grade 3 CIPN is more likely to be irreversible, diminishing patient's long-term quality of life. Wearable devices, smart objects and applications may provide early detection and monitoring of CIPN through objective measures of nerve damage or physical function. We systematically review data on wearables, sensors, and related devices to detect and/or monitor signs and symptoms of peripheral neurotoxicity in cancer patients at risk of or those with CIPN. Moreover, we provide directions and recommendations for future studies on wearable devices and smart solutions for CIPN detection and/or monitoring.

Methods:
A literature search using PubMed/MEDLINE, Web of Science, IEEE Xplore and CINHAL databases was conducted from database inception until March, 2021.

Results:
After duplicates removal, 1317 records were title and abstract screened, 24 full texts were assessed, and 9 were included. Five studies focused on wearables, sensors, and devices to detect or monitor CIPN, three studies examined devices already validated for the detection of other peripheral neuropathies, and one study used wearable devices for other purposes (CIPN rehabilitation). The retrieved papers were highly heterogeneous in terms of study design, sample size, CIPN severity, chemotherapy agents, type of wearable/sensor/device applied, parameters of interest and purpose, thus a meta-analysis was not possible.

Conclusions:
Despite the limited number and heterogeneity of retrieved studies, data are promising and provide preliminary evidence on the potential application of wearables, sensors, and applications for CIPN detection and monitoring. There are still several issues and knowledge gaps that should be addressed to improve their implementation in clinical contexts.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

**Keywords:** Toxic neuropathy, Evidence based medicine, Chemotherapy-induced peripheral neurotoxicity (CIPN), Information and communication technology (ICT); Telemedicine
Interactions Between Human Peripheral Sensory Neurons And Immune Cells

Poster No:
115b

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Introduction:
Immune cells such as macrophages and T-cells play an important role in the maintenance of tissue homeostasis and response to external cues. They can also contribute to inflammatory dysregulation and sensory disturbances. The main goal of our study is to understand how immune cells influence sensory neurons and contribute to peripheral neuropathies.

Methods:
We used spatial transcriptomics and single-cell datasets to map the interactions between peripheral sensory neurons and immune cells. We obtained human dorsal root ganglia (DRG) from organ donors. We used the publicly available human skin dataset (https://tabula-sapiens-portal.ds.czbiohub.org/) that contains data for several immune cells including naïve and memory B cells, mast cells, macrophages, T-cells and Langerhans cells.

Results:
Our results demonstrate that immune cells present in skin express several ligands that can interact with human sensory neurons. We detected several macrophage ligands that can interact with TRPV1, which is expressed in nociceptive fibers. Among those ligands are KNG1, FAAH and CALM1 which have known roles in peripheral pain. In addition, we also looked at the presence of non-neuronal cells in human DRG tissue using our spatial transcriptomics dataset. Immune cells such as T-cells and macrophages were detected throughout the DRG, including near neurons. We observed that CD14+ barcodes (macrophage marker) are in closer proximity to neuronal barcodes compared to CD4+ barcodes (a marker of T-cells). We have also generated bulk-RNA sequencing and spatial transcriptomics data from tibial and sural nerve samples obtained from diabetic patients having lower leg amputations. Our preliminary analysis suggests the presence of several immune cell markers in peripheral nerve tissue. IL-6, which is a pro-inflammatory cytokine linked to type 2 diabetes is detected and it's particularly high in specific sural samples.

Conclusions:
We anticipate that our data will advance our understanding of human peripheral neuropathies and facilitate the translation of basic pain neuroscience research.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

**Keywords:** interactions, sensory neurons, immune, axon, diabetic neuropathy
Acute Stress as a Modulator of Sensory Perception: Changes in Itch, Pain and Quantitative Sensory Test

Poster No:
116b

Authors:
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Introduction:
Evidence shows that symptomatology of atopic dermatitis (AD), such as chronic itch and pain, can be exacerbated by stress (a state of sensing actual or potential threats in the environment). However, the influence of acute stress on small fibers is not clear. We aim to determine the effect of acute stress on the somatosensory profile in patients with AD.

Methods:
We are performing a clinical study in adult patients with AD and healthy controls (HC). Each subject attended the study to evaluate their somatosensory profile by the Quantitative Sensory Test (QST) before and after an acute stress stimulus induced by the Montreal Imaging Stress Task (MIST) under heart rate monitoring.

Results:
Up to date, mean age was 29 ± 6.5 years in HC group (n=15, 53.3% females) and 28.1 ± 6.5 years in AD (n=10; 70% females). Our results showed an increase in the cardiovascular response after the MIST in HC and AD subjects (HC p-value<0.0001, AD p-value<0.01). Interestingly, we observed a significant reduction in the cold detection threshold of the QST after the stress session in both groups (HC p-value<0.01, AD p-value<0.05). Moreover, after the MIST, the warm detection threshold (HC p-value<0.05, AD p-value=0.0977) and mechanical detection threshold (HC p-value<0.05, AD p-value=0.7695) were reduced only in HC. Finally, the stress task did not modify the pain threshold in any of the evaluated parameters, neither for HC nor AD groups. Results of psychological questionnaires, IENFD, cortisol levels and skin proteomics are expected for 2022.

Conclusions:
These preliminary results showed a differential reduction in sensitivity for detecting stimuli after acute stress between HC and AD subjects, suggesting a lack of adaptation, altered stress response or differential functioning of small fibers in AD. The in-depth study of our future data shall provide crucial information to understand the neurobiological basis of how stress may modulate the somatosensory system.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support: Project supported by Millennium Nucleus for the Study of Pain (MiNuSPain) and PhD CONICYT scholarship N° 21190570.

Keywords: Itch, Pain, Stress, Small fibers, Atopic dermatitis
Mood Disorders Impact On Social Abilities And Satisfaction In Neuropathic Pain Patients

Poster No:
117b

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Institutions:
1IRRCS Fondazione Carlo Besta Neurological Institute, MILAN, Italy, 2Rare Neurodegenerative and Neurometabolic Diseases Unit, Department of Clinical Neurosciences, Fonda, MILAN, Italy, 3IRCCS Foundation “C. Besta” Neurological Institute, MILAN, Italy, 4UO Neurologia, Istituto Neurologica Carlo Besta, MILAN, Italy

Introduction:
The psychological and cognitive functioning of patients affected by chronic neuropathic pain has been poorly investigated. Indeed, most of the studies focused on mood and quality of life, albeit chronic pain has a profound impact also on social functioning (e.g. work, leisure activities, relationships and others). Moreover, the domain of Social Cognition (SC), a multidimensional construct that refers to people's ability to understand others' mind and feelings, that is crucial to correctly interpret social stimuli, has never been explored in these patients.

Methods:
With the aim to investigate different psychological domains in chronic neuropathic pain, we assessed social cognition, social satisfaction, personality traits, mood, and coping strategies of 36 patients (16 females; mean age 51yrs ±10) whose pain was caused by various conditions. We used Spearman correlation to evaluate possible associations between variables. Only correlations with p <0.005 were considered.

Results:
Descriptive statistics showed that SC tests were abnormal in 28% of patients, mainly in recognition and attribution of emotions, while 13% of patients were unsatisfied with their interpersonal relationships. The analysis of the psychological features demonstrated that 42% of patients suffered from anxiety and 33% were depressed. Moreover, 39% of patients used at least one maladaptive coping strategy (i.e., praying or catastrophizing). The most frequent personality traits were obsessive-compulsive (39%), histrionic (31%), and schizoid (28%), followed by psychopathological traits of anxiety (42%) and dysthymia (25%). Correlation analyses suggested that affective mood can influence social cognition and psychological health: the higher mood disorders, the lower SC performance (p<0.005). The presence of anxiety trait significantly increased the use of catastrophism coping style (p<0.001) and reduced the satisfaction in social relationships (p=0.005).

Conclusions:
Our findings suggest that at least one third of patients suffering from neuropathic pain have social and psychological difficulties. Mood balance can likely be crucial to disclosure their social and psychological functioning.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: Neuropathic pain, chronic pain, social cognition, psychological health
**Social Engagement Is Associated With Better Psychological Functioning In Small Fiber Neuropathy Patients: Preliminary findings**

**Poster No:**
118b

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**Institutions:**
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**Introduction:**
The psychological profile of small fiber neuropathy (SNF) patients has been poorly investigated. Few studies demonstrated mood disorders and fatigue, and reduced quality of life. Recently, Cognitive Reserve (CR) has been considered a protective factor for mental health disorders, shifting the focus toward factors possibly reducing the impact of chronic pain. CR is built through long-term life experiences, such as education, occupational attainment, leisure activities to help your brain better coping any failures it faces. To our knowledge, few studies investigated the relation between cognitive reserve and psychological profiles in chronic pain. In this study we aimed at exploring how CR impacts on psychological functioning of SFN patients.

**Methods:**
CR was measured in 10 SFN patients (6 females; mean age 52 yrs ±11.6) with a questionnaire assessing three different CR proxies: Education, Occupation and Midlife Leisure Activities. Patient personality traits, psychopathological profiles, and coping strategies were also assessed. We used Spearman correlation analysis with 95% interval (BCa) bootstrapping correction, considering only correlations with p <0.001 and BCa not crossing '0'.

**Results:**
Our results show that Schizoid personality trait (Rho=-.872; p=.001), Anxiety (Rho=-.771, p<.009) and Abnormal Thinking (Rho=-.908, p<.001) traits were severer in those patients with reduced social-leisurely involvement. Only the Midlife Leisure Activity Index is associated with coping strategies: higher catastrophism coping style (Rho=−.851, p<.002), characterized by Rumination (Rho=−.844, p<.002), Magnification (Rho=−.766, p=.010) and Helplessness (Rho=−.817, p<.004) states of mind, lower the involvement in leisure activities.

**Conclusions:**
These preliminary results suggest that social engagement, as a proxy of CR, might preserve to pain chronification, encouraging the cultivation of leisure activities for better healthcare.

**References:**
No

**References 1:**

**References 2:**

**References 3:**
References 4:

Grant Support:

Keywords: small fiber neuropathy, social reserve, psychological profiles, psychological health
Acute Relapsing Ataxic Sensory Neuronopathy with anti-FGFR3 Autoantibodies Mimicking Acute Myelopathy

Poster No:
119b

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Introduction:
Antifibroblast growth factor receptor 3 (anti-FGFR3) antibodies are recently described autoantibodies associated with sensory neuropathies, particularly sensory neuronopathies (SNN) (1,2), with a classical progressive course (1,2).

Methods:
We report herein the atypical case of a 39-year-old woman who has been hospitalized in the authors' department.

Results:
This patient, with a previous history of untreated discoid lupus erythematosus presented to our department for a 15-day history of distal paresthesia and hypoesthesia with rapid extension to the four limbs, trunk, and perineal area. Clinical examination found an ataxic gait with a four-limb ataxia. Spinal cord MRI was normal, cerebrospinal fluid analysis found an elevated protein level and electroneuromyography (ENMG) found diminished sensory nerve action potential (SNAP) amplitudes in the four limbs while motor nerves were normal. A variant of Guillain-Barré syndrome (GBS), named Acute Sensory Ataxic Neuropathy (ASAN), was considered and an intravenous immunoglobulin treatment was initiated and led to a steady clinical improvement. Eighteen months after the first episode, a relapse occurred with the same clinical presentation. On ENMG, no SNAP amplitudes were elicitable. Brachial plexus MRI, and nerve ultrasonography were normal. The final diagnosis was SNN and anti-fibroblast growth factor receptor 3 (FGFR3) antibodies were detected. the patient was treated by 6 monthly cyclophosphamide infusions associated with intravenous corticosteroids leading to a progressive significant clinical improvement.

Conclusions:
This case was considered instructive for these reasons: i) The clinical presentation was suggestive of myelopathy with trunk and perineal hypoesthesia that are atypical for peripheral neuropathies ii) Onset was acute with a nadir attained within 2 weeks whereas most patients with anti-FGFR3 antibodies present a progressive onset (2) iii) The clinical course included relapses and objective improvement iv) The patient had a promising response to cyclophosphamide and intravenous corticosteroids justifying future clinical trials in patients with neuropathies linked to FGFR3 antibodies.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: anti-FGFR3 antibodies, sensory neuropathies
**Update on the International Guillain-Barré syndrome Outcome Study (IGOS)**

**Poster No:**
120b

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**Introduction:**
Guillain-Barré syndrome (GBS) is a rare, acute, immune-mediated polyradiculoneuropathy with a highly variable clinical course and outcome. To develop better treatments and improve long-term outcome, it is necessary to get a better understanding of the pathophysiology and predictors of the disease course. The International GBS Outcome Study (IGOS) is a prospective multicenter cohort study on GBS that aims to identify both clinical and biological predictors of disease course and outcome.

**Methods:**
Patients are recruited from 21 countries across 5 continents. All patients are included within two weeks from onset of weakness, irrespective of age, disease severity and treatment. Data are collected at eight standard time points during follow-up of (minimal) 1 year to 3 years, and include clinical symptoms and signs, nerve conduction studies (NCS), biomaterial (including serum and cerebrospinal fluid) and outcome assessment through various questionnaires.

**Results:**
IGOS included the first patient in April 2012 and reached the goal of 2000 inclusions in May of 2021. Of these patients, 148 (7%) were excluded because of alternative diagnoses (n=105, of whom 62 have CIDP), insufficient data (n=8) or protocol violations (n=35). The median age in the cohort is 52 years (IQR 34-65), with 60% males. Samples from entry or week 1 are available for 1448 patients. The first 1000 patients have been tested for five infections previously associated with GBS (Campylobacter jejuni, Mycoplasma pneumoniae, hepatitis E virus, Cytomegalovirus and Epstein-Barr virus) and for anti-ganglioside antibodies. Electrophysiological data are available for 1442 patients, of which 1161 are now classified according to the criteria of Hadden et al.

**Conclusions:**
IGOS is working on completing the follow-up for all 2000 patients and is not including new patients anymore. At the PNS meeting we expect to have completed the follow-up up to a year after inclusion for all 2000 patients.

**References:**
No

**References 1:**

**References 2:**
References 3:

References 4:

Grant Support:

Keywords: Guillain-Barré syndrome, GBS, IGOS
The effects of implementing the EAN/PNS Guideline (second revision) on diagnosis and treatment of chronic inflammatory demyelinating polyneuropathy

Poster No:
121b

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Introduction:
The diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) depends on clinical, electrodiagnostic, imaging and laboratory features. In 2021, the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guideline (second revision) was published, replacing the 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guideline. In the EAN/PNS 2021 guideline the diagnostic categories were reduced from three (definite, probable, and possible CIDP) to two (CIDP and possible CIDP). Definitions of CIDP variants were added. The electrodiagnostic criteria underwent changes; notably, rules for sensory abnormalities were added. The objective is to compare the diagnostic accuracy of the 2021 EAN/PNS and 2010 EFNS/PNS guidelines.

Methods:
Patients with the clinical diagnosis of CIDP treated at a tertiary referral center between 2009-2021 were included if: 1) they met the 2010 EFNS/PNS electrodiagnostic criteria for possible, probable or definite CIDP, based on extensive nerve conduction studies (NCS); 2) they did not meet the 2010 EFNS/PNS electrodiagnostic criteria, but CIDP was still the most likely diagnosis based on the clinical evaluation, treatment response and ≥1 other supportive criterion. The control group consisted of age-, sex- and height-matched patients, suspected of having an acquired demyelinating neuropathy, who had another final diagnosis. The final diagnosis was reviewed six months after NCS. The sensitivity and specificity of the 2021 EAN/PNS criteria were compared to the 2010 EFNS/PNS criteria using the reference standard as described above.

Results:
In total 142 patients diagnosed with CIDP were compared to 142 controls. Further results will be presented at the congress.

Conclusions:
The implementation of the 2021 CIDP EAN/PNS guideline may influence diagnosis of CIDP.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

**Keywords:** chronic inflammatory demyelinating polyneuropathy, CIDP, Elektrophysiology, EMG, Diagnosis
OPTIC Trial: Intravenous Immunoglobulin And Intravenous Methylprednisolone As Induction Treatment In CIDP – study update

Poster No:
122b

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Introduction:
The OPTIC trial (ISRCTN15893334) is an investigator-initiated randomized double-blind placebo-controlled trial designed to assess whether combined induction treatment with intravenous immunoglobulins (IVIg) and methylprednisolone (IVMP) leads to more remissions than IVIg treatment alone.

Methods:
Adults diagnosed with definite or probable CIDP according to the EFNS/PNS criteria are being included, comprising three categories: 1) Treatment naïve patients; 2) Relapse patients following a year or more of stable disease; 3) Patients having received a single loading dose of IVIg in the last three months with initial improvement and subsequent deterioration. Patients are randomized to receive IVIg + IVMP (1000 mg) or IVIg + placebo (sodium chloride 0.9%) every three weeks for 18 weeks. IVIg treatment consists of a 2 g/kg loading dose over 3-5 days and six maintenance courses of 1 g/kg over 1-2 days. Primary outcome is the number of patients in remission at 52 weeks. Remission is defined as sustained improvement between week 18-52 without need for further treatment. Improvement is assessed at week 18 and defined as an increase of at least the minimal clinically important difference (MCID) on the Inflammatory Rasch-Built Overall Disability Scale (I-RODS) and/or improvement of ≥ 1 point on the Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale compared to baseline. Follow-up is two years and includes long-term safety and clinical assessments, including an extended economic evaluation.

Results:
Patient enrollment started in February 2018. As of January 5th 2022, 60 patients (out of 96) are enrolled, of which 39 completed the treatment protocol and week 52 follow-up visit. Of these 39 patients, 20 patients (51%) were in remission 8 months after completing the (blinded) treatment protocol. Five centers in the Netherlands and four in the United Kingdom are currently enrolling new patients. Four Australian centers are expected to start including patients from summer 2022 onwards.

Conclusions:
Results are expected in 2024.
References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Prinses Beatrix Spierfonds (Dutch Charity), ZonMw (the Netherlands Organization for Health Research and Development)

Keywords: CIDP, Chronic inflammatory demyelinating polyradiculoneuropathy, Corticosteroids, Intravenous immunoglobulins, Randomised controlled trial
Distal hereditary motor neuropathy: A Brazilian cohort study

Poster No:
123b

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Introduction:
The distal hereditary motor neuropathy (dHMN) is a rare form of hereditary neuropathy presenting as a length-dependent motor / predominant motor neuropathy. Additional features as upper motor neuron signs (UMN), respiratory distress and vocal cord involvement that together with the inheritance pattern are routinely used for clinical classification. We sought to describe the clinical and neurogenetic spectrum of 127 dHMN proband / family's diagnosed in our unit.

Methods:
We report 148 patients from 127 families (85 males; mean age 33.7y, range 2-78y), who were genetically investigated using next-generation sequencing techniques - targeted panel and / or WES.

Results:
The inheritance pattern observed was autosomal recessive in 20, dominant in 18 and sporadic in the remaining cases. Ten cases had also UMN signs, 19 had some proximal involvement, 6 had upper limb predominance and 1 had vocal cord involvement. A class 4 or 5 variant was identified in 26% and a VUS in 20% of proband / families. BSCL2 and DNAJB2 were the most frequent cause dHMN in our cohort, another causative gene found in one or two proband include AARS, DYNC1H1, VRK1, SIGMAR1, KIF1A, TK2, BICD2, DCTN, FBXO38, GARS, HSPB1, MORC2, IGHMBP2, TRPV4, HINT1, MME, PRPS1.

Conclusions:
We found wide phenotypic and genetic heterogeneity in our cohort of HMN.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:
Keywords: CMT, dHMN, NGS
IPSC-derived motor neurons reveal progressive mitochondrial dysfunction in axonal CMT subtypes

Poster No:
124b

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Introduction:
Human induced pluripotent stem cells (hiPSCs) were used as an in vitro cellular model to study axonal Charcot-Marie-Tooth (CMT) disease. We aimed to identify and study common hallmarks of axonal degeneration shared by different CMT2 subtypes.

Methods:
We differentiated motor and sensory neurons from five CMT2 patient iPSC lines, covering the most frequent CMT2 causal genes: MFN2, NEFL, HSPB1 and HSPB8, along with healthy control iPSC lines. An additional isogenic iPSC control was generated using CRISPR/Cas9 from the MFN2 patient line.

Results:
Our data demonstrated that patient-specific motor and sensory neurons recapitulate the disease signatures of CMT2. We revealed a common trend towards a decrease in the neurite network density, along with alterations in extracellular excitability (MEA). We also reported progressively affected axonal organelle trafficking as well as alterations in mitochondrial morphology. Differentiation of the same CMT2 iPSC lines into peripheral sensory neurons only gave rise to cellular phenotypes in subtypes with sensory involvement, supporting the notion that some gene mutations predominantly affect motor neurons. We revealed a common mitochondrial dysfunction in CMT2-derived motor neurons, supported by alterations in the expression pattern and oxidative phosphorylation. Inhibition of a dual leucine zipper kinase (DLK) partially ameliorated the mitochondrial disease phenotypes in CMT2 subtypes.

Conclusions:
Our data provide shared and novel insights into the molecular and cellular phenotypes across different CMT2 subtypes.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: Axonal CMT
A recurrent SPTAN1 variant with an HSP-HMN phenotypical spectrum

Poster No:
126b

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Introduction:
The SPTAN1 gene has been shown to display a remarkable phenotypical spectrum. Initially, mutations were identified to be causative of epilepsy and intellectual disability disorders, while we showed that nonsense mutations can be causative of Hereditary Motor Neuropathy (HMN). In recent research we have linked novel de novo and dominantly inherited SPTAN1 variants to Hereditary Spastic Paraplegia (HSP) and ataxia as well as intermediate spastic ataxic phenotypes. Of note is a recurrent p.Arg19Trp variant, that we identified in 7 different families with HSP.

Methods:
Whole Exome Sequencing (WES) was performed for family one in a diagnostic setting after a neuromuscular panel did not identify a cause for the family's clinical presentation. For family two, WES was available through the Genesis platform, a data-sharing and NGS analysis platform.

Results:
The p.Arg19Trp SPTAN1 variant was identified as a Variant of Unknown Significance through diagnostic work-up for family one. The variant segregates with a dominant inheritance pattern. The p.Arg19Trp variant was identified through re-analysis of the WES data in the Genesis platform for family two. Family one displays an HMN phenotype, with a steppage gait due to bilateral foot-drop. The index of family two has an early-onset (13 yo) HMN phenotype, with NCS confirming the axonal pure motor affectedness.

Conclusions:
The identification of the recurrent p.Arg19Trp variant in two HMN families shows that not only nonsense but also missense SPTAN1 variants can be causative of HMN. Although previously this mutation seemed to be specific for HSP, we now show that the known HMN-HSP phenotypical spectrum also applies here. We are setting up functional studies to denote the common pathomechanism.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Hereditary Motor Neuropathy, SPTAN1
Longitudinal Serum Neurofilament Light Chain Levels As Biomarker of Axonal Injury in Guillain-Barré Syndrome

Poster No:
127b

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Introduction:
Neurofilament light chain (NfL) is a promising biomarker to monitor axonal damage in diverse neurological disorders. The dynamics of NfL in the Guillain-Barré syndrome (GBS) is currently unknown. We aimed to study serum NfL (sNfL) levels longitudinally in patients with GBS in relation to disease severity, prognosis and treatment response.

Methods:
Serial serum samples of 286 GBS patients (median [IQR] age, 57 [43-68] years; 191 men [67%]) included in the Second IVIg Dose (SID)-GBS trial were measured for sNfL using the Simoa HD-x analyzer. Reference values were obtained from healthy controls. In multivariate analysis, we correlated sNfL levels with clinical outcome controlled for age and the modified Erasmus GBS outcome score (mEGOS).

Results:
sNfL was analyzed at pre-treatment (n = 149); 1 week (n = 260), 2 weeks (n = 223), 4 weeks (n = 195) and/or 12 weeks (n = 25) after start of treatment. Baseline sNfL was elevated compared with healthy controls (median 27 pg/ml, IQR 16-57 vs. 9 pg/ml; 7-11), continued to rise 1 week (94 pg/ml, 44-275) and 2 weeks (168 pg/ml, 70-492) post-treatment, remained elevated at 1 month (125 pg/ml, 50-447) and had declined at 3 months follow-up (24 pg/ml, 12-39). At every time point, sNfL levels correlated with disease severity (GBS disability score, MRC sumscore). In multivariate analysis, log(sNfL) at baseline, week 1, 2 and 4 significantly associated with the ability to walk at 1 and 6 months, independent of age and the mEGOS. No difference in sNfL dynamics was observed between groups stratified for a second IVIg course or placebo.

Conclusions:
Longitudinally measured sNfL levels in GBS reflect disease severity and predict outcome independent of current clinical prognostic factors. Longitudinal sNfL tests to monitor the extent of axonal damage may be used to evaluate treatment response in future clinical trials.

References:
No

References 1:
Grant Support: This work has been supported by a research grant from the Prinses Beatrix Spierfonds (W.OR19-24)

Keywords: Neurofilament light chain, Biomarker, Guillain-Barré syndrome, Longitudinal, Axonal damage
Population Pharmacokinetic Modeling of Intravenous Immunoglobulin Treatment in Patients with Guillain-Barré Syndrome

Poster No:
128b

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Introduction:
Intravenous immunoglobulin (IVIg) at a standard high dosage of 2g/kg is the treatment of choice for Guillain-Barré syndrome (GBS). The pharmacokinetics (PK), however, are highly variable between patients, and a rapid clearance of IVIg is associated with poor clinical recovery. We aimed to develop and validate a PK model for IVIg treatment in GBS patients, and to identify covariates influencing IVIg clearance.

Methods:
Non-linear mixed effects modeling software (NONMEM) was used to describe the PK of IVIg. Total IgG levels were measured in a model-building cohort consisting of 177 GBS patients with 589 sequential serum samples, and an independent validation cohort consisting of 177 GBS patients with 689 sequential serum samples. Model robustness was evaluated using goodness-of-fit plots, visual predictive checks, realistic parameter estimates, and shrinkage. Covariates were analyzed in a stepwise manner; forward inclusion followed by stricter backward elimination.

Results:
The PK of IVIg treatment in GBS was best described using a two-compartment model. Allometric scaling was used to correct for bodyweight. The PK model accurately described the daily increment in serum IgG levels during a standard IVIg course, followed by the initial rapid fall and gradual decline to steady-state levels. Apparent clearance of IgG increased with 31% in patients receiving concomitant methylprednisolone treatment, with 22% in patients with a GBS disability score of 3 or 4, and with 83% in patients with a disability score of 5. The model was successfully validated in the second cohort.

Conclusions:
This is the first model describing the PK of high dose IVIg in patients with GBS. Disease severity and concomitant methylprednisolone treatment were identified as important covariates to explain variability in IgG levels. The validated model provides a tool to predict the PK of alternative regimens of IVIg in GBS to design future trials and personalize treatment.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support: This work has been supported by an unconditional research grant from the Prinses Beatrix Spierfonds (grant W.OR11-27 and W.OR19-24).

Keywords: Pharmacokinetics, Intravenous immunoglobulin, Guillain-Barré syndrome, IgG, Methylprednisolone
Influence of tremor in CIDP on disability assessment

Poster No:
129b

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Introduction:
Tremor often occurs in chronic inflammatory demyelinating polyneuropathy (CIDP) and may, in addition to weakness and sensory impairment, lead to disability. We aimed to assess the influence of tremor in CIDP on disability assessment.

Methods:
In this cross-sectional study, we compared CIDP patients with and without a relevant tremor using the INCAT disability scale (INCAT-DS, arm and leg score separately) and the following impairment scales: the MRC sum score (MRC-SS), INCAT sensory score (INCAT-SS) and grip strength, using the Mann–Whitney U test. We defined a relevant tremor as an intention or postural tremor of > 1 cm or at least a moderate tremor during specific arm motor tasks measured using the Fahn-Tolosa-Marín subscale B (FTM-B) of at least one hand. Using multivariate linear regression models, we investigated the association between the INCAT-DS arm disability score as dependent variable and the presence of a relevant tremor (yes or no) or tremor severity, using the FTM-B sum score, as independent variables, when corrected for other impairment scales.

Results:
19 % (14/72) of patients had a relevant tremor. The INCAT arm disability score was significantly higher in patients with a relevant tremor compared to patients without (2.0 vs. 1.0 points, p=0.019), while there were no significant differences in grip strength, the MRC-SS and INCAT-SS of the arms. Presence of relevant tremor and tremor severity were independent predictors of INCAT arm disability score, when corrected for grip strength, the MRC-SS and INCAT-SS of the arms.

Conclusions:
In patients with CIDP, presence of tremor and tremor severity predict arm disability, independent of muscle strength and sensory deficits. This may be relevant for clinical practice and research, as tremor is thought to be less responsive to treatment than other causes of disability in CIDP.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: chronic inflammatory demyelinating polyneuropathy, tremor, disability
Increasing cAMP levels by inhibiting phosphodiesterase 4D improves nerve conduction and functional recovery in a mouse model for Charcot Marie Tooth 1A

Poster No:
130b

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Introduction:
Charcot-Marie-Tooth disease type 1A (CMT1A) is the most common inherited neuropathy of the peripheral nervous system for which no therapy is currently available. It is caused by a duplication of the peripheral myelin protein 22 gene (PMP22), primarily causing Schwann cell dedifferentiation and demyelination leading to decreased nerve conduction and subsequent motor and sensory deficits. Cyclic adenosine monophosphate (cAMP) is an important second messenger molecule involved in Schwann cell maturation and differentiation. Increasing cAMP by inhibiting its natural regulators, phosphodiesterases (PDE), may be an interesting target. In this study, the therapeutic potential of the specific PDE-4D inhibitor Gebr32a was tested in C3-PMP22 mice, an animal model for CMT1A.

Methods:
4-month-old C3-PMP22 mice were injected subcutaneously twice a day with Gebr32a (0.3mg/kg) or vehicle control for 7 weeks (n=9 mice/group). Wildtype littermates (n=12) were included as controls and received vehicle injections. All mice were functionally tested at baseline and at the end of the treatment.

Results:
Electrophysiological recordings showed that axonal functions were comparable between Gebr32a treated mice and controls. In contrast, nerve conduction in the sciatic nerve of treated mice was significantly increased compared to controls, indicating improved myelination. In addition, treated C3 PMP22 mice traversed a 7mm wide beam significantly faster compared to controls. These mice also made significantly less foot slips on the grid walk test compared to untreated animals, indicating improved sensorimotor functions. Gebr32a treated mice were also able to run longer on an accelerating rotarod compared to untreated mice, not reaching significance. Finally, we observed that the grip strength of all limbs was significantly increased in treated C3-PMP22 mice.

Conclusions:
To conclude, we found that inhibition of PDE-4D with Gebr32a can be used to improve the functional outcome in an animal model for CMT1A disease. The clinical relevance of this drug and how it improves myelination remains to be elucidated.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Research Foundation of Flanders (FWO Vlaanderen; 12Z2620N)

Keywords: CMT1A, PMP22, Demyelination, PDE inhibitors, Functional recovery
Exome sequencing in the diagnosis of neuromuscular diseases: a single Centre experience

Poster No:
131b

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Introduction:
Focused exome sequencing and whole-exome sequencing (WES) are valuable research tools for the identification of molecular defects in patients with suspected genetic diseases. To this end, WES harbors a diagnostic yield between 19-45\% if applied to Charcot-Marie-Tooth (CMT) or other Mendelian disorders. The aim of our study was to evaluate the effectiveness of these methods in achieving a molecular diagnosis in CMT disease and related disorders, myopathies and hyperCKemia.

Methods:
We prospectively enrolled n=40 consecutive patients from a single tertiary referral Centre (IRCCS Mondino Foundation, Pavia, Italy). After excluding PMP22 duplication/deletion in CMT1 cases, SPG4 and SPG7 mutations by multiplex ligation-dependent probe amplification if spasticity was present, and biallelic RFC1 expansion in case of sensory chronic idiopathic axonal polyneuropathy, respectively, n=16 patients underwent focused exome sequencing and n=24 underwent WES in London, UK. Mutations were classified according to the 2015 ACMG guidelines. Likely pathogenic / pathogenic mutations were confirmed by Sanger sequencing.

Results:
N=40 index patients enrolled included: CMT1 (n=2), CMT2 / intermediate CMT (n=16), distal hereditary motor neuropathy (n=4), hereditary sensory neuropathy (n=2), hyperCKemia (n=5), genetic myopathy (n=11). Mean age at genetic testing was 53 ± 15 years. A molecular diagnosis was achieved in 12/40 (30\%) of subjects: LITAF (n=1), MPZ (n=1), NEFL (n=1), AARS1 (n=1), SIGMAR1 (n=1), TRPV4 (n=1), GJB1 (n=1), RNF170 (n=1), GNE (n=2), LMNA (n=1), RYR1 (n=1), ANO5 (n=1). WES helped to make a diagnosis of CMT due to GJB1 pathogenic mutation (p.Tyr151Cys) in a patient previously diagnosed with chronic inflammatory demyelinating polyneuropathy. Also, two patients with GNE homozygous mutations were reclassified as affected by GNE myopathy.

Conclusions:
A genetic diagnosis was reached in the 30\% of cases and this proportion was in agreement with previous data. Non-phenotype guided exome sequencing proved as valuable research tool in achieving a molecular diagnosis of neuromuscular diseases in a clinical scenario.

References:
No
References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Exome sequencing, CMT
Disruption of endosomal sorting in Schwann cells leads to defective myelination and endosomal abnormalities observed in Charcot-Marie-Tooth disease

Poster No:
132b

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Introduction:
Endosomal sorting plays a fundamental role in directing neural development. Several genes linked to inherited demyelinating peripheral neuropathies, known as Charcot-Marie-Tooth disease (CMT), encode proteins that directly interact with components of the endosomal. We previously demonstrated that a point mutation in hepatocyte growth factor-regulated tyrosine kinase substrate (HGS), an endosomal scaffolding protein that sorts internalized cell surface cargo on the endosome, causes a peripheral neuropathy in the neurodevelopmentally-impaired teetering mice.

Methods:
Here, we constructed a Schwann cell-specific Hgs knockout to determine the role of endosomal sorting during myelination. We utilize molecular, electrophysiological and behavioral test to examine the effects of HGS knockout on peripheral nerve myelination.

Results:
Inactivation of HGS in Schwann cells resulted in motor and sensory deficits, slowed nerve conduction velocities, delayed myelination and hypomyelinated axons, which occur in demyelinating forms of CMT. Consistent with a delay in Schwann cell maturation, HGS-deficient sciatic nerves displayed increased mRNA levels for several promyelinating genes and decreased mRNA levels for genes that serve as markers of myelinating Schwann cells. Loss of HGS also increased the abundance and activation of the ERBB2/3 receptors which are essential for Schwann cell development.

Conclusions:
These findings suggest that HGS plays a critical role in endosomal sorting of the ERBB2/3 receptors during Schwann cell maturation, adding to the evidence implicating endosomal dysfunction in inherited peripheral neuropathies.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support: NIH–National Institute of Neurological Disorders and Stroke Grant NS110744

Keywords: CMT, Schwann cell, myelin, endosome, hepatocyte growth factor-regulated tyrosine kinase substrate
Genetic modifiers in hereditary and acquired TTR amyloidosis: a genome-wide association study

Poster No:
133b

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Introduction:
Hereditary transthyretin (ATTRv) amyloidosis is a rare systemic and life-threatening condition caused by mutations in the transthyretin (TTR) gene. To date, considerable variability has been observed in age of onset (AOO), penetrance, progression rate and response to treatment, both across families and countries. This variability in ATTRv amyloidosis cannot be entirely explained by the specific mutation in TTR gene, as well as factors favoring wild-type TTR deposition in acquired age-related amyloidosis
(wtATTR), are still unknown. Therefore, a role for genetic modifiers has been hypothesized for these two conditions.

**Methods:**
The aim of this multicenter study is to identify genetic modifiers in ATTRv and wtATTR amyloidosis, employing an unbiased genome-wide approach.

**Results:**
In patients with ATTRv amyloidosis we will perform a genome-wide association study (GWAS) to identify loci harboring genetic variations that alter 1) age of neurological onset; 2) clinical phenotype and progression; 3) response to anti-amyloidogenic treatments. Patients affected by wtATTR amyloidosis will also be tested in a complementary case-control GWAS. The TTR locus as well as significant loci from the GWAS will be further explored by long-read sequencing.

**Conclusions:**
The proposed research will identify novel genetic risk factors, informing disease prognosis and guiding monitoring and treatment. Also, it will provide seminal information about the mechanisms involved in amyloid deposition, potentially leading to the identification of novel drug targets. The study is actively enrolling, and we would be pleased for additional Centres to join (if interested: andrea.cortese@unipv.it; l.obici@smatteo.pv.it).

**References:**
No

**References 1:**

**References 2:**

**References 3:**

**References 4:**

**Grant Support:**

**Keywords:** ATTRv, wtATTR, Genetic modifiers, AOO, GWAS
Genomic instability in the last exon of HSPB8 primes for frameshift mutations with a common pathomechanism

Poster No:
134b

Authors:
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Introduction:
Mutations in small heat shock protein HSPB8 cause neuromuscular diseases like Charcot-Marie-Tooth (CMT) disease and myofibrillar myopathy. There is an unusual high amount of frameshift mutations in the C-terminus of HSPB8, which has not been observed for other small heat shock proteins. These frameshifts change the reading frame and lead to the formation of new extended peptide sequences whose pathomechanisms have not been investigated so far. Here, we elucidated why HSPB8 has accumulated such a high amount of frameshift mutations and reveal what pathomechanisms underlie these group of frameshift mutants.

Methods:
Different methods, including CoIP, western blot, proximity labeling, state-of-the-art electron and light microscopy methods, were employed to decipher the underlying molecular pathomechanisms.

Results:
Our unpublished work reveals different frameshifts in the C-terminus of HSPB8, all resulting in the same peptide extension, which is highly aggregation-prone. Expression of these frameshift mutants leads to the formation of vesicle-like structures, which form independent from membranes as revealed by correlation light-electron microscopy (CLEM). We employed super-resolution expansion microscopy to gain insight into the internal composition of these vesicle-like structures. Not surprisingly, the content of these vesicle-like structures was enriched for proteins that exposed hydrophobic domains. We then employed APEX2 proximity-labeling coupled to mass spectrometry to characterize the proteins trapped in these chaperone-surrounded structures. This has provided insights into putative chaperone-clients, which have so far remained elusive for HSPB8, and may explain how various C-terminal frameshifts mutations in HSPB8 form a new common pathomechanisms for small heat shock proteins.

Conclusions:
Our work reveals that HSPB8 harbors a genomic instability in the last exon, that primes for frameshift mutations, and which results in the establishment of neuromuscular disorders. This work not only opens the door towards the development of new therapies but will also be instrumental in guiding future genetic findings in HSPB8

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: small heat shock proteins, protein aggregation, pathomechanism
Activating Proteasomes Is Therapeutic In A Mouse Model Of Charcot Marie Tooth 1B

Poster No:
135b

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Introduction:
Protein degradation by the Ubiquitin Proteasome System is slowed in the peripheral nerves of the S63del mouse model of Charcot Marie Tooth 1B (CMT1B) neuropathy. Consequently, the causative mutant protein accumulates in the affected Schwann cells, along with other un-degraded, potentially toxic proteins. Such impairment of the proteasome's degradative abilities is also seen in aging, and in many neurodegenerative diseases.

Methods:
A newly appreciated mechanism of regulating the proteasome is subunit phosphorylation. We recently reported that phosphorylation by the cyclic GMP-dependent kinase (PKG) increases the proteasome's ability to degrade polyubiquitinated proteins and occurs in cells, tissues, and organisms in response to physiological signals and pharmacological agents that raise cGMP. To investigate whether activation of the proteasome may be therapeutic in chronic diseases in which protein degradation is impaired, we treated S63del mice with two classes of pharmaceutical compounds that are well-tolerated in humans and activate PKG by raising cGMP through distinct mechanisms: phosphodiesterase 5 (PDE5) inhibitors (e.g. sildenafil, tadalafil) which block cGMP's breakdown, and soluble guanylyl cyclase (sGC) stimulators (e.g. CYR-119) which increase cGMP's synthesis.

Results:
Treatment of S63del mice with sildenafil twice a day for 14 days via intraperitoneal injection restored proteostasis, myelin thickness, and nerve conduction to levels seen in wild type littermates. Sildenafil has a short half-life in mammals and limited access to the nervous system, potentially limiting its use as a treatment for patients with CMT1B. Therefore, we also treated S63del mice per os for 14 days with tadalafil, a PDE5 inhibitor with more desirable pharmacokinetics than sildenafil, or CYR-119, a novel sGC stimulator that enters the nervous system. Excitingly, these treatments also increased proteasome function and nerve conduction.

Conclusions:
Raising cGMP and activating proteasomes may be a promising therapy for CMT1B, which is currently untreatable, and possibly other diseases in which protein degradation is impaired.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Charcot Marie Tooth, Proteostasis, cGMP, Proteasome
A severe case of neuroleukemiosis in B cell chronic lymphocytic leukemia presenting as mononeuritis multiplex.

Poster No:
136b

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Introduction:
A 58 years old woman was diagnosed with B cell chronic lymphocytic leukemia in Mars 2020. She secondarily developed leukemic infiltration in her left breast, granulomatous rosacea (both histologically proven) and bilateral ear chondritis. Blood work disclosed type I cryoglobulinemia and severe hypogammaglobulinemia. In August 2021, she experienced rapidly progressing dysesthesias in her left hand, then to her right hand within a few days. In the two following weeks, she noticed progressive weakness and atrophy in both hands (left predominance), limiting daily activities as bottle-opening. Neurological examination found left predominant amyotrophic paralysis of hand muscles (abductor pollicis brevis M4, dorsal interossei M2), with normal strength elsewhere, normal reflexes and bilateral glove-pattern hypoesthesia.

Methods:
Investigations included nerve conduction studies, imaging and nerve biopsy.

Results:
Nerve conduction studies were compatible with mononeuritis multiplex with predominantly axonal, non-length dependent and asymmetrical sensorimotor neuropathy. Brachial plexi MRI was normal but brain MRI showed diffuse hypertrophic pachymeningitis; CSF examination showed pleiocytosis (10 leucocytes, normal <5) with normal protein level. CSF cytology showed 59% of white cells with the same immunophenotype as the known CLL. Radial nerve biopsy showed a diffuse perineural B cell infiltrate (CD20+, CD79a+, CD5+), with the same characteristics found in the previous breast biopsy. Hematologic assessment did not find any evidence of transition to lymphoma. In order to control the severely symptomatic neuroleukemiosis, the patient received steroid and cytoreductive treatment with slight improvement of sensory symptoms (follow-up: 4 weeks).

Conclusions:
Mononeuritis multiplex caused by neuroleukemiosis in CLL is an exceptional diagnosis. Because of the positive cryoglobulinemia, we could have considered the diagnosis of peripheral nerve vasculitis and not performed the nerve biopsy. This case supports the interest of nerve biopsy in such rare and atypical cases, as steroids alone in order to treat a suspected vasculitis are not expected to be efficient on the lymphocytic proliferation.

References:
No

References 1:
References 3:

References 4:

Grant Support: N/A

Keywords: Neuroleukemiosis, Mononeuritis multiplex, Chronic lymphocytic leukemia
Race and Ethnicity Subcategories Implementation Project

Poster No:
137b

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Introduction:
The Inherited Neuropathy Consortium (INC) currently categorizes race for Charcot-Marie-Tooth (CMT) patients using the National Institute of Health's (NIH) recommended categories: American Indian or Alaska Native, Asian, Black, or African American, Native Hawaiian, or Other Pacific Islander, and White and for ethnicity selecting Hispanic, Latino, or Spanish origin or Not Hispanic, Latino, or Spanish origin. These categories may not accurately capture the race and ethnic identity of all subjects, and especially those enrolled at study sites outside the United States. The intention is to capture data on our enrolled subjects to ensure that we are truly serving the affected population.

Methods:
We selected three sites within the INC that are both high enrolling and located in areas whose local population is comprised of comparatively unique demographic breakdowns. These sites will use an expanded version of the NIH's standard race and ethnic categories: Americas, Asian, Black, Middle East/North African, Mixed/ multiple ethnic groups, Oceana, White, and any other ethnic background. We are capturing data from three consortium sites located in cities with vastly different demographic makeups, with one outside of the USA.

Results:
Our team will compare baseline demographics at each site to the demographic data collected while using the expanded categories and compare data across sites.

Conclusions:
We expect to determine whether expanding race categories enables the capture of greater diversity in our CMT patients' demographics.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01)
Keywords: Demographics, Charcot-Marie-Tooth
Workforce Development Through a New Diversity, Equity, and Inclusion Internship Role

Poster No:
138b

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Introduction:
The Inherited Neuropathy Consortium (INC) has created a Diversity, Equity, and Inclusion (DEI) internship to provide an opportunity for a junior research team member to develop their skills as a leader in addressing racial, ethnic, gender, and socioeconomic disparities in rare disease clinical research. The position is open to any Rare Disease Clinical Research Network (RDCRN) or National Center for Advancing Transitional Science (NCATS) member. The main goal is for the selected intern to be familiar with best practices in recognizing disparities and improving outcomes within populations that are traditionally underrepresented in clinical research.

Methods:
This position was designed for an individual who is planning to attend a graduate program, is passionate about DEI work, and who is planning to use what they learned in their future career. The INC intern was selected as part of a competitive application process throughout the 20 different consortia that make up the RDCRN.

Results:
The selected intern is a First Generation-Mexican American who has witnessed firsthand the disparities in both patient care and in the workforce. These disparities have been a driving force to change and adopt new ways to meet the diverse needs of current and future patients to create an inclusive experience.

Conclusions:
In addition to the knowledge and leadership skills the INC intern will be gaining as a member of the diversity committee, she will be facilitating a multi-site project that aims to help create better descriptive demographics data for our consortium enrolled site and by assisting with a project that will allow the Iowa INC site to enroll patients who are Spanish-dominant. This will serve as a pilot to increase INC outreach to patients who are Spanish dominant and provide a model to reach out to patients who are dominant in a language other than English.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support: The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01)

Keywords: Diversity, Inclusion, Equity
Characteristics of Patients with Hereditary Transthyretin Amyloidosis-Polyneuropathy (ATTRv PN) in NEURO-TTRansform, a Phase 3 Study of Eplontersen

Poster No:
139b

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Introduction:
Hereditary transthyretin-mediated amyloidosis (ATTRv) is a severe, progressive, debilitating and ultimately fatal disease caused by systemic deposition of transthyretin (TTR) amyloid fibrils, leading to multiorgan failure. The investigational drug eplontersen (ION-682884) causes degradation of TTR mRNA in the liver, inhibiting TTR protein synthesis, and has a similar sequence to inotersen (approved for the treatment of ATTRv with polyneuropathy, ATTRv-PN). Eplontersen is studied in the phase 3 randomized, controlled NEURO-TTRansform trial (NCT04136184) for the treatment of ATTRv-PN. We report here the baseline characteristics of these patients.

Methods:
As reported in Coelho et al, Neurol Ther 2021, study participants will receive subcutaneous eplontersen every 4 weeks or inotersen weekly for 35 weeks (interim analysis timepoint) and then eplontersen until end of treatment at Week 81. Participants include adults with ATTRv-PN (Familial Amyloid Polyneuropathy stage 1 or 2), a documented TTR mutation, and signs/symptoms consistent with polyneuropathy (including Neuropathy Impairment Score ≥10 and ≤130). Baseline characteristics were analyzed descriptively.

Results:
The NEURO-TTRansform study enrolled 168 patients. The majority of patients were male (69% [116/168]) and white (80% [132/166]). Mean (±SD) age was 52.8 (±14.88) years, and 56% of patients had the V30M sequence variant. 68% (114/168) of patients received previous treatment with tafamidis or diflunisal. 80% (134/168) had stage 1 neuropathy; mean time from diagnosis to enrollment was 46.1 (±57.38) months. PND scores were I for 40% of patients, II for 42%, III for 11%, and IV for 7%.

Conclusions:
The recruited population is similar to the one enrolled in a previous phase 3 trial of inotersen, with minor variations in baseline characteristics that likely reflect greater disease awareness in recent years. The results of this study will provide important information on clinical, health-related quality of life, and exploratory efficacy outcomes to better inform future treatment choices for patients with ATTRv.
References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: amyloidosis, transthyretin, eplontersen, clinical trial, patient characteristics
Proteomics Based Discovery Of Biomarkers For Disease Activity In CIDP

Poster No:
140b

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Institutions:
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Introduction:
Objective biomarkers for disease activity in chronic inflammatory demyelinating polyneuropathy (CIDP) are lacking, impeding treatment decisions. Using proteomic profiling, we aimed to identify candidate serum protein biomarkers for disease activity.

Methods:
Two prospective cohorts of CIDP patients were studied: 1) patients starting induction treatment (IT cohort, N:51) measured at baseline and six months after starting treatment, 2) patients on maintenance treatment starting withdrawal (MT cohort, N:40), measured at baseline and six months after withdrawal or at time of relapse. Using a proximity extension assay (Olink), 1463 proteins were analyzed in serum. IT patients were classified as responders based on changes in I-RODS scores at follow-up; patients with delta I-RODS > 4 were classified as responders and others as non-responders. For MT patients, a relapse was defined as a delta I-RODS < -4 at follow-up. Candidate proteins were selected based on the observed fold-change in NPTX values (log10 fold change > 0.5 or < -0.5) and p-value (<0.05) in baseline samples in the IT cohort. The area under the ROC curve (AUC) was calculated to assess discriminatory potential. To validate findings in another clinical scenario, we assessed which of the candidate proteins differed in baseline samples of MT patients with or without relapse.

Results:
Overall, 29/51 (56.9%) IT patients were classified as responders. In total, 23 candidate proteins out of the 1463 proteins differed between responders and non-responders in the IT cohort. AUC values ranged between 0.79 – 0.60. In the MT cohort, 21/40 (52.5%) patients relapsed after treatment withdrawal. Thirty-nine out of 1463 and 2 out of 23 candidate proteins also differed between MT patients with or without relapse.

Conclusions:
Using proteomic profiling, we found several candidate biomarkers for disease activity in CIDP, of which two were associated with changes in disease activity in different clinical scenarios.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

**Keywords**: CIDP, biomarkers, disease activity, proteomics
Serum Neurofilament Light Chain and Contactin-1 As Biomarkers In Anti-MAG Polyneuropathy

Poster No:
141b

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Introduction:
In anti-myelin-associated glycoprotein IgM paraprotein related peripheral neuropathy (anti-MAG PN) there is a lack of reliable biomarkers to select patients for treatment, and for evaluating treatment effects, both in routine practice and in clinical trials. Neurofilament light chain (NfL) and contactin-1 (CNTN1) can serve as markers of axonal or paranodal damage, respectively. We therefore hypothesized that serum NfL and CNTN1 may function as biomarkers of disease activity in anti-MAG PN.

Methods:
We included 22 treatment-naïve patients with anti-MAG PN (mean age 69 years, 57% male) that had IgM paraproteinemia, a high IgM MAG-antibody, and clinical diagnosis of anti-MAG PN by a neurologist specialized in peripheral nerve disorders. As controls, 10 treatment-naïve patients with an IgM Monoclonal gammopathy of undetermined significance (MGUS) or Waldenström's Macroglobulinemia (mean age 69 years, 60% male) without clinical signs of neuropathy were included (non-PN). NfL was measured using Simoa; CNTN1 was measured using Luminex®. Abnormal NfL levels were defined as at or above the 95th percentile of age-specific cut-off values in healthy controls. Abnormal CNTN1 levels were defined as below the 5th percentile of values in healthy controls (N: 222).

Results:
Serum NfL levels did not differ between anti-MAG PN and non-PN patients (P = 0.3). Abnormal serum NfL levels were present in 4 (17%) anti-MAG PN patients (range serum NfL: 29.7-42.8 pg/mL) and in 1 (10%; 59.2 pg/mL) non-PN patient. Elevated serum NfL levels could not be explained by age, gender, clinical phenotype (including an acute phenotype) or disease duration. Serum CNTN1 levels also did not differ between anti-MAG PN and non-PN patients (P = 0.4). Abnormal CNTN1 levels were present 1 (4%) anti-MAG PN patient and 1 (10%) non-PN patient.

Conclusions:
Our results do not support serum NfL or CNTN1 as potential biomarkers of disease activity in anti-MAG PN.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: anti-MAG neuropathy, neurofilament light chain, contactin-1, biomarkers
The role of nerve ultrasound as observational tool and prognostic marker in nerve trauma

Poster No: 144b

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Introduction: Traumatic nerve lesions can cause long-time disability and affect quality of life. An early diagnosis and grading of nerve injury are important for further therapy and prognosis. Nerve conduction studies, needle myography and clinical examination are the gold standard, but both methods entail a diagnostic uncertainty, especially in the first months after trauma. High resolution ultrasound is a useful tool in diagnosis of mononeuropathies and peripheral nerve tumors. So far, its value in diagnosis of nerve trauma has only been proven in case series.

Methods: Ultrasound data of traumatic nerve injuries in context of clinical and electrophysiological development and its influence on therapeutic decisions were retrospectively analyzed and compared in 152 patients at screening visit and follow up visit.

Results: CSA enlargement correlated significantly with the amount of measurable nerve damage, both at first (R²=0.131, p<0.0001) and at follow up visit (R²=0.281, p<0.0001). The amount of EMG pathology (according to our classification) correlated significantly with the nerve Cross-sectional area (CSA) at both visits (R²=0.144, p<0.0001 and R²=0.323, p<0.0001). At screening visit, fascicle visibility was the only sign with prognostic impact (favorable >50% and unfavorable <50% of CSA), whereas at follow up visit persisting CSA enlargement >150% at damage site, >150% distal to the damage and less than 50% fascicle visible were associated with no further amelioration (ROC curve analysis: AUC=0.793, p<0.0001, Sens. 80%, Spec. 68.9%, AUC=0.762, p>0.0001, Sens. 84.0%, Spec. 70.0%, AUC=0.769, p>0.0001, Sens. 80.0%, Spec. 68.9%).

Conclusions: High resolution nerve ultrasound is very efficient tool in analyzing nerve damage.

References: No

References 1:

References 2:

References 3:

References 4:

Grant Support: none
Keywords: nerve ultrasound, nerve trauma, electrodiagnostics in nerve trauma, nerve trauma pattern, diagnostic tool nerve trauma
Epigenetic Regulation of Schwann Cells Suppresses Prolonged Inflammation to Promote Sciatic Nerve Regeneration

Poster No:
145b

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Introduction:
Activated Schwann cells (SCs) after peripheral nerve damage release cytokines to initiate the events of inflammation. This activation of myelinating SCs to repair SCs is associated with alterations in the histone deacetylases (HDACs). SCs and infiltrated macrophages work coherently to remove myelin and axonal debris to generate a conducive microenvironment for axonal growth. The inflammatory response dampens after 2-3 weeks of injury. However, severe nerve injuries often lead to an exaggerated inflammation resulting in impaired nerve regeneration. Investigations to understand the effects of HDAC modulation on chronic inflammation and peripheral nerve regeneration are yet not done.

Methods:
HDAC inhibitor sodium phenylbutyrate (PBA) was utilized to modulate the HDACs profile in an in vitro SC inflammation model and sciatic nerve transection injury model to study the effect on the alleviation of chronic inflammation if any. We further assessed the impact of suppression of prolonged inflammation on regenerative outcomes by immunohistochemical studies.

Results:
Upon treatment of LPS-induced RT4 SCs with PBA, the expression levels and secretion of TNF-α were reduced. Transient activation of the nuclear factor κB (NFκB)-p65 pathway was also affected. Furthermore, the elevated HDAC3 expression and activity were suppressed. Similarly, PBA administration resulted in a significant decline in the levels of pro-inflammatory cytokines at the injury site in comparison to the hydrogel control group (no PBA). The improvement in the nerve regenerative capacity in the PBA group was also observed as evident by a marked increase in SC number (S100), regrowth of axons (PGP9.5), and myelination of SCs (MBP). Improved relative gastrocnemius muscle weight percentage and reduced muscle atrophy in the PBA group signified better reinnervation of the targeted gastrocnemius muscle.

Conclusions:
Suppression of the persistent levels of pro-inflammatory cytokines using PBA improved axonal regeneration and remyelination. The elevated levels of pro-inflammatory cytokines were controlled by the inhibition NFκB-p65 pathway and HDAC3 levels.

References:
Yes

References 1:
Keywords: Regeneration, Schwann cells, Inflammation, Histone deacetylases, Cytokines
A Novel Variant In CADM3 Causes Charcot-Marie-Tooth Type 2FF In A Malian Family

Poster No:
146b

Authors:
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Introduction:
Charcot-Marie-Tooth disease type 2FF caused by CADM3 variants was recently reported in three Caucasian families. We report here a novel variant in CADM3 in a Malian family with CMT

Methods:
A careful clinical examination, and nerve conduction studies (NCS) were done. DNA was extracted from peripheral blood. CMT gene panel (50 genes + PMP22 duplication) testing and Whole Exome Sequencing (WES) were performed. Putative variant was confirmed through Sanger sequencing and segregation analysis was done. Western blot and Immunofluorescence analysis were performed.

Results:
Seven patients (six males and one female) and their unaffected relatives from a large family were enrolled. The disease distribution was consistent with an autosomal dominant inheritance pattern. The mean age at diagnosis was 35.7 years, ranging from 12 to 65 years, and walking difficulty was the most common starting symptom. Neurological examination showed a distal muscle weakness and wasting, steppage gait, absent reflexes, mild sensory loss, and pes cavus. A high clinical variability was noted, but overall, symptoms were more pronounced in the upper limbs compared to the lower limbs. NCS were performed in four individuals and were consistent with an axonal-type neuropathy with marked motor involvement. CMT gene panel testing was first done and was negative. However, WES revealed a novel pathogenic missense variant at position c.1102G>T (Gly368Cys) in CADM3, segregating with the disease in the family. In addition, Western blot and Immunofluorescence analysis showed a significant decrease in the levels of CADM3-Gly368Cys mutant protein in the membrane and suggest that the new cysteine might interfere with the native disulfide bond important for the formation of the Ig-like loops.

Conclusions:
We report a novel variant in CADM3, and provide further evidence of its implication in axonal-type CMT. A large collaborative study including patients from different genetic backgrounds may unveil several novel CMT genes or variants and inform the disease mechanism

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support: NIH Grant U01HG007044

Keywords: CMT, Next generation sequencing, CADM3, Novel variant, Mali
Pre-clinical studies in induced Pluripotent Stem Cell (iPSC) lines with SORD mutations linked to a recessive neuropathy

Poster No:
147b

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Introduction:
Recently, mutations in the gene coding for sorbitol dehydrogenase (SORD) were associated with a new form of recessive inherited neuropathy. To model this CMT type, we developed induced-Pluripotent Stem Cells (iPSCs) from patients with SORD-related neuropathy and differentiated them into spinal cord motor neurons. We are using these cells to identify disease-specific phenotypes to evaluate therapeutic strategies for SORD related neuropathy.

Methods:
Motor neurons were differentiated using a previously published protocol. Sorbitol levels were measured by a colorimetric assay as well as by mass spectrometry. Size of the motor neurons was measured by Flow Cytometry. Supernatant Neurofilament Light Chain content was measured by NFL ELISA.

Results:
Previously, we had successfully developed 3 patient induced pluripotent stem cell (iPSC) lines and were then able to differentiate them into motor neuron lines for disease modeling experiments. We first measured the sorbitol content of the motor neurons by colorimetric assay as well as by mass spectrometry, confirming that they have elevated levels of intracellular sorbitol content, replicating an important disease phenotype. Using these motor neurons, we are conducting an in-depth study of the neurofilament light chain (NFL) supernatant profile under various stressing conditions. We are also investigating a potential increase in cell volume due to osmotic swelling by measuring light scattering differences between the patient lines and control lines. Lastly, we are characterizing a potential time-dependent cell loss phenotype in the SORD motor neurons. These experiments will help elucidate potential disease mechanisms of the SORD neuropathy and provide measures of therapy efficacy.

Conclusions:
Patient-derived SORD motor neurons were shown to have elevated intracellular levels of sorbitol when compared to controls, replicating an important phenotype seen in patients. The analysis of other cell and axonal phenotypes will help us identify key cellular features of SORD neuropathy that can be used to understand pathophysiology and assess treatment efficacy.

References:
No

References 1:
References 2:

References 3:

References 4:

Grant Support: NIH

Keywords: Charcot-Marie-Tooth Disease, Motor Neuron, SORD, Neuropathy, iPSC
Clinical and pathophysiological characterization of anti-Pan-Neurofascin associated nodo-paranodopathy

Poster No:
148b

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Introduction:
Recently, the description of anti-pan-neurofascin antibodies with IgG subclasses other than IgG4 in patients with severe, acute-onset autoimmune neuropathy has broadened the spectrum of nodo-paranodopathies. The role of IgG subclasses in pathomechanism, clinical phenotype and treatment response has not been thoroughly investigated.

Methods:
We therefore assessed antibody binding characteristics, IgG subclass and complement binding considering the effects of IVIg in anti-pan-neurofascin compared to anti-neurofascin-155 mediated neuropathy, and furthermore clinical data, neurofilament light chain (NfL) levels and therapy response, using ELISA, Ella and cell-based assays.

Results:
We included n=10 patients with anti-pan-neurofascin and n=8 patients with anti-neurofascin-155 antibodies. IgG3/4 was the predominant subclass in anti-pan-neurofascin, and IgG2/4 in anti-neurofascin-155. In contrast to anti-neurofascin-155, anti-pan-neurofascin antibodies had direct access to nodes in non-fixated murine DRG/Schwann myelinating cocultures. Complement C1q binding in ELISA-based assays was significantly higher in patients with anti-pan-neurofascin and correlated to IgG3 levels. Complement preincubation increased cytotoxicity on preincubated Neurofascin-transfected HEK cells and lead to a destruction of nodo-paranodal architecture in presence of anti-pan-neurofascin antibodies in myelinating cocultures. Anti-pan-neurofascin patients showed a more severe phenotype, with significantly increased GBS disability scale and ICU and ventilation rates, and mortality of 20%. NFL levels were significantly increased in anti-pan-neurofascin compared to anti-neurofascin-155 and correlated with the overall disability scale score. IVIg treatment reduced C1q binding in vitro, but only initially lead to clinical improvement. Corticosteroids and PE also had no permanent effects, but rituximab and additional immunosuppression lead to improvement and even remission with corresponding titer and NfL decrease.

Conclusions:
In conclusion, we describe predominance of IgG3/4 in pan-neurofascin associated neuropathy with complement binding and complement-associated damage in vitro, and indirect signs of axonal damage in vivo. Screening including subclass-analysis in patients with this severe, but reversible condition is crucial. Therapy regimens including antibody-depleting and complement-targeted therapy need to be investigated in future studies.

References:
References 1:

References 2:

References 3:

References 4:

Grant Support: L. Appeltshauser and K. Doppler are supported by research fellowships by the Interdisciplinary Center of Clinical Research of the Medical Faculty of Würzburg. J. Messinger and J. Linke are supported by a grant of the University of Würzburg Graduate School

Keywords: nodo-paranodopathy, neurofascin, inflammatory neuropathy, complement, IgG subclass
Targeting the Sigma 2 receptor/TMEM97 to treat neuropathic pain

Poster No:
149b

Authors:
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Introduction:
Neuropathic pain is a major medical problem that is poorly treated with existing therapeutics. The Sigma 2 receptor was described pharmacologically more than 3 decades ago but its genetic identity was only recently identified as TMEM97. We and others have shown that TMEM97-binding compounds produce analgesia in mouse neuropathic pain models particularly spare nerve injury (SNI). We sought to understand this unique anti-neuropathic pain effect by addressing whether TMEM97-modulating compounds act selectively via the TMEM97 receptor.

Methods:
We generated global TMEM97-knockout (KO) mice and subjected them to spared nerve injury (SNI) in order to assess their susceptibility to developing neuropathic pain. We further treated both TMEM97KO and wild-type (WT) littermates with novel TMEM97 modulators, UKH-114, and FEM-1689, to ascertain the specificity of each compound.

Results:
Global TMEM97-KO demonstrated no aberrant phenotype and were otherwise comparable to wild-type (WT) littermates. Following SNI, male and female TMEM97KO and WT mice developed robust mechanical pain hypersensitivity. TMEM97KO animals presented with more pronounced pain responses than WT mice in the SNI model supporting the conclusion that positive modulators of TMEM97 would be desired as analgesics. As such, treating TMEM97KO and WT mice following SNI with a previously published TMEM97-binding compound, UKH-1114, and a novel TMEM97-binding compound, FEM-1689, reversed mechanical hypersensitivity in WT mice for at least 72 hours but had no effect in TMEM97KO littermates. This suggests that these compounds require the presence of Tmem97 to produce analgesia in neuropathic pain models. We also demonstrate that TMEM97 is expressed widely in human and mouse sensory neurons.

Conclusions:
Our results validate TMEM97 as a target for further development for the treatment of neuropathic pain.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support: This work was supported by Postdoctoral Fellowship Program of Natural Sciences and Engineering Research Council of Canada and by NIH grant NS0655926.

Keywords: Sigma 2 receptor, TMEM97, Pain, Drug discovery, Dorsal root ganglion
Gut microbiota as a therapeutic target to ameliorate neural injury in autoimmune neuropathy

Poster No:
150b

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Introduction:
Acute inflammatory demyelinating polyneuropathy (AIDP) and Chronic Inflammatory Demyelinating Polyradiculoneuropathies (CIDP) are part of a continuum of autoimmune inflammatory demyelinating neuropathies. Accumulating evidence suggests that there is a close relationship between altered intestinal microbiota and autoimmune diseases. Short chain fatty acids (SCFAs), one important class of metabolites derived from microbiota, are important signaling molecules that stabilize the gut epithelial barrier and modulate immunological responses. Abnormally decreased intestinal levels of SCFAs or SCFA-producing gut bacteria can be found in patients with certain autoimmune disorders. This application is focused on testing the hypothesis that gut dysbiosis, a pathological change in microbiota, could contribute to the pathogenesis or disease progression in AIDP and CIDP using the spontaneous autoimmune peripheral polyneuropathy (SAPP) model (B7-2-null NOD mice), an animal model that is pathologically similar to inflammatory demyelinating neuropathies.

Methods:
To determine the role of gut microbiome in the development of inflammatory neuropathy in the SAPP model, we will alter the gut microbiota in SAPP mice through fecal transplants. Further, the efficacy of a SCFAs-producing probiotic cocktail will be tested in SAPP mice.

Results:
Our preliminary data suggest that there are remarkable alterations in gut microbiome community and significant reduction of SCFAs in symptomatic SAPP mice compared to pre-symptomatic mice.

Conclusions:
We hypothesize that gut dysbiosis contributes to the immune-mediated peripheral nerve injury in SAPP model, and therapeutic interventions focused on reversing dysbiosis, such as SCFA-producing probiotic treatment, could ameliorate inflammation and its associated nerve injury. We believe the proposed study could provide a conceptual basis for exploring new translational therapeutic approaches targeting the gut microbiome to treat inflammatory neuropathies.

References:
No

References 1:

References 2:

References 3:

References 4:
**Grant Support:** GBS/CIDP Discovery Awards

**Keywords:** Inflammatory peripheral neuropathy, Microbiota, Short chain fatty acids, Spontaneous autoimmune peripheral polyneuropathy, Immune response
Balance Confidence in Individuals with Charcot-Marie-Tooth

Poster No:
151b

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Introduction:
Balance and function impairment is common in individuals with Charcot Marie Tooth disease (CMT). Many individuals with CMT use ankle foot orthoses (AFOs) on a daily basis to improve balance and function. The aim of this study was to evaluate the balance confidence, fall frequency, and perceived effect of AFOs on balance in individuals with CMT who use AFOs.

Methods:
A survey including the Activities Specific Balance Confidence Scale (ABC) and questions related to fall frequency and perceived effect of AFOs on balance was distributed to individuals with CMT via e-mail, through the Inherited Neuropathy Consortium Contact Registry.

Results:
306 individuals participated in this study. Participants reported decreased balance confidence across a range of activities, with highest confidence for level ground walking and standing tasks (>60%), markedly decreased confidence when walking on stairs, slopes or with external stimuli (40-55%), and poor confidence when walking on icy sidewalks, when bumped, or on unsteady surfaces (<40%). Many participants reported daily (14.1% of participants) or weekly (37.6% of participants) falls and 77.8% of participants indicated their AFOs improved their balance.

Conclusions:
Results from this study will help to focus future studies to refine AFO design and prescription to better improve balance, reduce falls, and meet the needs of individuals with CMT. Further, the results provide objective data that can be used in developing rehabilitative interventions and educating individuals with CMT on activities of greatest concern.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:
Keywords: CMT, AFO, ABC, Balance, ankle foot orthoses
Variation of Anterior Interosseous Nerve Syndrome: A case series

Poster No:
152b

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Introduction:
The anterior interosseous nerve (AIN) innervates three muscles in the forearm; the flexor pollicis longus (FPL), the flexor digitorum profundus (FDP), and the pronator quadratus (PQ). An isolated palsy of these muscles is known as AIN syndrome. Variations have been reported a few cases, who were involved pronator teres (PT). We reported two cases of AIN syndrome involved the PT and the flexor carpi radialis (FCR).

Methods:
Case 1: A 40-year-old male who could not flex his left interphalangeal (IP) joint of the thumb and the distal IP joint of the index finger after slipping-down injury and visited our hospital 7 months later. Manual muscle test of the thumb IP flexion and index finger distal IP flexion was grade 0. Muscle atrophy was detected on the left FCR muscle. Typical 'OK' sign was seen. Electrodiagnostic study was revealed as follows: 1) Normal compound muscle action potential (CMAP), sensory nerve action potential (SNAP) and normal latency in the left median, ulnar, and radial nerves, 2) Abnormal spontaneous activities (ASAs) at the left PQ, FCR, FPL, flexor digitorum superficialis, PT in the needle electromyography.

Results:
Case 2: A 37-year-old male who had weakness on his right thumb flexion after developing forearm pain 4 months ago. He had received unknown injection in his right elbow from local clinic, and the pain was improved without any improvement of the weakness. Muscle power of thumb flexion was grade 2. Muscle atrophy of right FCR was obvious. 'OK' sign was seen. Electrodiagnostic results were as follows: 1) Normal CMAP, SNAP and normal latency in the right median, ulnar and musculocutaneous nerves, 2) Decreased SNAP amplitude in the lateral antebrachial cutaneous nerve, 3) ASAs at right biceps brachii, FPL, FCR, PQ and PT muscles in the needle electromyography.

Conclusions:
We reported two cases with the AIN variation, which is rarely involved the FCR muscle.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** anterior interosseous nerve, nerve variation, FCR
Data sharing to close the diagnostic gap for inherited neuropathies on the GENESIS platform

Poster No:
153b

Authors:
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Introduction:
The enormous genetic heterogeneity of monogenic neurodegenerative diseases is causing challenges to diagnostics and treatment development. Despite over 90 genes linked to inherited neuropathies, fewer than 50% of patients with axonal forms receive a diagnosis in large gene panels or exomes. It is thus paramount to further study the genomes of these patients in order to identify the underlying alleles and genes. An example of recent success is the SORD gene neuropathy, which represents up to 10% of all patients with CMT2/dHMN phenotypes and was only recently discovered.

Methods:
To further enable a high pace of genetic studies and allow for better diagnosis we have created a software platform and database of variation in CMT and related disorders. This GENESIS platform is used by many active investigators in the field from all continents. With now nearly 16,000 exomes/genomes from rare neurodegenerative disorders, GENESIS presents one of the largest data aggregations in this area.

Results:
GENESIS has aided over 80 gene discoveries (27 in CMT), genetic matchmaking, and also rare variant burden analysis and modifier gene studies. Most importantly, GENESIS functions as a genomic data-sharing and archiving tool for the academic community. Users of the database have instant access to precomputed comprehensive annotations of all variants and can leverage cutting edge methods to study structural variation, non-coding variation, and tandem repeat expansions. New features include a machine learning score MAVERICK (see abstract Danzi et al), SpliceAI, fully synchronized ClinVar annotation, and more.

Conclusions:
We will present the latest research adoption of this unique, user friendly variant browser, new features, and opportunities for data sharing in the CMT field.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:
Keywords: Genetic Diagnosis, Genetic Variant Analysis, CMT, Data Sharing, Mendelian Inheritance
Plasma-based approach to prevent neuropathic pain development

Poster No:
154b

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Introduction:
Neuropathic pain is a condition that occurs when the somatosensory nervous system is affected due to lesions and dysfunction in central and peripheral nervous systems. Neuropathic pain manifests as a diverse combination of positive (allodynia, hyperalgesia) and negative (hypoesthesia) sensory symptoms. Patients with neuropathic pain are difficult to treat, and it is sometimes impossible to relieve the pain syndrome. Peripheral sensory neurons activate a pro-regenerative program after nerve injury to enable axon regeneration and functional recovery. In parallel to the changes in the activity of neuronal systems, non-neuronal cells, especially glial cells, are increasingly recognized as essential in the development and maintenance of neuropathic pain.

Methods:
In the present study, we focus on the impact of plasma fraction (PF) on the microglial state, regeneration and neuroinflammation in a model of pain in aged mice. We are using a Chronic Constriction Injury model (CCI) which induces many anatomical and neurochemical changes in sciatic nerve, DRG, spinal cord, and possibly in the CNS.

Results:
We previously demonstrated that a human plasma fraction (PF) reverses age-related decline of neurogenesis and neuroinflammation. As neuropathic pain has been shown to further exacerbate these mechanisms, PF may be beneficial to prevent downstream consequences. CCI injured mice are characterized by activated microglial state and a profound inflammatory response, in which the immune system interacts with the sensory nervous system contributing to persistent pain states. We explore the mechanism of neuropathy prevention by PF by assessing its effect on inflammation and enhanced recovery of the injured nerve via Schwann cells activation.

Conclusions:
Our studies are driving a comprehensive molecular understanding of this novel plasma fraction as a therapeutic.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** sciatic nerve, neuroinflammation, regeneration, Chronic Constriction Injury model, plasma fraction
Serum creatine but not neurofilament light is elevated in spinal muscular atrophy Jokela type

Poster No:
155b

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Introduction:
Spinal muscular atrophy Jokela type (SMAJ, MIM#615048) is an adult onset SMA characterized by muscle cramps and gradually progressive muscle atrophy. The cause of SMAJ is dominant p.G66V mutation in CHCHD10, which is also a disease gene for amyotrophic lateral sclerosis (ALS) and mitochondrial myopathy. CHCHD10 is a mitochondrial protein of unknown function. We performed targeted measurements of disease markers and unbiased metabolic screens to understand the systemic consequences of SMAJ and find potential biomarkers for the disease.

Methods:
We performed a chart review and collected blood samples from 49 individuals with SMAJ and gender- and age-matched controls without neurological disease. We measured serum creatine kinase (CK) and creatinine at clinical laboratory, neurofilament light (NFL) and glial fibrillary acidic protein (GFAP) with single molecule array (Simoa), and fibroblast growth factor 21 (FGF-21) and growth/differentiation factor 15 (GDF-15) by ELISA. We then performed an unbiased metabolomics screen using ultra-high performance liquid chromatography coupled to high-resolution mass spectrometry.

Results:
We confirmed that SMAJ elevated CK, more prominently in males. The level of axonal degeneration marker NFL was unchanged but astrogliosis marker GFAP was somewhat reduced. Metabolomics screen revealed six altered molecules including the mitochondrial metabolites succinate and pyruvate, although lactate and the mitochondrial integrated stress response (ISR) markers FGF-21 and GDF-15 were not changed. The level of creatine was elevated and showed correlation with clinical symptom severity.

Conclusions:
Our results highlight SMAJ as a motor neuronopathy with cramps and CK elevation. The absence of NFL elevation is a distinguishing factor from aggressive motor neuron diseases like ALS. Metabolic alterations were consistent with the mitochondrial origin of SMAJ, but pathogenesis differs from other mitochondrial diseases as the systemic markers of mitochondrial ISR activation did not change. Finally, elevation of creatine could suggest a role for muscle in disease pathogenesis. Future studies may evaluate creatine as a clinical biomarker.

References:
No

References 1:
Keywords: spinal muscular atrophy, hereditary neuropathy, biomarker, mitochondrial disease, CHCHD10
Hypogeusia as the sole initial symptom in facial onset sensory and motor neuronopathy

Poster No:
156b

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Introduction:
Facial onset sensory and motor neuronopathy (FOSMN) is a rare neurological disorder with only about 100 cases reported worldwide. Facial disturbances such as numbness and paresthesia are the most characteristic initial symptoms, followed by bulbar symptoms with facial muscle weakness and wasting. Clinical diagnosis and management of patients with FOSMN remain a challenge.

Methods:
Patient case was followed for 10 years. Neurological examinations were performed. Electrophysiological tests and muscle biopsy were performed.

Results:
A 64-year-old female presented with a 14-year history of dysgeusia as the primary complain. The patient experienced hypogeusia as the initial symptom at the age of 50. She could not percept sweet and salty, but had normal warm and cold sensations. Her symptoms persisted and slowly aggravated. At the age of 54, she started to have oral paresthesia. She could not feel the position, shape and texture of food in her mouth. Whereafter, the symptoms of weakness in chewing and salivation occurred. She also developed neck soreness, weakness in raising her head and left-hand numbness. Neurological examinations revealed that hypogeusia in the entire tongue and weakened bilateral pharyngeal and tendon reflexes. We observed bilateral pathological signs, no ataxia or dysautonomia. We followed this patient for 10 years and obtained several electrophysiological follow-up results: blink reflex was not elicited from normal to bilateral R1; bilateral R2 latency was prolonged; the amplitude of sensory nerve action potential (SNAP) of both upper limbs was decreased. Muscle biopsy (left biceps) showed signs of neurogenic related damage. We diagnosed her as having FOSMN with the sole initial symptom of dysgeusia.

Conclusions:
Our report indicates that FOSMN could present with hypogeusia as the sole initial symptom. Moreover, our electrophysiological data and neurogenic related muscle damage suggest that this FOSMN case may be a variant of ALS.

References:
Yes

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: Facial onset sensory and motor neuronopathy, Hypogeusia, amyotrophic lateral sclerosis
A double-blind, placebo controlled trial of IVIG in Patient with Small Fiber Neuropathy Associated with Autoantibodies to TS-HDS and FGFR3

Poster No:
157b

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Institutions:
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Introduction:
Small fiber neuropathies (SFN) have many potential causes but >50% remain idiopathic. Two autoantibodies, TS-HDS and FGFR-3, are associated with ~20% of idiopathic SFN cases with reports touting IVIG for treatment of presumed autoimmune SFN. The objective of this study was to determine the efficacy of IVIG on nerve fiber density, pain and examination scores in a double blind placebo controlled pilot study of patients with SFN associated with TS-HDS and FGFR3.

Methods:
Twenty subjects with SFN confirmed by history, examination and skin biopsy with elevated autoantibodies to TS-HDS and/or FGFR3 received either IVIG (or blinded placebo) dosed at 2 grams/kg followed by 1 gram/kg every 3 weeks for a total of 6 treatments. All subjects had detailed small fiber examinations (UENS), questionnaires and skin biopsies taken from adjacent sites at the distal leg. Skin biopsies were stained for PGP9.5 and intra-epidermal nerve fiber density (IENFD) reported. Final follow up occurred 3 weeks after the final treatment (24 weeks).

Results:
Twenty subjects were enrolled; 18 completed treatment (9 IVIG, 9 placebo completers - 2 did not have final data due to COVID-19). Over 24 weeks the change in pain scores (11 point VAS scale) was -0.88±0.99 in the placebo group, and -0.56±2.8 in the IVIG group (P=NS), the UENS neuropathy score improved by 3.8±8.8 in the placebo group and improved by 3.7±4.1 in the IVIG group (P=NS). Skin biopsy IENFD improved by 1.24±1.79 fibers/mm in the placebo group and improved by 0.81±1.67 fibers/mm in the IVIG treated group (P=NS).

Conclusions:
This small double blind placebo controlled trial showed no difference between IVIG and placebo in any measurable outcome and does not support the use of IVIG for SFN associated with autoantibodies to TS-HDS and/or FGFR3.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

**Keywords:** Small fiber neuropathy, IVIG, Immune mediated, TS-HDS, FGFR3
Topiramate as a Disease Modifying Therapy for Cryptogenic Sensory Peripheral Neuropathy (CSPN): a NeuroNEXT Trial

**Poster No:**
158b

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**Institutions:**
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**Introduction:**
CSPN is highly prevalent yet there are no FDA approved treatments. Obesity and metabolic syndrome increase risk. Lifestyle approaches may be effective but are often unsustainable. Topiramate (TPM) causes weight loss and improves insulin sensitivity even at low doses.

**Methods:**
TopCSPN was a 96-week phase 2 trial performed by NeuroNEXT. The objective was to determine if TPM slows progression of CSPN associated with metabolic syndrome. Distal thigh intraepidermal nerve fiber density (IENFD) and Norfolk Quality of Life Diabetic Neuropathy (NQOL-DN) were co-primary outcomes. A positive result was predefined as efficacy in one and non-inferiority in the other. Secondary outcomes included the Brief Pain Inventory Diabetic Neuropathy, the Utah Early Neuropathy Scale, and nerve conduction studies.

**Results:**
211 participants were screened and 132 randomized, 66 in each group. 59 in each group completed 96 weeks of follow up. 10 TPM patients (15%) discontinued treatment due to an adverse event by 16 weeks (9 due to cognitive complaints) compared to 2 (3%) in the placebo group (p=0.03). There was no significant difference in change versus placebo for IENFD or NQOL-DN in the intent to treat population (both met non-inferiority criteria). In the per-protocol population (defined by one compliant post-baseline serum TPM level without a major protocol deviation) change in NQOL DN (-3.69) was superior but IENFD was non-inferior (TPM group had 0.56 fibers/mm less decline). There was no difference in change in the BPN-DPN or UENS. BMI declined 1.02 kg/m2 in the TPM compared to -0.18 in the placebo group (p=0.004) at 52 weeks. By 96 weeks there was no difference (-0.29 vs. -0.15).

**Conclusions:**
Although the primary ITT analysis did not meet the criteria for a positive study, these findings suggest that when tolerated TPM may improve neuropathy-specific quality of life. TPM results in only transient weight loss, suggesting alternative mechanisms may be relevant.

**References:**
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: cryptogenic neuropathy, metabolic syndrome, topiramate
A Model For Therapeutic Screening Of Chemotherapy-Induced Peripheral Neuropathy Using A Nerve-on-a-Chip Microphysiological System

Poster No:
159b

Authors:
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Introduction:
Organs-on-Chip mimicking in vivo physiology can identify neuroprotection and neuroregeneration following drug exposure without relying on animal models. Toxicity is a leading reason drugs are withdrawn from the market, with neurotoxicity responsible for 16%. Peripheral nerves are particularly susceptible to off-target effects resulting in permanent sensory-motor deficits, and chemotherapy induced peripheral neuropathy (CIPN) occurs with a 68% incidence rate and 30% retaining effects after 6 months. CIPN can also affect clinical outcomes, with 91% of cases leading to dose reduction and a 45% discontinuation rate. Increasingly, therapeutic development is focusing on mitigation or recovery for peripheral neuropathies. We designed a biomimetic nerve-on-a-chip construct with axon growth analogous to mature nerve anatomy and the first 3D in vitro platform to collect electrophysiological and histomorphological metrics, gold standard methods for in vivo neuropathophysiology.

Methods:
Here, we cultured embryonic rat dorsal root ganglia in a hydrogel construct to screen for nerve dysfunction in CIPN. After 28 days of growth in vitro, myelinated nerve-on-a-chip constructs were exposed to bortezomib, oxaliplatin, paclitaxel, or vincristine for 7 days. Then, axons were electrically stimulated to elicit compound action potentials, used to assess nerve conduction velocity (NCV) and peak amplitude (AMP), which are clinically analogous metrics. Histological analysis and cell viability assays were also performed to observe underlying mechanistic changes in the tissue.

Results:
All chemotherapeutics showed a concentration-dependent decrease in NCV and AMP. Histopathology revealed hallmarks of peripheral neuropathy, including decreases in myelinated fiber density and increased degenerated fibers. IC50 values indicate significant decreases in electrical function occurred before decreased viability. Data suggest that electrophysiology collected from our platform tracks pathological changes in nerve function, with distinction between electrical deficits and general cytotoxicity. The ability to collect clinically relevant data is an effective tool for in vitro modeling of CIPN towards screening of therapeutics for neuroprotection and neuroregeneration.

Conclusions:
Our Nerve-on-a-Chip results suggest that electrophysiology recordings can closely track subtle pathological changes in nerve function, with distinction between electrical functional deficits, histological pathologies, and general cytotoxicity. Our platform is unique in that it provides characteristic output metrics of both in vitro and in vivo studies, and the ability to collect clinically relevant data suggests it can be an effective tool for in vitro preclinical screening of therapeutics for chemotherapy induced peripheral neuropathy.
Clinical performance of different testing platforms for detection of acetylcholine-receptor and muscle-specific kinase antibodies in myasthenia gravis

Poster No:
160b

Authors:
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Institutions:
¹BC Neuroimmunology labs, Vancouver, Canada, ²Department of Medicine, University of British Columbia, Vancouver, Vancouver, Canada

Introduction:
Acquired myasthenia gravis (MG) has an autoimmune nature targeting acetylcholine receptor (AChR). AChR antibodies (Abs) are detected in approximately 50% of ocular and 85% of generalized MG. Moreover, 1–10% of MG cases have Ab-against muscle-specific tyrosine kinase (MuSK). The diagnostic evaluation of clinical MG is performed by serologic testing including radioimmunoprecipitation assay (RIPA)/ Radio receptor assay (RRA), ELISA and cell-based assays (CBA) however, the test sensitivity and specificity has been an issue, so we clinically validated in-house live CBA and compared the results with commercial RIPA/RRA and ELISA for anti-AChR and MuSK Abs detection.

Methods:
50 AChR and 50 MuSK Ab positive patients' serum with definite MG and 50 healthy individuals were selected. Samples were run in duplicate for detection of AChR Abs by commercial IBL/RRA, EUROIMMUN ELISA assays and AChR CBA (BC Neuroimmunology Lab developed/Oxford University). For detection of MuSK Ab samples were analysed blindly and in duplicate by BC Neuroimmunology Lab developed RIPA, commercial IBL ELISA and MuSK live CBA (BC Neuroimmunology Lab developed/Oxford University). All samples were analyzed by 3 scorers blinded.

Results:
The sensitivity and specificity of AChR CBA (100%) was higher than ELISA and RRA. Although, the specificity of AChR RRA assay was higher than AChR Ab detection by ELISA, but sensitivity was much lower. Both MuSK CBA and MuSK ELISA had the same sensitivity, and specificity in detecting anti MuSK Abs.

Conclusions:
The in-house AChR CBA showed significantly better accuracy. The commercial RRA is a specific assay, however, lacks sensitivity to AChRAbs. Ach RAb ELISA had less sensitivity than RIPA. For MuSK Ab assays, both in-house CBA and the commercial IBL ELISA have unacceptable low sensitivity. Although every sample was very well defined clinically and analytically, the power in this study was limited by the low number of samples tested.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: myasthenia gravis, acetylcholine receptor, muscle-specific tyrosine kinase, Cell based assay, neuroimmunology
Detection of Nodal and paranodal autoantibodies in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Poster No:
161b

Authors:
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Institutions:
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Introduction:
CIDP is the most common form of treatable chronic inflammatory neuropathy (CIN). Over the past few years, antibodies targeting proteins at paranodal cell-adhesion molecule such as contactin-1 (CNTN1), neurofascin-155 (NF155), contactin-associated protein 1 (CASPR1), and nodal neurofascins-NF140 and NF186, have been discovered in CIDP patients. The identification of these autoantibodies has potentially significant clinical implications especially in the management of CIDP patients with poor response to IVIg. Here we discuss a highly specific and sensitive fixed cell-based assay (CBA) method for the accurate and efficient measurement of nodal and antibodies in CIDP patients and clinical correlation of seropositive cases.

Methods:
Between August 2021 and January 2022, at BC Neuroimmunology laboratory, Vancouver we have screened a total of 120 sera of patients for detecting nodal and paranodal antibodies with a fixed CBA. These patient sera were assayed for the presence of NF140, NF155, NF186, CNTN1, and Caspr1 antibodies. The final diagnosis and response to therapy of twenty cases were evaluated by a questioner requested from their physicians.

Results:
Of 120 sera screened, 20 cases evaluated clinically in depth. Of the 20, 7 cases were positive for CIDP nodal and paranodal antibodies CBA. The mean age of positive cases was 53 years. The final clinical diagnosis of 3/7 positive patients were clinical CIDP. All the seropositive patients had good response to IVIg and Rituximab treatment. The final diagnosis of 13 seronegative cases, 3 were not CIDP, and one case had diabetic neuropathy with atypical CIDP and the diagnosis of the rest was not determined.

Conclusions:
We identified a subgroup of 7 patients with CIDP nodal and paranodal antibodies with better response to IVIg and rituximab therapy. In addition, the CBA was found a highly accurate method for detecting CIDP autoantibodies with better clinical diagnosis and management of CIDP patients.

References:
Yes

References 1:
Luis Querol et. al. Antibodies against peripheral nerve antigens in chronic inflammatory demyelinating polyradiculoneuropathy, Scientific Reports volume 7, Article number: 14411 (2017)

References 2:
References 3:

References 4:

Grant Support:

**Keywords:** Nodal autoantibodies, Paranodal autoantibodies, Chronic inflammatory demyelinating polyradiculoneuropathy (CIPD), Cell based assay CBA
Circulating Sorbitol Levels Correlate with Severity of Disease in Patients with Sorbitol Dehydrogenase (SORD) Deficiency

Poster No:
162b

Authors:
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Institutions:
¹Applied Therapeutics, New York, United States, ²Applied Therapeutics, New York, NY

Introduction:
Sorbitol Dehydrogenase Deficiency (SORD Deficiency) is a hereditary neuropathy affecting approximately 3,000 patients in the US, and 4,000 patients in Europe. Patients with SORD Deficiency are unable to process sorbitol, leading to accumulation of this toxic metabolite in blood and tissues. In vitro and in vivo studies have recently demonstrated that treatment with AT-007, a potent, selective and CNS penetrant inhibitor of aldose reductase prevents accumulation of sorbitol in a SORD deficient animal model of disease and in cultured human fibroblasts from SORD Deficiency patients.

Methods:
The present qualitative report investigates the relationship between circulating blood sorbitol levels and the severity of disease in a cross-sectional cohort of patients who were diagnosed with SORD Deficiency. The study cohort was comprised of 8 patients (4F, 4M) mean age 31.9 (19-54). All 8 patients carried the same SORD genotype (representing the most common SORD mutation), resulting in absence of any detectable SORD enzyme activity. Sorbitol was measured by a validated LC-MS-MS assay.

Results:
While all patients showed elevated sorbitol levels, the degree of excess sorbitol varied from approximately 25,000 ng/ml to greater than 45,000 ng/ml. Similarly, the clinical manifestation of the disease was significantly different among this group of patients. The present analysis suggests that within groups of subjects of a similar age, a higher level of sorbitol is associated with greater severity of disease and a faster disease progression. Higher level of sorbitol is associated with greater lower limb deficits (need to wear leg braces) and eventual loss of mobility and ambulation deficit, more significant balance problems, and upper limb neuropathy and tremor.

Conclusions:
In summary, SORD Deficiency is a severe and progressive neuropathy caused by abnormally elevated levels of sorbitol. An ongoing placebo-controlled Phase 2/3 study is evaluating the effect of AT-007 on clinical outcomes in SORD Deficient patients.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: SORD Deficiency, Sorbitol, Hereditary Neuropathy, Charcot Marie-Tooth Type 2, Aldose Reductase Inhibitors
Inter-laboratory validation of nodal/paranodal antibody testing

Poster No:
163b

Authors:
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Institutions:
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Introduction:
Accurate detection of antibodies directed against cell-adhesion molecules of the node/paranode of Ranvier is crucial for the diagnosis of autoimmune nodopathies. The performance characteristics of different diagnostic assays are currently unknown. We aimed to assess inter-laboratory variability and to establish reference laboratories and testing standards to facilitate the harmonisation and consistency of further test centres.

Methods:
Four European testing centres participated. Each submitted 30-50 serum samples, along with their initial, unblinded results, to an independent co-ordinating centre. Samples were pre-classified into 3 groups; seropositive autoimmune nodopathies, seronegative inflammatory neuropathies, and unrelated disease/healthy controls. The co-ordinating centre then recoded all samples and returned them to the testing centres for analysis according to their established local methods. A protocol for the evaluation of the re-submitted results was agreed in advance. Accuracy calculations were based on an estimated seropositivity rate in the usual test population of 7.5%.

Results:
There was a high level of agreement in the overall results returned (positive or negative), with complete concordance for 142/159 (89.3%) of samples. Overall sensitivity ranged from 80% to 87.3%, and specificity from 98.3% to 100%, with accuracy between 96.9% and 99%. Testing approaches varied. Some labs used a single assay and others performed additional confirmatory tests either routinely or for only a subset of samples. Live cell-based assay (CBA) was the most accurate (98.8% to 99.2%), closely followed by other CBAs (96.6% to 98.8%) and ELISA (90.6% to 98.7%). Immunohistochemistry with teased nerve fibres was performed for a subset of samples, and judged as positive in 7/19 patients with seropositive autoimmune nodopathies and 1/6 controls. Absolute end-point titre ranges varied between centres and across different antigens, but relative titres were strongly correlated for contactin-1/Caspr1 antibodies and moderately correlated for neurofascin-155 antibodies. There was greater inter-laboratory variability in IgG4 detection.

Conclusions:
Cell-based assays and ELISA are accurate methods to detect nodal/paranodal antibodies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

**Keywords:** antibody, inflammatory neuropathy, node of Raniver, autoimmune nodopathy
Patient-Reported Symptom Burden Of Charcot-Marie-Tooth Disease Type 1A (CMT1A): Findings From A Real-World Digital Study

Poster No:
166b

Authors:
Florian Thomas¹, Teresa Sevilla², Rafael Sivera³, Filippo Genovese⁴, Amy Gray⁵, Simon Bull⁶, Xavier Paoli⁷, Thomas Senechal⁷, Laura Day⁸, Samuel Llewellyn⁸, Mark Larkin⁸, Youcef Boutalbi⁷

Institutions:
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Introduction:
This analysis aimed to examine patient-reported symptom burden for Charcot-Marie-Tooth disease type 1A (CMT1A) in European and US real-world practice.

Methods:
Adults with CMT1A were recruited to an ongoing international observational study exploring the real-world impact of CMT. Data were collected via CMT&Me, a bespoke digital app developed for this study, through which participants were asked questions via patient-reported outcome measures. This interim analysis examined participants (n=937) from France, Germany, Italy, Spain, the UK and the US.

Results:
The CMT1A symptoms ranked with highest importance by participants (n=826 patients who responded to this question) were weakness in hands and fingers (most important, 32%), difficulty walking (15.5%), weakness in the feet (13.0%), fatigue (8.7%), weakness in the legs (5.7%), and problems with balance (sixth most important, 4.2%). The majority of participants reported the severity of their symptoms to be moderate (58.5%, n=400/684) or severe (24.4%, n=167/684), with almost half of participants (48%, n=310/662) experiencing a worsening of CMT1A symptom severity from initial diagnosis. Anxiety and depression were each reported by over a third of participants (39.3%, n=247/628 and 37.9%, n=238/628 respectively), higher than the prevalence in the general global population. There was a high recorded use of rehabilitative interventions (of 445 respondents, 86.5% reported using physical therapy), medications (of 404 respondents, 72.5% reported using painkillers), and orthotics/walking aids (of 477 respondents, 48.6% reported using off-the-shelf insoles). There was a similar reported use of these across all countries.

Conclusions:
Patients with CMT1A experience a high level of symptom burden, aligned with clinical observations and literature describing a wide variety of symptoms. Patient first suffer in using limbs, fatigue, pain symptoms, and depression, conducing to impairment to quality of life. It is apparent that there remains a high unmet need in CMT1A caused by the burden on patients.

References:
No

References 1:
Keywords: Charcot-Marie-Tooth disease, Symptom burden
E-Posters
Topical treatments for neuropathic pain: survey of real-world patient experience from a peripheral nerve clinic

Poster No: 1e

Authors: Ahmed Abbas\textsuperscript{1}, Robert Hadden\textsuperscript{1}

Institutions: \textsuperscript{1}King's College Hospital, London, United Kingdom

Introduction: Peripheral neuropathic pain is common, with many diverse etiologies. Oral treatments for neuropathic pain are often ineffective or cause unacceptable systemic side effects. Topical treatments for neuropathic pain are generally better tolerated, but many are unlicensed and lack high quality evidence of efficacy. Most clinicians are unfamiliar with the very wide range of products available without prescription, and data is lacking to guide the choice.

Methods: We designed a web-based survey and invited 172 patients with painful neuropathy to respond anonymously. Subjects were identified by searching for keywords capsaicin OR menthol OR lidocaine, in clinical letters on patients who had attended our specialist neuropathy clinic between 2019-2021. Patients with painful neuropathy of any cause were included, small or large fibre. We defined 'topical treatment' as anything applied to the skin for treating neuropathic pain or dysaesthesia in that part of the body. Our questions encompassed creams, gels, sprays or patches with various active ingredients including capsaicin, menthol, local anesthetics, non-steroidal anti-inflammatories and others. We also included mechanical topical devices such as heating/cooling socks/gloves or transcutaneous electrical stimulators. We asked about the quality of neuropathic pain symptoms, as derived from Neuropathic Pain Symptom Inventory and Douleur Neuropathique 4 (DN4) questionnaires, including burning, freezing, squeezing, pressure, electric shocks, stabbing; pain worsened by brushing, pressure or cold; pain associated with numbness, pins and needles, tingling or itching. For each treatment we asked which of these symptoms it benefited most, as well as general benefit, side effects, and if the patient is still using it. We asked about concomitant painful conditions including fibromyalgia, and any oral treatments for neuropathic pain.

Results: Results will be presented at the PNS meeting.

Conclusions: This survey will provide real-world data about which topical treatments patients feel most benefit their symptoms.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Pain, Neuropathic, Topical, Small-fibre, Skin
Usefulness and pitfalls of combined Muscle and Nerve Biopsy in Neuropathy Cases

Poster No: 2e

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Institutions: 1Ottawa University, Ottawa, Canada, 2Montreal Neurological Institute, Montreal, Canada

Introduction: Nerve biopsies are performed in the diagnostic evaluation of neuropathies, mainly when inflammatory or infiltrative pathology is suspected. A concurrent adjacent muscle biopsy can increase the diagnostic yield in cases of vasculitic or amyloid neuropathy. However, multiple reports have demonstrated conflicting findings between the muscle and nerve pathologies, complicating final diagnosis.

Methods: We performed a retrospective review of combined muscle and nerve biopsies evaluated at the Montreal Neurological Hospital in 2014-2021. The clinical characteristics and pathological results were collected though medical charts.

Results: Forty-two cases were identified. 36 (86%) muscle biopsies were compatible with a neuropathic process. Five (12%) had myopathic changes on the muscle biopsy and one (2%) had non-diagnostic muscle tissue. 4/5 patients had no myopathic changes on EMG nor clinical suspicion for superimposed myopathy after detailed evaluation. 1/5 had necrotizing myopathy possibly related to polyoma virus and a longer-standing axonal neuropathy. 2/5 patients had TDP-43 inclusions, with severe axonal loss on the nerve biopsy. 1/5 had necrotizing myopathy, and axonal neuropathy confirmed genetically to be inherited. 1/5 patient had abundant whorled fibers on muscle biopsy but was diagnosed with MGUS-associated polyneuropathy. Nine patients were diagnosed with vasculitic neuropathy. 2/9 (22%) had inflammatory changes in the muscle biopsy only, 5/9 had changes in the nerve only, 1/9 had changes in both and 1/9 had no changes in either but was diagnosed clinically.

Conclusions: Concurrent muscle and nerve biopsies during evaluation of neuropathic disorders can improve diagnostic yield in suspected vasculitis. Unexpected myopathic findings are often seen in neurogenic disorders.

References: Yes


References 3:

References 4:

Grant Support:

Keywords: Nerve biopsy, Vasculitis
POEMS Syndrome: Clinical and Laboratory features from a Brazilian cohort

Poster No:
3e

Authors:
Trajano Gonçalves¹, manoella bueno², Camila Donadel², Fernando Henrique Alves³, João Marcus de Lima Brito Alves⁴, Jose Rosemberg Lima Filho⁶, Renan Melo⁴, Pedro Manoel Garibaldi⁴, André José dos Santos³, Caroline Moreira⁶, Osvaldo José do Nascimento⁷, Pedro Tomaselli⁸, Wilson Marques Jr⁹

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Introduction:
Polyneuropathy, organomegaly, endocrinopathy, Monoclonal-protein and skin changes (POEMS) is a rare paraneoplastic syndrome, whose diagnosis can be late, especially in areas with few specialists in the field. In this study we sought to describe clinical, laboratory and electrophysiological characteristic found in 19 patients diagnosed in a Brazilian referral centre.

Methods:
POEMS diagnosis was based according to current diagnostic criteria. Clinical data was retrospectively collected.

Results:
Fourteen out of 19 patients were male (73.7%). The mean age at onset was 48,6 years old (range 38 to 66) and the mean time for diagnosis was 13,7 months (range 5 to 48) and 9 month median. Nerve conduction studies from all patients revealed a sensory-motor demyelinating neuropathy. Six patients underwent nerve biopsy, and none had inflammatory infiltrate. Papilledema was present in 7 patients (36.8%). All cases had albuminocytological dissociation. A lambda monoclonal component was detected in serum from all cases, but clonal plasma cells on bone marrow biopsy were found in only 8 cases. Bone lesions was found in 18 cases (94,7%). Sixteen (84%) had typical skin changes. Endocrinopathy was present in 18 cases (89,9%), lymphadenomegaly in 6 (31,5%), splenomegaly in 9 (47%), hepatomegaly in 6 (31,5%) and thrombocytosis in 13 (68,4%), respectively. Two cases had Castleman's disease.

Conclusions:
POEMS syndrome is a rare condition. Our data suggest that the prevalence of endocrinopathy and bone lesions in our cohort were more frequently found than expected, and may be related to a longer time of disease duration leading to more severe disease.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: POEMS syndrome, cidp, paraneoplastic syndrome, demyelinating neuropathy
Integrating Sensory Neurons with Keratinocytes to Model Painful Diabetic Neuropathy on a Chip.

Poster No: 4e

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Institutions: 1Northwestern University, Feinberg School of Medicine, Chicago, IL

Introduction: Painful diabetic neuropathy (PDN) is one of the most common and intractable complications of diabetes. PDN is characterized by small-fiber degeneration and neuropathic pain. Uncovering the mechanisms underlying neurodegeneration in PDN remains a major challenge to finding effective and disease-modifying therapy. Keratinocytes are closely juxtaposed to cutaneous nerve terminals potentially enabling communication between keratinocytes and cutaneous afferents. The aim of this study is to explore mechanisms by which keratinocytes communicate with cutaneous afferents and how this communication impacts the DRG neuron axonal degeneration underlying neuropathic pain in PDN.

Methods: We have established a Xona microfluidic co-culture device to compartmentalize murine DRG neurons and keratinocytes to model the skin in vitro and investigated the effects of activated K14 keratinocytes on DRG neurite outgrowth and neuron excitability.

Results: We found that co-cultured DRG neurites grew towards keratinocytes within 7 days. Additionally, we found that once the neurites grew in the microchannels, they are unable to turn back and continue to grow into the adjacent compartment, where they form connections with cultured keratinocytes. Using electrophysiological and calcium images studies on these microfluidic devices we revealed a dynamic interplay between the neuronal activity and keratinocytes. For example, we have used this system to test the effects on DRG neurons neurite outgrowth and excitability upon application different stimuli including class III semaphorins and chemokines (neutrophil chemo-attractant genes such as CXCL10), known to be secreted by keratinocytes. More recently, we have used this platform to study interaction between human iPSCs derived DRG neurons and human keratinocytes.

Conclusions: This platform can be used to explore mechanisms by which keratinocytes communicate with cutaneous afferents and how this communication impacts the DRG neuron axonal degeneration underlying neuropathic pain in PDN.

References: No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: keratinocyte, painful diabetic neuropathy, sensory neurons, degeneration, plasticity
Acute-onset Chronic Inflammatory Demyelinating Polyradiculoneuropathy after Ad26.COV2.S COVID-19 Vaccination

Poster No:
5e

Authors:
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Institutions:
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Introduction:
Guillain-Barré syndrome (GBS) has been reported after coronavirus disease 2019 (COVID-19) vaccination. To our knowledge, only one case of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) after COVID-19 vaccination has been reported in the literature so far. We describe a patient who developed acute-onset CIDP after Ad26.COV2.S (Johnson & Johnson) vaccination with acute onset facial diplegia and progressive quadripareisis past eight weeks.

Methods:
A 67-year-old man presented with one-week history of progressive left facial droop, unsteady gait, slurred speech, double vision, and patchy numbness; he reported Ad26.COV2.S vaccination three weeks before presentation. On initial examination, he had left facial palsy, partial left abducens nerve palsy, generalized areflexia, severe lower extremities ataxia, and diminished vibratory sensation in toes. Cerebrospinal fluid analysis showed albuminocytologic dissociation. He received intravenous immunoglobulin (IVIG) for five days for presumptive diagnosis of GBS. Electrodiagnostic studies demonstrated impersistent F-waves, decreased recruitment in lower extremities, and bilaterally absent blink reflexes. He developed right facial weakness on day three and asymmetric appendicular muscle weakness on day five of treatment.

Results:
Seven weeks after symptom onset, the weakness in his lower extremities worsened, and received a second cycle of IVIG. The lower extremity weakness did not improve but remained stable until seventeen weeks after symptom onset when he returned with progressive upper extremities weakness and shortness of breath. Electrodiagnostic studies demonstrated demyelinating features consistent with CIDP(1). Neuromuscular ultrasound demonstrated multifocal median nerve enlargements at non-entrapment sites. At this point, given the clinical course, electrodiagnostic and ultrasonographic findings, he was diagnosed with CIDP.

Conclusions:
This patient's acute-onset CIDP and other reported GBS cases after adenoviral vector COVID-19 vaccinations shared similar and atypical presenting symptoms, which were not seen in GBS after mRNA COVID-19 vaccinations(2,3). While a causal relationship cannot be established to his COVID-19 vaccination, this case adds to the evolving literature of COVID-19 vaccination-associated neurological events.

References:
Yes

References 1:
References 2:

References 3:

References 4:

Grant Support:

Keywords: COVID 19 Vaccination, Adenoviral vector vaccination, Chronic Inflammatory Demyelinating Polyradiculoneuropathy
Validation of the CMT-FOM: Baseline data from the Accelerate Clinical Trials in Charcot-Marie-Tooth Disease (ACT-CMT) Study

Poster No:
6e

Authors:
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Institutions:
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Introduction:
To ensure clinical trial readiness in CMT well characterized clinical cohorts and clinically responsive outcome measures are required. The CMTPedS and CMTInfS are responsive and reliable measures of functional disability from birth to 20 years of age. The Charcot-Marie-Tooth Functional Outcome Measure (CMT-FOM) is a clinical outcome assessment developed to address the gap in measurement of disease severity and physical performance in adults with CMT. Aim 1 of the ACT-CMT study is to validate the CMT-FOM for use in multi-site CMT1A trials, yielding a primary outcome for labelling of therapeutics that aim to slow functional decline or improve patient function.

Methods:
Five international sites recruited and enrolled participants aged 18-75 years with CMT1A. The 13-item CMT-FOM was administered in a sequence by carefully trained clinical evaluators. Concurrently, the CMT Exam Score- Rasch (CMTES-R), Overall Neuropathy Limitations Scale (ONLS), CMT-Health Index (CMT-HI), as well as electrophysiologic measures, MRI and Meissner corpuscle biomarkers were administered as part of the broader study.

Results:
To validate the CMT-FOM a total of 214 individuals with CMT1A were enrolled. The participants are 58% female with a mean age of 44 + 14.9; (range 18-75). To measure performance on the 13 CMT-FOM items, raw scores were converted to z-scores based on age and gender matched normative reference values collected mostly from the 1000 Norms project and published data. The mean CMT-FOM total score (range 0-52) was M 24 + 9.8; (range 4-48). The CMT-FOM demonstrated good internal consistency (α = 0.85) for the 13-item scale and adequate convergent validity with CMT-FOM total score and the CMTES-R (p=0.63; p=0.001).

Conclusions:
Recruitment for the validation of the CMT-FOM was completed. The next steps are item-level analysis including RASCH analysis. Validation of the CMT-FOM will complete whole of life measurement of functional performance and disease severity in CMT1A.
References:  
No

References 1:  

References 2:  

References 3:  

References 4:  

Grant Support: Supported by NIH grant # NIH 1 U01 NS109403-03 to DNH  

Keywords: Clinmetrics, Clinical Outcome Assessment, Measurement
Unveiling the microvascular network alterations in the central and peripheral nervous system of rats exposed to neurotoxic chemotherapy

Poster No:
8e

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Introduction:
Neurotoxicity is a disabling adverse effect of chemotherapy. Symptoms are typical of a sensory peripheral neuropathy, including paraesthesia, disaesthesia, sensory ataxia, tingling and numbness. Patients can develop allodynia and hyperalgesia, experiencing neuropathic pain. Preliminary evidence in other pain models showed an abundant microvascular angiogenesis in the central somatosensory pathway. In order to elucidate the relation between chemotherapy-induced neuropathic pain and vascular alterations, we evaluated the microvasculature in central and peripheral nervous compartments of rats exposed to neurotoxic chemotherapy (paclitaxel, PTX or cisplatin, CDDP).

Methods:
We employed 48 rats: 12 were treated with PTX 10 mg/kg once a week for 4 weeks, 12 with CDDP 2mg/kg twice a week for 4 weeks and 24 were exposed to only vehicles and used as internal controls. Animals were tested for neurophysiological abnormalities and pain before and after the treatments. Post-mortem samples were analyzed at synchrotron radiation resources by X-ray Phase-Contrast Tomography (XPCT) Imaging and processed for quantitative and morphological analyses of microvascular structures. Complementarily, histochemical evaluations were performed to validate the results.

Results:
PTX and CDDP rats developed a painful sensory axonopathy and a painless mild sensory neuronopathy, respectively. A significant increased number of microvessels (<15 micron) was found in central and peripheral samples from PTX animals, suggesting an angiogenesis at the capillary level in a painful condition. PTX samples showed a significant decrement of the number of branch points and the tortuosity, factors showed to compromise normal microcirculation and neuronal activity. These events were confirmed by the positivity to vessel neogenesis to tomato lectin staining. Similar analyses were conducted on CDDP animals: a preliminary analysis is showing remarkable differences to be further confirmed.

Conclusions:
Evidence of vascular neo-ogenesis at capillary level was found in rats with pain symptoms derived from chemotherapy, shedding light on new pathogenetic mechanisms and potential novel therapeutic approaches for painful CIPN.

References:
No
References 1:

References 2:

References 3:

References 4:

Grant Support:

**Keywords:** neuropathic pain, microvascularization, X-Ray Phase-Contrast Tomography, chemotherapy, neurotoxicity
A new familial ATTR mutation with large phenotypic spectrum: first results of treatment

Poster No:
9e

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Introduction:
Transthyretin-related amyloidosis (ATTR) are systemic amyloidose caused by mutations in TTR (Transthyretin gene). The transmission of this disease is autosomal dominant. To date, about 200 TTR mutations have been described and most of them are associated with either neuropathy or cardiomyopathy. If not treated, this disease could be fatal around 10 years after the first symptoms.

Methods:
A 67-years-old patient presented with peripheral neuropathy (Patient A). Peripheral blood was collected into EDTA tubes after informed consent was obtained. DNA extraction was performed using standard methods. PCRs were performed to amplify the four TTR exons with a padding of 15 nucleotides and sequenced by Sanger sequencing. Additional five family members have been also tested. Patient A started a treatment using RNAi therapeutics.

Results:
A new mutation in TTR exon 3 has been identified in Patient A. This mutation is a missense mutation never reported as familial ATTR mutation. Among the five additional family members tested recently, three presented the mutation associated with either peripheral neuropathy symptoms or cardiac symptoms. Patient A started RNAi therapeutics few months ago. The evaluation of this treatment on this new mutation will be presented.

Conclusions:
New mutations involved in ATTR are still discovered nowadays. For some of them, different phenotypes can be observed in members of the same family. Whatever the symptoms, it seems that RNAi therapeutics could be a good strategy to treat the patients.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:
Keywords: Amyloidosis, ATTR, TTR
The diagnostic value of magnetic resonance imaging in chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review and meta-analysis

Poster No: 10e

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Introduction: The diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is still difficult. Magnetic resonance imaging (MRI) can reflect the characteristics of the pathophysiological process in CIDP patients. The current diagnostic value of MRI in CIDP patients is limiting. It is important to compare various MRI parameters in the diagnosis of CIDP and to determine the best performing one.

Methods: Through literature searches in the PubMed, Embase and Cochrane databases from September 1988 to October 19, 2021, we determined the sensitivities and specificities of quantitative MRI parameters. A single-arm meta-analysis of the rate of MRI abnormal patterns in CIDP patients was also conducted.

Results: Eleven MRI quantitative studies with nineteen results gave a pooled sensitivity of 70% (95% CI 0.63-0.77), a pooled specificity of 88% (95% CI 0.83-0.92). The area under the curve (AUC) was 0.88 (95%CI 0.84-0.90). Subgroup analysis of quantitative parameters showed the fractional anisotropy (FA) with a highest sensitivity of 84% (95% CI 0.73-0.92) and cross-sectional area (CSA) with the highest specificity of 95% (95% CI 0.83-0.99). While the subgroup analysis of nerve sites showed the lumbosacral plexus with higher sensitivity (75%) and specificity (90%) than brachial plexus. In thirteen qualitative studies, the pooled rate of abnormal MRI patterns including hypertrophy, hyperintensity and contrast enhancement in CIDP patients was 0.71 (95% CI 0.63-0.80).

Conclusions: Based on the qualitative analysis of abnormal patterns with hypertrophy, hyperintensity and contrast enhancement detected by MRI in CIDP patients, quantitative MRI parameters have considerable diagnostic value in CIDP patients. FA and CSA can be promising parameters in the future diagnosis of CIDP patients.

References: No

References 1: 

References 2: 

References 3: 

References 4:
Grant Support:

Keywords: Chronic inflammatory demyelinating polyradiculoneuropathy, Magnetic resonance imaging, Diagnosis, Meta-analysis, Systematic review
Subgrouping of Peripheral Neuropathic Pain Patients According to Sensory Symptom Profile Using the Korean Version of the PainDETECT Questionnaire

Poster No:
12e

Authors:
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Introduction:
A culturally validated Korean version of the PainDETECT Questionnaire (PD-Q) was used to identify neuropathic pain components (NeP) in patients suffering from chronic pain. The purpose of this study was to determine if the Korean PD-Q can be used to subgroup patients with peripheral NeP according to sensory symptom profiles.

Methods:
This study included 400 Korean patients with peripheral neuropathic pain diagnosed as probable or definite NeP. The total scores and subscores for each item in PD-Q were transformed into a Z-score for standardization. Hierarchical cluster analysis was performed to identify clusters of subjects by PD-Q scores.

Results:
The mean total PD-Q score of the study participants was 14.57 ± 6.46. A hierarchical cluster analysis identified 5 clusters with distinct pain characteristic profiles. Cluster 1 had relatively severe burning and tingling sensations. The mean total PD-Q score for cluster 2 was the lowest of the 5 clusters. Cluster 3 tended to be vulnerable to pain in response to cold/heat stimulation. Cluster 4 showed relatively severe pain induced by physical stimuli, such as light touch or slight pressure. Cluster 5 had high scores for all NeP symptoms.

Conclusions:
This study demonstrates the ability of patients to cluster by symptoms using the Korean PD-Q. Subgrouping of peripheral neuropathic pain by sensory symptom profile may be useful in making effective drug treatment decisions.

References:
No

References 1:

References 2:

References 3:

References 4:
**Grant Support:** This research was sponsored by Viatris Korea (2021).

**Keywords:** Peripheral Nervous System Diseases, Polyneuropathies, Mononeuropathies, Postherpetic; Pain, Cluster Analysis
Repositioning of Niaspan/Niacin for the therapy of CMT neuropathies with focal hypermyelination

Poster No:
13e

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Introduction:
Charcot-Marie-Tooth (CMT) neuropathies are one of the most frequent forms of neuromuscular disorders with a prevalence of 1:2500 and no available treatment. CMT4B1 with myelin outfoldings and HNPP (hereditary neuropathy with liability to pressure palsies) with tomacula are demyelinating neuropathies with focal hypermyelination. Axonal neuregulin-1 (NRG1) type III controls PNS myelination and is negatively regulated by TACE secretase, whose activity can be enhanced by Niacin (nicotinic acid). We hypothesized that Niacin, by enhancing TACE activity and reducing NRG1-mediated myelination signaling, may represent an efficient strategy to ameliorate CMT neuropathies with focal hypermyelination.

Methods:
We first provided proof-of-principle that Niaspan (a FDA-approved drug, extended-release formulation of Niacin), administered by intraperitoneal injection, is able to increase TACE activity and to ameliorate CMT4B1 and HNPP phenotypes in both in vitro and in vivo models. To corroborate previous results and to improve the treatment protocol, we set up long-term preclinical trials in mice using a novel long-lasting formulation of niacin to be administered to mice by gavage. To this aim, we encapsulated niacin in coated beads microparticles of 200-400 micron in average (Niacoat) by applying an ethylcellulose-based membrane to niacin granules using a fluid bed apparatus.

Results:
We explored Niacoat efficacy first in Mtmr2 KO mice (CMT4B1 model) by gavage administration from P10 to 6 months to score morphological and functional outcome measures. Our preliminary results showed that Niacoat treatment significantly ameliorated nerve conduction velocity in Mtmr2 KO mice and positively modulated other outcome measures (transcriptomic analyses and neurofilament light chain plasmatic level).

Conclusions:
Niaspan/Niacin repositioning strategy may represent a promising treatment strategy for CMT neuropathies with focal hypermyelination.

References:
No
References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth neuropathies, myelin, nicotinic acid, animal models
Standardization And Metrological Traceability Of Anti-Ganglioside Antibodies ELISA

Poster No:
14e

Authors:
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Institutions:
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Introduction:
Multiparametric anti-ganglioside antibodies ELISAs allow for a targeted investigation of immune-mediated neuropathies. There are no recognized reference materials nor reference measurement procedures for anti-ganglioside antibodies. To ensure consistency of results over time, we guarantee a transparent traceability chain. This is achieved by using an internal reference material (IRM) to produce standardized calibrators. Due to the similar structure of gangliosides, anti-GM1 antibodies can serve as a surrogate standardization.

Methods:
Sialic acid residues determine fine specificities of anti-ganglioside antibodies. GM1 represents the antigenic core structure of four C6 sugars and one sialic acid, that is commonly shared among different gangliosides. Therefore, anti-GM1 antibodies were used exemplarily to standardize multiparametric anti-ganglioside antibodies ELISAs. An IRM was generated from monoclonal anti-GM1 IgG and IgM antibodies. Following the protocol by Blirup-Jensen et al., 2008, the value of the IRM is assigned to a calibrator stock, which is subsequently gravimetrically diluted into calibrators.

Results:
Based on the anti-GM1 antibodies standardization, the total relative uncertainty of the calibrators of the Ganglioside-ELISAs was 29% (IgG) and 17% (IgM). The IRM traceable Ganglioside-ELISAs will be compared to the current version in a validation stage. The assays will be submitted to IVDR, the new European regulatory basis for in vitro diagnostic medical devices.

Conclusions:
Based on the modularity and structural similarity of various gangliosides, that are targeted by autoantibodies in neuropathies, anti-GM1 antibodies can serve as a surrogate standardization. The transparent anti-GM1 antibodies-based traceability chain of the anti-ganglioside antibodies ELISAs truly display the uncertainty of the assays.

References:
Yes

References 1:
Blirup-Jensen et al., 2008 DOI 10.1515/CCLM.2008.289

References 2:

References 3:

References 4:
Grant Support: N.A.

Keywords: in vitro diagnostic autoimmune assay, anti-ganglioside antibodies, Standardization and Metrological Traceability, immune-mediated neuropathies, rare autoimmune-disease
Standardization And Metrological Traceability Of Anti-MAG (Myelin Associated Glycoprotein) Antibodies ELISA

Poster No:
15e

Authors:
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Introduction:
The Anti-MAG Antibodies ELISA (MAG-ELISA) is the acknowledged gold standard in vitro diagnostic ELISA, to reliably quantify MAG-IgM Antibodies in demyelinating neuropathies, a rare autoimmune disease. There are no recognized reference materials or reference measurement procedures for Anti-MAG Antibodies. We guarantee measurement consistency for the end-users over time, with a transparent traceability chain. This is achieved by using an internal reference material (IRM) to produce standardized calibrators. The anti-MAG Antibodies ELISA is therefore ready for IVDR, the new European regulatory basis for in vitro diagnostic medical devices.

Methods:
An IRM was generated, from pooled individual patient sera, positive for MAG-IgM Antibodies. Following the protocol by Blirup-Jensen et al., 2008, the value of the IRM is assigned to a calibrator stock, which is subsequently gravimetrically diluted into calibrators. The IRM traceable MAG-ELISA was compared to the current version. In addition, within-laboratory precision, repeatability and reproducibility were assessed, measuring five samples covering the measurement range. Within-laboratory precision and within-run repeatability were assessed with 20days*2runs*2replicates (n total=80), reproducibility with 3instruments/lots/operators*5days*1run*5replicates (n total=75).

Results:
The total relative uncertainty of the MAG-ELISA calibrators was 22%. The IRM traceable calibrators demonstrate acceptable trueness when compared to the current calibrator material: a mean bias of 8.1% was determined for the measuring range of the MAG-ELISA, (Bland-Altman analysis). Within-laboratory precision was 5.5-15.9%CV, within run repeatability 3.2-11.8%CV and total precision reproducibility was 10.0-21.6%CV.

Conclusions:
The transparent traceability chain of the anti-MAG Antibody ELISA not only truly displays the assay's uncertainty and leads to stable results, but also confirms the gold standard status.

References:
Yes

References 1:
Blirup-Jensen et al., 2008 DOI 10.1515/CCLM.2008.289

References 2:

References 3:
References 4:

Grant Support: N.A.

Keywords: in vitro diagnostic autoimmune assay, myelin associated glycoprotein, Standardization and Traceability, autoimmune demyelinating neuropathies, rare autoimmune-disease
**Fundamental role of Na+/H+ exchanger isoform-1 in oxaliplatin- and paclitaxel-induced acidification in sensory neurons**

**Poster No:**
16e

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**Introduction:**
INTRODUCTION: Chemotherapy-induced peripheral neurotoxicity (CIPN) remains a common dose-limiting side effect of several anticancer agents. Due to the largely incomplete knowledge on CIPN pathogenesis, pharmacological treatments are often ineffective in both preventing and treating this side effect. Recently, we found that oxaliplatin (OHP) leads to cytosolic acidification in mouse dorsal root ganglion (DRG) neurons influencing channel activity and neuronal excitability. Herein, we evaluated the effect of CIPN-inducing drugs on Na+/H+ exchanger isoform-1 (NHE1), a plasma membrane protein that plays a pivotal role in intracellular pH homeostasis in many cell types, including nociceptors.

**Methods:**
METHODS: For in vitro studies, neurons from adult male Balb/C mice were treated with paclitaxel (PTX, 100 µM) and OHP (0.1 µg/ml). OHP and PTX effect on NHE1 activity was assessed using the pH ratiometric fluorescent probe, BCECF-AM, to measure the steady-state of pHi and the rate of pHi recovery after a standard acid loading procedure. Moreover, we evaluated gene and protein expression both in cultured DRG and in DRG cells from mice treated with a single injection of OHP (5 mg/kg, i.v.) and PTX (70 mg/kg, i.v.).

**Results:**
RESULTS: PTX treatment induced a marked intracellular acidification in neurons already after a short incubation period (0.5-2 hours). Furthermore, both OHP and PTX significantly inhibited NHE1 activity, without affecting the intrinsic buffer capacity of neurons. The mean rate of pHi recovery was strongly reduced compared with vehicle-treated controls, becoming similar to that obtained in presence of cariporide (30 µM), a specific NHE1 antagonist. Finally, molecular analyses reveal transcriptional downregulation following a 6-h OHP and PTX treatment.

**Conclusions:**
CONCLUSION: Altogether, our results suggest that chemotherapy-induced intracellular acidification of DRG neurons largely depends on NHE1 inhibition, revealing new details about the mechanisms of neuronal hyper-excitability in the acute OHP and PTX neurotoxicity suitable for new therapeutic approaches. Work supported by MIUR-PRIN Grant n. 2017ZFJCS3.

**References:**
No
Keywords: Chemotherapy-induced peripheral neurotoxicity, DRG neurons, cytosolic acidification, Na+/H+ exchanger isoform-1 (NHE1)
Face Mask Adherence in Neuromuscular Clinics During the Covid-19 Pandemic

Poster No:
17e

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Introduction:
The Covid-19 pandemic has impacted health care and health care delivery worldwide. Many neuromuscular patients, with underlying disease and immunosuppression, have multiple risk factors for severe infection from Covid-19. Face coverings, as well as physical distancing, frequent handwashing, and vaccination are effective strategies to mitigate the spread of infection.

Methods:
This prospective observational study examined patient masking behaviors in outpatient neuromuscular clinics in Vermont. Over two months, medical providers recorded whether patients wore face masks appropriately, defined as covering the nose and mouth, for the duration of the visit. For those not masked correctly, the way in which they were inappropriately masked was recorded, as well as whether the patient adjusted their masked appropriately when asked to do so.

Results:
Masking behavior was recorded for a total of 107 patients. 88 (82.2%) patients demonstrated appropriate mask use. Of the 19 (17.8%) who did not wear a mask correctly, 12 (63.2%) patients adjusted their mask when asked to do so. Younger patients (<65 years old) had significantly increased odds of correct mask use compared to older patients (OR = 3.52, 95% CI 1.12-10.62). Mask adherence behaviors did not differ significantly between genders (p > 0.05).

Conclusions:
Given the potential for multiple underlying risk factors for severe Covid-19 infections in the neuromuscular population, the findings support the need for more targeted guidance, such as pamphlets, posters, and patient-provider interactions, to clarify mask use expectations, including in settings in which face coverings are mandatory. Instances of improper mask use provide an opportunity for medical providers to review individual aspects of health that may contribute to a severe Covid-19 disease course for their neuromuscular patients.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: Covid-19, High-risk population, Face covering, Neuromuscular clinic, Immunosuppression
Comparison of neuroprotective effect of several angiotensin receptor blockers on experimental autoimmune neuritis

Poster No:
18e

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Introduction:
Popular antihypertensive agent angiotensin receptor blockers (ARB) have many functions. Above all, anti-inflammatory and neuroprotective effects are potential therapeutic strategy in neurology although they remain to be elucidated.

Methods:
Synthetic peptide of 26 amino acids sequence (aa53-78) of bovine P2 protein was injected subcutaneously with complete Freund's adjuvant to female Lewis rats to induce EAN. For each ARB, i.e. losartan (LO), candesartan (CAN), and irbesartan (IRB), 50 rats were divided into two groups, received ARB or vehicle (carboxyl methylcellulose) using gastric tube daily from two days post-immunization (dpi) through 26 dpi. The doses of ARB were LO 30mg/kg, CAN 10mg/kg, and IRB 10mg/kg. Rats were checked daily for the motor impairment. Cauda equina (CE) from the rats in 26 dpi were fixed by 10% buffered formalin, embedded in paraffin and examined for S-100 or CD68 immunoreactivity. CE, collected at base line, pre-symptomatic, disease onset, peak, and recovery stages (n=5 in each time points) from ARB-treated and CMC-treated rats were served for cytokine mRNA expression investigation using real time PCR or quantitative competitive PCR. This experiment was approved by the institutional Animal Experiment Committee (12-55-84, 11-54-84, 10-53-84, 13-51-215, 14-52-215, 15-53-215, 16-54-215, 17-55-215, ARC/TUSM-R-16-6).

Results:
All rats developed EAN at 11 dpi. Motor symptoms peaked at 14~16 dpi, and improved spontaneously thereafter. IRB-treated rats have significantly mild clinical course and pathological changes compared to other two ARB-treated groups. This suppression coincides with suppression of interferon-gamma mRNA expression and, reciprocally, up-regulation of IL-10 mRNA expression in disease active stage.

Conclusions:
ARB may suppress EAN presumably by shifting cytokine balance towards Th2 dominance. CCR2b antagonism, which is unique for IRB, may accentuate IRB superiority in suppression of EAN. IRB can be a therapeutic option for human GBS although its effect against other receptors (vitamin D receptor) that may influence immune system remains unclear.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: angiotensin receptor blocker, neuritis, rat
Long-read Sequencing in SORD Neuropathy: A Proof-of-Principle Study

Poster No:
19e

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Institutions:
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Introduction:
Biallelic mutations in sorbitol dehydrogenase (SORD) are a common cause of recessive axonal Charcot-Marie-Tooth neuropathy (CMT2). It was theorized that pathogenic SORD variants in CMT2 were initially overlooked due to 1) the highly homologous non-functional SORD2P pseudogene and 2) difficulties phasing biallelic mutations when using short-read sequencing. As a proof-of-principle, we aimed to assess a novel long-read sequencing approach to overcome these current limitations in SORD neuropathy diagnostics.

Methods:
Whole exome sequencing (WES) data from our Australian cohort was screened to identify homozygous or compound heterozygous SORD variants. This cohort consisted of 237 individuals with genetically unsolved CMT, of which 97 had a clinical CMT2/dHMN diagnosis. Individuals detected with SORD mutations underwent Oxford Nanopore Tech (ONT) long-read sequencing, clinical assessment, and serum sorbitol analysis to confirm SORD neuropathy.

Results:
Previously reported compound heterozygous truncating mutations in SORD exon 7, NM_003104.5:c.625C>T (p.Arg209Ter) and NM_003104.5:c.757del (p.Ala253GllnfsTer27) were identified in one individual. Subsequent ONT long-read sequencing successfully differentiated the SORD gene from the SORD2P pseudogene. ONT long-read sequencing also confirmed that the mutations were biallelic through haplotype-resolved analysis. Subsequent clinical assessment revealed an axonal sensorimotor polyneuropathy (CMT2) typical of SORD neuropathy. Unusually, burning neuropathic pain in the forearms and feet was also reported. The individual reported that pain was exacerbated by alcohol consumption and improved with alcohol cessation. UPLC–tandem mass spectrometry confirmed elevated serum sorbitol levels (12.0 mg/L) consistent with levels previously reported in SORD neuropathy.

Conclusions:
ONT long-read sequencing can successfully discriminate disease-relevant genes (SORD) from confounding pseudogenes (SORD2P), whilst also phasing biallelic mutations in recessive disease. Our study is the first report of long-read sequencing for an individual with CMT and demonstrates the utility of this approach for clinical genomics where SORD neuropathy is suspected.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth, SORD, Long-Read Sequencing, Sorbitol dehydrogenase, CMT2
Robust Network Provides Support for Phase 2 Clinical Trials of Novel Non-addictive Pain Therapies.

Poster No:
20e

Authors:
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Institutions:
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Introduction:
The National Institute of Neurological Disorders and Stroke (NINDS) Early Phase Pain Investigation Clinical Network (EPPIC-Net), opened in 2019, is part of the NIH Helping to End Addiction Long-term (HEAL) Initiative. EPPIC-Net focuses on understanding pain mechanisms and developing opioid-alternative treatments for pain, through design and conduct of early phase clinical trials for non-addictive pain therapeutics, to include small molecules, biologics, and novel or repurposed drugs and devices.

Methods:
EPPIC-Net developed a robust clinical trial infrastructure that includes a Clinical Coordinating Center, Data Coordinating Center, and 12 Specialized Clinical Centers with broad outreach to diverse pain populations. Resources include a collaborative network of multi-disciplinary pain experts who provide novel clinical trial designs, study conduct, and data analysis, for early phase trials incorporating proof-of-concept testing and biomarker validation. NINDS utilizes a unique, rigorous, 3-stage application and review process, with trials funded under NIH's 'Other Transactions' Authority. Trials built around accepted assets are run by the NIH-funded network at no cost to asset providers, while the asset owner retains intellectual property rights to their therapeutic asset.

Results:
In the first 2 years of operation, 3 asset clinical trials have been funded. The first trial, testing a novel small molecule for knee osteoarthritis, is currently open to enrollment. EPPIC-Net is developing an innovative master platform protocol for therapeutics targeting painful diabetic peripheral neuropathy, for the study of the 2 additional assets. The master protocol will run in parallel with clinical trials for additional accepted therapeutics addressing other pain conditions of high unmet need.

Conclusions:
EPPIC-Net provides a robust, readily accessible network of pain experts and research sites for early phase trials incorporating proof-of-concept testing, biomarker validation, and novel study design. EPPIC-Net continues to accept and review applications from academic and industry sponsors worldwide on a rolling basis.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: pain, non-addictive therapeutics, early phase clinical trials, biomarkers, diabetic peripheral neuropathy
TRPV4 mutation caused CMT2C and scapuloperoneal spinal muscular atrophy in a Chinese family

Poster No:
21e

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Introduction:
Transient receptor potential cation channel, subfamily V, member 4 (TRPV4) is a calcium-permeable channel expressed in multiple cells of the nervous system. TRPV4 gene mutation was reported in inherited peripheral neuropathies and motor neuron diseases, including Charcot-Marie-Tooth disease type 2C (CMT2C) and scapuloperoneal spinal muscular atrophy (SPSMA), congenital distal spinal muscular atrophy (CDSMA), congenital spinal muscular atrophy and arthrogryposis (CSMAA), and distal hereditary motor neuropathy (dHMN).

Methods:
We presented a Chinese family with inherited neuropathy due to TRPV4 mutation. The clinical characteristics and auxiliary examination results were described.

Results:
The proband is a 58-year-old man who presented progressive weakness in four limbs for ten years. He did not participate well in sports since early childhood. In the past three years, his muscle weakness and atrophy exacerbated, while numbness in the stocking-glove pattern developed. A Winged scapula was observed. Nerve conduction studies suggested axonal damage in motor and sensory nerves. Sural nerve biopsy was performed, and reduced myelinated fiber density and atypical onion bulbs formation were found. A similar but mild clinical manifestation was observed in his son. A Winged scapula was also presented. Electrophysiological studies showed a neurogenic pattern, with diffuse impairment of the anterior horn. TRPV4 c.946C>T mutation was found in both the proband and his son. The proband was diagnosed as Charcot-Marie-Tooth disease type 2C (CMT2C) with scapuloperoneal, while the son as scapuloperoneal spinal muscular atrophy (SPSMA).

Conclusions:
Herein, we presented the first family with TRPV4 mutation-related neuropathy spectrum disorder in China. We observed an overlap in the clinical manifestation of CMT2C and scapuloperoneal of the proband, which was rarely reported in previous cases. Also, mild clinical manifestations and definite electrophysiological characteristics could be present in asymptomatic patients with TRPV4 mutation. These findings may help in the early recognition and diagnosis of TRPV4 mutation-related spectrum disorders.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: TRPV4, CMT, SMA
Microneurography confirms small fiber dysfunction in suspected small fiber neuropathy with normal intraepidermal nerve fiber density

Poster No:
22e

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Introduction:
Although intraepidermal nerve fiber density (IENFD) on skin biopsy is the most specific diagnostic test for small fiber neuropathy, it lacks sensitivity and is normal in a significant minority. Microneurography is an intraneural electrophysiological technique that can identify pathological spontaneous activity of individual C-nociceptor fibers. We aimed to compare the clinical utility of these tests.

Methods:
We included all 66 patients at a single specialist center with clinically suspected small fiber neuropathy who had both skin biopsy and microneurography performed. All patients had symptoms suggestive of small fiber neuropathy as assessed by a specialist peripheral nerve neurologist. We classified each result as either abnormal (if IENFD reduced below published age/sex-matched normal limit; or spontaneous C-nociceptor activity) or normal. Our department's practice was usually to perform skin biopsy first, then microneurography only if IENFD was normal.

Results:
58 patients had normal IENFD, of which 38 (66%) had abnormal microneurography and 20 (34%) had normal microneurography. Eight patients had abnormal IENFD, of which seven (88%) had abnormal microneurography and one (12%) had normal microneurography. The presence of burning pain symptoms in the distal legs/feet was strongly associated with abnormal microneurography

Conclusions:
Microneurography showed small fiber dysfunction in two-thirds of patients with symptoms of small fiber neuropathy but normal IENFD on skin biopsy. Microneurography may be useful in clinical practice to confirm objective evidence of small fiber abnormality in patients with suspected small fiber neuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: small fibre neuropathy, burning pain, microneurography, intraepidermal nerve fibre density
RECIPE: a phase II randomized controlled trial of rituximab for refractory CIDP with IgG4 autoantibodies

Poster No:
23e

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Introduction:
To evaluate the efficacy and safety of rituximab (anti-CD20 monoclonal antibody) in treatment-refractory CIDP, including autoimmune nodopathy (anti-NF155, anti-CNTN1), in a Japanese multicenter, placebo-controlled, randomized, partial-blind, parallel-group study (Phase II).

Methods:
Twenty-five cases with definite CIDP according to the revised EFNS/PNS criteria (2010) participated in our trial, in which fifteen cases were IgG4-predominant autoantibody-positive, and ten cases were negative. ELISA evaluated autoantibody, and all were IgG4-predominant anti-NF155 positive. Ten anti-NF155 antibody-positive cases were randomized to rituximab and five to placebo in a double-blind fashion. Moreover, ten autoantibody-negative patients received rituximab under open-label. All participants were allowed to continue the existing standard therapies during the study period, but new induction or dose increase of immunomodulating drugs (e.g., steroids, IVIg, plasma exchange, immunosuppressant) was restricted. The primary endpoint was the percentage of subjects with 1-point or more improvement on the adjusted INCAT Disability Scale at either of the three-time points: 26, 38, or 52 weeks after the start of treatment. Secondary endpoints were grip strength (Martin-vigorimeter), R-ODS, MRC Sum Score, motor nerve conduction study, CSF protein concentration, autoantibody titer, serum neurofilament light chain (Nf-L), and so on.

Results:
Twenty-five patients were enrolled between March 2019 and June 2020, and two patients withdrew from the study prior to administration. The response rate of the primary endpoint in eligible subjects with autoantibody-positive was 66.7% for rituximab (20% for placebo, n=5), and that in the autoantibody-negative subjects (n=9) was 66.7%. Grip strength, R-ODS, motor nerve conduction, antibody titer, Nf-L show improvement or clear tendency in the rituximab group with the anti-NF155 autoantibody and the autoantibody-negative group. No safety issues due to rituximab were observed.

Conclusions:
Our study (RECIPE trial) indicates that rituximab is promising for treatment-resistant CIDP, including IgG4 subclass autoantibody-positive cases.

References:
No
References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, autoimmune nodopathy, therapeutics, rituximab
Guillain-Barré syndrome following COVID-19 vaccination

Poster No:
24e

Authors:
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Introduction:
Amidst growing concern about an increased risk of Guillain–Barré syndrome (GBS) following COVID-19 vaccination, clinical and electrodiagnostic features have not been fully characterized.

Methods:
We retrospectively reviewed medical records of the patients diagnosed with GBS and its variants following COVID-19 vaccination at four referral hospitals during the period of the mass vaccination program in South Korea (February to October 2021).

Results:
We identified 13 patients with GBS and variants post COVID-19 vaccination: AstraZeneca vaccine (Vaxzevria) in 8, and Pfizer-BioNTech vaccine (Comirnaty) in 5. The mean time interval from vaccination to symptom onset was 15.6 days (range 4-30 days). Electrodiagnostic classification was demyelinating in 7, axonal in 4 and normal in 2 cases. Clinical manifestations were diverse with varying severity: classical GBS in 8 cases, paraparetic variant in 3, Miller-Fisher syndrome in 1 and acute cervicobrachial weakness in 1. Four patients developed respiratory failure, and 2 of them showed treatment-related fluctuations.

Conclusions:
Our observations suggest that COVID-19 vaccines may be associated with GBS of distinctive clinical features characterized by severe quadriplegia, disproportionately frequent bilateral facial palsy or atypical incomplete variants. Continuous surveillance and further studies using robust study designs are warranted to fully assess the significance of the association.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Guillain-Barré syndrome, COVID-19, vaccination, neurological complications
Hereditary Transthyretin Amyloidosis Misdiagnosed as Demyelinating Neuropathy: A Report of Three Cases

Poster No:
25e

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Introduction:
Transthyretin amyloidosis (aTTR) is a life-threatening type of systemic amyloidosis and amyloid deposition in peripheral nerves causes a form of polyneuropathy known as familial amyloid polyneuropathy (FAP). However, the electrophysiological results of FAP could be similar to those in chronic inflammatory demyelinating polyneuropathy. We report on 3 patients diagnosed with aTTR who were initially diagnosed and treated for demyelinating neuropathy.

Methods:
We performed a retrospective review of 3 patients initially treated as acquired demyelinating neuropathy such as CIDP but finally confirmed as aTTR.

Results:
Case 1: A 38-year-old male presented of limb weakness and paresthesia. The result of his electrophysiological study met the diagnostic criteria of CIDP and was treated for it. However, since he developed cardiac and autonomic symptoms, he underwent genetic test and aTTR was confirmed. Case 2: A 45-year-old female showed limb weakness and urinary incontinence. The electrophysiological study revealed demyelinating polyneuropathy, but her symptom was worsening despite adequate treatment. During treatment, she complained of visual dimness. Her ophthalmologic examination suggested amyloid deposition on her vitreous and she confirmed aTTR by genetic testing. Case 3: A 46-year-old male complained of distal limb weakness, paresthesia, and uncontrolled diarrhea. In his electrophysiological study, conduction blocks and increased duration of CMAP more than two nerves were noted. However, since orthostatic hypotension, diarrhea, and limb weakness progressed, aTTR was suspected. And he was confirmed aTTR by genetic testing.

Conclusions:
The electrophysiological findings of FAP can mimic the findings of demyelinating neuropathy like CIDP. Even in patients initially diagnosed with CIDP but refractory in treatment, it is necessary to recheck their family history and periodically evaluate whether they develop autonomic or cardiac symptoms. If these symptoms suggestive amyloidosis deposition, genetic testing should be considered.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Amyloidosis, chronic inflammatory demyelinating polyradiculoneuropathy, aTTR, Polyneuropathy, Polyradiculoneuropathy
A comparative study of mouse models of dominant and recessive Charcot-Marie-Tooth disease type 2E

Poster No:
26e

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Introduction:
Charcot-Marie-Tooth disease type 2E (CMT2E) is a slowly progressing peripheral neuropathy caused by mutations in neurofilament protein L (NEFL). Neurofilaments are space-filling cytoskeletal polymers that accumulate in myelinated axons, contributing to the expansion of axon caliber and consequent increase in axonal conduction velocity during postnatal development. CMT2E-causing mutations can be dominant (mostly missense) or recessive (null). The NeflN98S/+ mouse, which is heterozygous for the N98S missense mutation, is an established model of dominant CMT2E. The Nefl-/ 'knockout' mouse, which is homozygous for a null mutation, is a potential model of recessive CMT2E.

Methods:
We are characterizing the nerve conduction, sensorimotor function, axon morphology and axon ultrastructure in these mice to understand how both missense and null mutations in the same gene cause disease.

Results:
The Nefl-/ and NeflN98S/+ mice exhibited similar impairments in tail nerve conduction, but the NeflN98S/+ mice were more impaired in horizontal ladder and open-field locomotor tests. Histologically, the sciatic nerves of Nefl-/ and NeflN98S/+ mice were indistinguishable, with a similar reduction in myelinated axon number, caliber and g-ratio. Neurofilaments were largely absent from the peripheral axons of both Nefl-/ and NeflN98S/+ mice, but NeflN98S/+ mice exhibited neurofilament accumulations proximally.

Conclusions:
In conclusion, the phenotype of the Nefl-/ and NeflN98S/+ mice appears to converge on a lack of neurofilaments in peripheral myelinated axons, leading to a failure of these axons to expand during postnatal development, but diverge in the soma and proximal axons. The nerve conduction defects likely reflect the reduced axonal caliber, whereas the greater locomotor impairment in the NeflN98S/+ mice suggests an additional toxic gain of function acting proximally or centrally. Thus, it is possible that there are multiple disease mechanisms at work in CMT2E that act at different locations in the neuron and/or nervous system.

References:
No

References 1:

References 2:
References 3:

References 4:

**Grant Support:** This work was supported by grants from the NIH and Charcot-Marie-Tooth Association.

**Keywords:** Charcot-Marie-Tooth, Neurofilament, Axon, Myelin, Nerve
A case of neuroleukemiosis: The usefulness of nerve ultrasound as a diagnostic tool.

Poster No:
27e

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Introduction:
Neuroleukemiosis is a condition in which leukemic blasts infiltrate peripheral nerves. Neuroleukemiosis is considered a predictor of systemic relapse in acute myeloid leukemia (AML). Therefore, its early diagnosis is critical for patients with leukemia to receive appropriately timed treatment. Herein, the authors report a patient with AML for whom peripheral nerve ultrasound was helpful for the diagnosis of neuroleukemiosis in the tibial nerve.

Methods:
Case: A 52-year-old female with AML became aware of paresthesia of the left lower limb. She had been diagnosed with M5b type AML one year prior to the onset of the symptom, and undergone remission induction and consolidation therapy. After achieving remission, she had also undergone allogeneic hematopoietic stem cell transplantation 6 months prior to the neurological symptom onset. The patient was seen for neurological evaluation 4 months after onset of paresthesia. On neurological examination, the patient had paresthesia and sensory disturbance in the left sole and weakness in the left gastrocnemius muscle.

Results:
Nerve conduction studies (NCS) showed a decreased compound muscle action potential amplitude and a decreased conduction velocity in the left tibial nerve. Ultrasound of the left tibial nerve showed nerve enlargement and loss of fascicular architecture with hypoechoic change inside the nerve. MRI revealed a nodule on the left tibial nerve. Cerebrospinal fluid findings and bone marrow evaluation were not suggestive of leukemia relapse. However, positron emission tomography - computed tomography using 18F-fluorodeoxyglucose and a biopsy of the left inguinal lymph node revealed an extramedullary relapse of AML. After the reinduction chemotherapy, the left tibial nerve enlargement on ultrasound showed improvement although neurological and NCS findings did not improve significantly. The nerve enlargement in this case was considered as the finding reflecting neureoleukemiosis.

Conclusions:
Peripheral nerve ultrasound is useful for early recognition and the diagnosis of neuroleukemiosis in patients with AML.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: neuromuscular ultrasound, neuroleukemiasis, acute myeloid leukemia
Elucidating incidence and risk factors of treatment-induced neuropathy of diabetes after rapid glycemic control - A preliminary analysis

Poster No:
28e

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Introduction:
Treatment-induced neuropathy of diabetes (TIND) is an uncommon, acute, painful, small-fibre and autonomic neuropathy following an abrupt improvement in glycemic control. Previously, a prevalence of 10% was reported among patients referred to a tertiary neuropathy clinic. Risk factors however remain unclear. We sought to clarify if glycemic variability, in addition to rapid glycemic control, predispose patients to TIND, and explored putative biomarkers (e.g. vascular endothelial growth factors).

Methods:
We conducted a prospective nested case-control study at a single tertiary diabetes centre and included patients with diabetes mellitus (DM) and HbA1c drop of at least 2% in 3 months or 4% in 6 months. These patients were interviewed at 4, 8 and 12 weeks intervals to identify neuropathic and/or autonomic symptoms suggestive of TIND, corroborated with validated questionnaires (Michigan Neuropathy Screening Instrument (MNSI), COMPASS-31 and Likert scale). Those with symptoms would be 'cases' while an equal number without symptoms at the end of follow-up period would serve as 'controls'. Cases and controls then undergo detailed glucose profiling, neurophysiological tests (autonomic and neuropathic), retinal assessments and blood biobanking for biomarker testing, to identify any phenotypic differences between the groups at diagnosis and 1 year. Demographics, diabetes history and relevant laboratory data are also compared.

Results:
Fifty-five patients have been recruited. Mean age is 52(22-77) years, 34(61.8%) males. Fifty-three(96.3%) has Type 2 DM. Mean duration of diabetes is 8.6(0-40) years, 14 of whom are newly-diagnosed. Fourteen(25.5%) has microvascular complications at baseline. Median drop in HbA1c is 4.2(2.0-8.6)% at study entry. Median baseline MNSI, COMPASS-31 and Likert scale scores are 2, 11.7 and 0 respectively. Thirty-three(60%) patients have completed the 12-week follow-up period. Five(9.1%) patients have symptoms suggestive of TIND.

Conclusions:
At present, TIND symptom development appears to be uncommon in our cohort. Ongoing recruitment and comparison of cases and controls will help to verify this.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

**Keywords:** diabetic neuropathy, small-fibre, TIND, DM neuropathy, insulin neuritis
Plasma exchange and immunoadsorption in CIDP - A multicenter retrospective cohort study

Poster No:
29e

Authors:
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Introduction:
Plasma exchange (PE) is one of the treatments in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) but is less frequently chosen as it is a more invasive treatment. As an alternative to PE, immunoadsorption (IA) has been suggested. The evidence on the efficacy of PE and IA in CIDP is, however, limited.

Methods:
We performed a retrospective international observational study using data from eight CIDP referral centers in Europe. Data from health records on CIDP patients receiving PE or IA between 2010 and present was extracted using a case report form (CRF). The CRF included questions on demographics, previous and concurrent CIDP treatments, and technique and schedules to address practice variation. The primary outcome was treatment response, defined as improvement as judged by the treating physician at four weeks after the last session of the induction treatment (improvement/stable/deterioration). In addition, we used disability and impairment data where available. Data on maintenance treatment (three months or more) was collected as well.

Results:
Eighty-nine patients were included of whom 63 (71%) patients received various schedules of PE and 23 (26%) patients IA. Data from two additional centers will be presented at the meeting. All 23 patients who received IA were from a single center. Seventy-three (82%) patients were refractory to or deteriorating while on intravenous immunoglobulins (IVIg) and/or corticosteroids. Within four weeks of the last PE/IA session of the induction treatment, improvement was seen in 44 (49%) patients. Anti-nodal/paranodal autoantibodies were detected in 10/51 (20%) patients. The presence of autoantibodies was the only variable associated with worse treatment response in the short term.

Conclusions:
Short-term improvement after PE/IA induction was seen in about half of the patients who were previously refractory to IVIg and/or corticosteroids. There was considerable variation of PE/IA schedules that did not seem to influence the efficacy of treatment.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Chronic Inflammatory Demyelinating Polyradiculoneuropathy, Plasma Exchange, Immunoadsorption, Autoantibodies
Guillain-Barre Syndrome Following Influenza Vaccination A 27-year nationwide population-based case-control study

Poster No:
30e

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Introduction:
Vaccination may increase the risk of developing Guillain-Barré syndrome (GBS) due to an elicited immune response, but the exact relationship is unclear. We investigated the magnitude, population-attributable fraction and duration of associated GBS risk following influenza vaccination.

Methods:
We conducted a nationwide population-based case-control study of all patients with first-time hospital-diagnosed GBS in Denmark between 1990 and 2016 and ten age, sex and index date-matched population controls per case. For the primary analyses, we identified incident influenza vaccination one month prior to the GBS index date. For each individual, we used medical registries to ascertain a complete hospital contact history of all pre-existing morbidities within ten years prior to GBS, categorized by the CCI. To examine the impact of time from influenza vaccination to subsequent GBS occurrence, we repeated the analysis for five consecutive 30-day risk periods prior to the GBS index date.

Results:
Of the 2,181 GBS cases and 21,599 controls, 20 cases (0.9%) and 119 controls (0.6%) received an influenza vaccination within four weeks, respectively, yielding a matched comorbidity-adjusted odds ratio (OR) of 1.9 (95% confidence interval (CI), 1.1-3.2) for GBS. Stratification by calendar time, gender and age showed similar results for the association between influenza vaccination and GBS. The population-attributable fraction was 0.5 %. When examining longer risk intervals after influenza vaccination, the increased risk of developing GBS was largely confined to only one month following influenza vaccination.

Conclusions:
In this large nationwide epidemiologic study, influenza vaccination was associated with an approximately doubled risk of GBS occurrence for one month after vaccination. However, only 1% of GBS cases in our population were associated with recent influenza vaccination. The benefit of influenza vaccines in preventing influenza infection, decreasing mortality and influenza-associated morbidity, including GBS risk, needs to be weighed against the risk of GBS.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Guillain-Barré syndrome, Inflammatory neuropathy, Epidemiology
Increased risk of depression after Guillain-Barre syndrome A nationwide population-based cohort study

Poster No:
31e

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Introduction:
The life threatening disorder Guillain-Barré syndrome (GBS) may be followed by depression in some patients. We determined the short- and long-term risk of depression following GBS and compared this risk to depression risk in the general population.

Methods:
Individual-level data from nationwide medical registries were linked in this population-based matched cohort study of all first-time hospital-diagnosed GBS patients in Denmark between 1987 and 2016 and individuals from the general population, matched on age, sex, and index-date of incident GBS. We computed cumulative depression rates during follow-up and used Cox regression analyses to calculate matched depression hazard ratios (HRs) following GBS, assessing short-term (0-2 year) and long-term (> 2 year) depression risk.

Results:
During our 30-year study period, we identified 2,387 incident GBS patients and recruited 23,470 age-, sex-, and index matched individuals from the general population. Short-term depression within 2 years was observed in 8.0% (95% CI, 6.9-9.0) of GBS patients and 3.2% (95% CI, 2.0-3.4) of general population members, respectively, resulting in a matched HR of 4.1 (95% CI, 2.5-6.8). The highest depression HR was observed within the first 3 months after GBS (HR, 9.6; 95% CI, 5.8-14.6). After the first two years, GBS patients and the general population members had similar depression risks with a long-term HR of 0.9 (95% CI, 0.7-1.3). Stratified results showed similar depression HRs associated with GBS in subgroups according to sex, age, comorbidity -and calendar period strata.

Conclusions:
During the first 2 years after GBS admission, patients with GBS had a 4-fold increased depression risk compared with the background population. The relative risk of developing depression was highest during the first 3 months after GBS. Two years after GBS, the risk of depression had become similar to that of the background population.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Guillain-Barré syndrome, Inflammatory neuropathy, Epidemiology, Depression
Morbidity and surgery as risk factors for developing Guillain-Barré syndrome

Poster No:
32e

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Introduction:
To determine the association of pre-existing morbidity and surgery with risk of subsequent Guillain-Barré syndrome (GBS) development.

Methods:
We conducted a nationwide population-based case-control study of all patients with first-time hospital-diagnosed GBS in Denmark between 2004 and 2016 and ten age, sex and index date-matched population controls per case. For each individual, we used medical registries to ascertain a complete hospital contact history of all pre-existing morbidities within ten years prior to GBS, categorized by the CCI. We also identified all incident major surgery performed within five months prior GBS.

Results:
In the 13-year study period, there were 1,086 incident GBS cases, whom we compared with 10,747 matched controls without GBS. Pre-existing morbidity was observed in 27.5% of GBS cases and 20.0% of controls, yielding an overall adjusted OR (aOR) of 1.4 (95% CI, 1.2-1.6) for GBS associated with pre-existing morbidity. The strongest associations for individual morbidities were observed for leukemia (aOR, 3.9; 95% CI, 1.4-10.7), diabetes with end-organ damage (aOR, 1.7; 95% CI, 1.1-2.5), and myocardial infarction (aOR, 1.6; 95% CI, 1.1-2.4). GBS risk was strongest for morbidities diagnosed for the first time within five months before incident GBS (aOR, 2.9; 95% CI, 2.1-4.0). Surgical procedures within five months prior to the GBS/index date were observed in 10.6% of cases and 5.1% of controls, resulting in a GBS aOR of 1.7 (95% CI, 1.4-2.2) associated with recent surgery. Risk of developing GBS was highest within the first month following surgery (aOR, 2.9; 95% CI, 2.1-4.1).

Conclusions:
In this large nationwide epidemiologic study, individuals with pre-existing morbidity and recent surgery had considerably increased risks of GBS.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:
**Keywords:** Guillain-Barré syndrome, Inflammatory neuropathy, Epidemiology
Longitudinal Trajectories of Clinical, Neurological and Patient-Reported Chemotherapy Induced Peripheral Neurotoxicity Following Treatment Completion

Poster No:
33e

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Introduction:
Chemotherapy-induced peripheral neurotoxicity (CIPN) is a common side effect of neurotoxic cancer treatment. Although CIPN may persist for years post-treatment completion, little is known about CIPN outcomes in cancer survivors. This longitudinal study aimed to evaluate the natural history of CIPN improvement using clinical and neurological grading, patient reported outcomes (PRO) and semi-objective sensory measures.

Methods:
Patients were recruited prior to commencing treatment with neurotoxic cancer treatment (taxanes, platinum, vinca-alkaloids, bortezomib, thalidomide) and assessed at three timepoints post-treatment completion (T1=3-4months, T2=6-8months, T3=15-25months post-treatment). Outcome measures included the National Cancer Institute (NCI, range 0-4) sensory neuropathy scale, Total Neuropathy Score, clinical version (TNSc, range 0-24), a sensory neuropathy PRO (CIPN8, range 0-100), and semi-objective sensory measures on the upper limb (grating orientation task (GOT), range 0.75-12mm), Von Frey monofilaments (VF), range 0.125-512mN). Assessment scores were assessed between timepoints using paired t-test. Results presented as mean±SD.

Results:
163 patients (mean age 55.2±11.8years, 67.3% female) were assessed at all three timepoints, with 106 patients (65.0%) having developed CIPN of any grade by T1. There was significant improvement in mean NCI grade over time (P<0.001). Patient reported CIPN severity improved by T2 compared to T1 (CIPN8=21.2 ± 15.8 vs 16.5 ± 14.9, P<0.001), but remained stable at T3 (CIPN8= 16.6±15.9). On neurological grading scale (TNSc) and both semi-objective sensory measures, there was no improvement until T3 compared to T1 (TNSc= 3.8 ± 2.6 vs 4.7± 2.6, P<0.001, GOT= 3.7± 1.7mm vs 4.3± 2.5mm, P<0.01, VF= 0.4± 0.5mN vs 2.7 ± 10.4mN, P<0.05).

Conclusions:
CIPN affected 65.0% of cancer survivors treated with neurotoxic treatment. Patient-reported symptoms improved by 6-8 months, but remained stable at later timepoints. In contrast, neurological and sensory tests did not show improvement until 15-25 months post-treatment, suggesting differences between patient perception and objective assessment of neurotoxicity.

References:
No

References 1:
Grant Support:

Keywords: Chemotherapy-induced peripheral neurotoxicity, Assessment tools, Longitudinal, Cancer survivors, Outcome measures
Lysosomal enzymes and their role in Charcot-Marie-Tooth disease type 1A.

Poster No:
34e

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Introduction:
Charcot-Marie-Marie Tooth disease type 1A (CMT1A) is the most common demyelinating peripheral neuropathy. CMT1A is caused by a duplication of the peripheral myelin protein 22 (PMP22) gene. The exact mechanism causing dysfunctional Schwann cells is yet to be defined, however, disrupted proteostasis due to PMP22 aggregation has been described previously. Lysosomes are key degradative compartments in protein homeostasis by digesting misfolded proteins via enzymes such as cathepsins. A disruption in proteostasis and cathepsins has been reported in several neurodegenerative diseases such as Alzheimer's Disease and Parkinson's Disease. Nevertheless, cathepsin alterations in CMT1A have not been explored yet.

Methods:
To elucidate cathepsin levels in CMT1A, we monitored cathepsin D (CTD), B (CTB) and S (CTS) expression levels in nerves of 1-, 2-, 4-, 8- and 52-week old C3-PMP22 and WT mice.

Results:
For CTD, CTB and CTS, an increased expression was visible starting in 2-week old CMT1A mice, persisting until the age of 52 weeks. CTD levels increased significantly at 4- (103%, p=0.04) and 8-week-old (240%, p=0.02) CMT1A mice, and remained increased in 52-week-old mice (123%, p=0.16). CTS gene expression levels were significantly higher at the age of 4 weeks (92%, p=0.01), and its increase was still visible at 8 weeks (57%, p=0.55) and 52 weeks (48%, p=0.99). CTB expression was observed to be increased in 4- (65%, p=0.08) and 8-week-old mice (213%, p= 0.07), and was significantly increased in 52-week-old mice (p=0.04, 123%).

Conclusions:
Taken together, we observed an increased gene expression of cathepsins in C3-PMP22 mice compared to WT starting in 2 week-old-mice, peaking at 4-8 weeks and continuing to be visible at the age of 52 weeks. Nevertheless, further research is crucial to explore the consequences of these lysosomal enzyme changes in CMT1A.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support: FWO fundamental grant application.

Keywords: Charcot-Marie-Tooth, Schwann cells, Lysosomes
Guillain-Barré syndrome (GBS) following recent COVID-19 mRNA vaccination appears similar to GBS in the pre-COVID era

Poster No:
35e

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Introduction:
GBS following COVID vaccination has been reported following mass vaccination exercises. We wondered if patients developing GBS after mRNA COVID-19 vaccination differed from cases not temporally related to the vaccination.

Methods:
From December 2020 to June 2021, we identified patients fulfilling Brighton criteria for GBS from our ongoing prospective multi-centre study of patients reporting neurological complaints, within 6 weeks of recent mRNA COVID-19 vaccination. Clinical, laboratory and electrodiagnostic data were collected and compared against GBS patients in our institutional prospective GBS registry, recruited during an equivalent 6-month period prior to the COVID-19 pandemic.

Results:
We compared 3 post-vaccination GBS patients against 7 occurring in an equivalent period pre-COVID. All post-vaccination GBS patients were male, median age 71 (range 65-75) years, and received Tozinameran at median 3 (range 0-18) days prior; the pre-COVID group had a median age of 54 (range 19-63) years, male-female ratio of 0.4, with 57% reporting antecedent respiratory/gastrointestinal illness at median 8 (range 7-11) days prior – the post-vaccination group had no antecedent infective symptoms. The predominant clinical subtype was classic sensorimotor GBS in the post-vaccination group (67%) and Miller-Fisher Syndrome in the pre-COVID group (57%). Unlike reports of facial diplegia following mainly vector-based COVID-19 vaccination, none of our patients had bifacial weakness. Two of 3 in the post-vaccination group and 14% in the pre-COVID group had unilateral facial weakness. Two (29%) in the pre-COVID group and none in the post-vaccination group developed respiratory failure. Post-vaccination GBS patients had longer hospitalisations (median 20 (range 6-21), vs 8 (5-16) days in the pre-COVID group). The median mRS on discharge was 1 (range 1-3) and 2 (range 0-4) in the pre-COVID and post-vaccination groups, respectively.

Conclusions:
We identified 3 patients temporally related to the COVID vaccination; there were no characteristic features distinguishing them from the 7 GBS patients in an equivalent time-frame pre-COVID.

References:
Yes

References 1:

References 3:

References 4:

Grant Support:

Keywords: Guillain-Barre Syndrome, COVID-19 vaccination
Clinical Profile of Chronic Inflammatory Demyelinating Polyneuropathy with Anti-Neurofascin 186 antibody

Poster No:
36e

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Introduction:
Different subtypes of chronic inflammatory demyelinating polyneuropathy (CIDP) with novel antibodies presented specific clinical features. However, antibody against neurofascin 186 (NF186) was rarely reported. We report a cohort of patients with anti-NF186 antibody and describe the clinical profile of them.

Methods:
In this retrospective study, 195 patients diagnosed with CIDP and immune mediated idiopathic neuropathies were enrolled. Cell-based assay was used to detect anti-NF186 and anti-NF155 antibodies in 195 serum samples. Clinical data were collected and analyzed.

Results:
Anti-NF186 antibody was detected in 13 patients (13/195, 6.7%). 20 patients were found with anti-NF155 antibody (10.3%). In anti-NF186 antibody positive group, 12 patients were diagnosed with CIDP. Among the CIDP group, seven patients (58.3%) presented acute or subacute disorder onset. Four patients (33.3%) were found to have asymmetric weakness or numbness. Distal weakness and/or numbness was the core feature. Sensory ataxia, tremor and central nervous system demyelination were rarely observed. Nerve conduction studies revealed demyelinating predominance with/without axonal loss. Brachial plexus MRI was observed normal in the majority of CIDP patients (6/7, 85.7%). Five patients (5/9, 55.6%) showed partially response to intravenous immunoglobulin. Eight patients (8/10, 80.0%) showed partially response to steroids. All patients (3/3, 100%) responded to rituximab.

Conclusions:
We concluded the clinical characteristics of anti-NF186+ CIDP. The diversity of clinical features, electrophysiology results and pathological findings was specific in anti-NF186+ CIDP. Screening of autoantibody against NF186 in acute-onset neuropathy was recommended.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** Chronic inflammatory demyelinating polyneuropathy, Anti-neurofascin 186 antibody
Predictive factors of response to Tafamidis in a cohort of ATTRv patients from a non-endemic area

Poster No:
37e

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Introduction:
Hereditary amyloid transthyretin (ATTRv) amyloidosis is a rare disease with a broad clinical spectrum that varies between endemic and non-endemic areas. The first treatment approved for ATTRv was Tafamidis, a TTR stabilizer. Our objective was to study predictive factors of response to Tafamidis in a cohort of ATTRv patients from a non-endemic area.

Methods:
Retrospective study with prospective data collection of patients with ATTRv on Tafamidis treatment for ≥6 months. The patients were divided into three groups based on their response to Tafamidis (Good-Responders, Partial-Responders or Non-Responders). Demographic, clinical, and laboratory data were collected and correlated with response to Tafamidis.

Results:
40 patients with ATTRv on Tafamidis treatment were evaluated. 19 patients were women (47.5%) and 21 men (53.5%). Mean age of disease onset was 61 years. Val50Met mutation was found in 17 patients (42.5%, of which 16 were late-onset), followed by Ser97Tyr in 7 (17.5%), Glu109Lys in 4 (10%), and Val142Ile and Ser43Asn in 3 respectively (7.5% and 7.5%). Mean time of treatment with Tafamidis was 38 months. At last follow-up, 20 patients were on Tafamidis treatment (50%), 16 underwent a change in treatment (40%), and 4 died (10%). 16 patients were Good-Responders (42.1%), 6 Partial-Responders (15.8%) and 16 Non-Responders (42.1%). Predictive factors of non-response to Tafamidis were an initial PND stage II (p=0.021), initial large fiber involvement (p=0.006), significant weight loss (p=0.008) and a history of spinal stenosis (p=0.009). Initial PND stage I (p=0.02), initial NIS≤15 (p=0.001), initial Norfolk ≤25 (p=0.002) and initial RODS>40 (p=0.025) were associated with good response to Tafamidis.

Conclusions:
In this study, initial PND stage I, NIS≤15, Norfolk ≤25 and RODS>40 were associated with a good response to Tafamidis, while the presence of an initial PND stage II, large fiber involvement, weight loss and spinal stenosis were predictive factors of non-response to treatment with Tafamidis.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: ATTRv, Tafamidis, Amyloidosis, Transtirretin, Neuropathy
Response predictors to Patisiran treatment in non-endemic ATTRv patients

Poster No:
38e

Authors:
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Introduction:
Hereditary amyloid transthyretin (ATTRv) amyloidosis is a rare disease with different clinical manifestations in endemic and non-endemic areas. Patisiran, a small interference RNA that inhibits hepatic synthesis of TTR, was recently approved for the treatment of ATTRv. Our objective was to study predictive factors of response to Patisiran in a cohort of non-endemic ATTRv patients.

Methods:
Retrospective study with prospective data collection of patients with ATTRv on Patisiran treatment for ≥6 months. The patients were classified into Good-Responders, Partial-Responders or Non-Responders according to their response to treatment. Demographic, clinical, and laboratory data were collected and correlated with response to Patisiran.

Results:
22 patients with ATTRv on Patisiran treatment for ≥6 months were evaluated. 8 patients were women (36.4%) and 14 were men (63.6%). All patients had neuropathy, and 20 patients had cardiomyopathy (91%). Mean age of disease onset was 62 years (SD 10.7). Val50Met mutation was found in 13 patients (59.1%, of which 12 patients were late-onset), followed by Ser97Tyr and Glu109Lys in 2 respectively (9.1% and 9.1%). Mean time of treatment with Patisiran was 27.6 months (SD 18.4). At last follow-up, 19 patients were on Patisiran treatment (86.4%), 1 underwent a change in treatment (4.5%), and 2 died (9.1%). 13 patients (59.1%) were previously treated with Tafamidis. 11 patients were Good-Responders (50%), 8 were Partial-Responders (36.4%) and 3 were Non-Responders (36.4%). Predictive factors of good response to treatment were male gender (p=0.006: Good-Responders=90.9% vs Partial and Non-Responders=36.4%), initial PND stage ≤IIIA (p=0.002: Good-Responders=100% vs Partial and Non-Responders=50%) and sustained NTproBNP<300 (p=0.027: Good-Responders 40% vs Partial and Non-Responders 0%).

Conclusions:
In this study, male gender, initial PND stage ≤IIIA, and sustained NTproBNP<300 were predictors of good response to Patisiran.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: ATTRv, Patisiran, Amyloidosis, Transtirretin, Neuropathy
Development of standardized ELISA kits for IgG4 anti-neurofascin 155 and anti-contactin-1 antibodies

Poster No:
39e

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Introduction:
Disease-specific IgG4 antibodies against paranodal proteins, such as neurofascin 155 (NF155) and contactin-1 (CNTN1), have been recognized in subsets of chronic inflammatory demyelinating polyneuropathy (CIDP). However, standardized in vitro diagnostics for these autoantibodies are not currently available. The aim of this study is to develop standardized ELISA kits for IgG4 anti-NF155 antibody (NF155-Ab) and IgG4 anti-CNTN1 antibody (CNTN1-Ab).

Methods:
Extracellular domains of human NF155 and CNTN1 expressed by HEK293 cells were used as antigens. Purified IgG from each patient with NF155-Ab or CNTN1-Ab was adopted as reference material. We defined 1 µg of IgG4 as 100 unit (U). Concentration of IgG4 autoantibody in sera was determined based on the standard curve. Tests were performed in 74 healthy controls (HCs), 42 patients with CIDP, and 21 patients with demyelinating peripheral neuropathies other than CIDP. CIDP patients in this study were selected based on their antibody positivity status previously obtained by cell-based assay (CBA); 33 patients were tested for NF155-Ab, of whom 31 were positive for the antibody, and 9 patients were examined for CNTN1-Ab, all of whom were positive for the antibody. Concordance rate between CBA and ELISA was assessed within CIDP patients for each antibody.

Results:
Serial dilution of three sera samples showed good linearity and the coefficients of variation in repeatability and reproducibility were less than 6% in both ELISA kits. Neither NF155-Ab nor CNTN1-Ab were detected in HCs and patients with other demyelinating peripheral neuropathies. When the cut-off value of NF155-Ab by ELISA was tentatively determined as 2 U/ml, the concordance rate between CBA and ELISA was 100%. Results of ELISA and CBA for CNTN1-Ab were also consistent.

Conclusions:
Our ELISA kits are robust test systems that can determine concentrations of NF155-Ab and CNTN1-Ab, providing more precise diagnosis for the new diagnostic category of autoimmune nodopathies.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: ELISA, neurofascin 155, contactin 1, autoimmune nodopathy, Nodes of Ranvier
Phosphorylated TDP-43 aggregates in peripheral motor nerves of patients with motor neuropathy and neuronopathy

Poster No:
41e

Authors:
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Introduction:
One of the pathological hallmarks of ALS are phosphorylated TDP-43 (pTDP-43) aggregates in the cytoplasm of motoneurons and neuroglia in the brain. Although the axon exceed the total volume of motoneuron soma of several orders of magnitude, systematic studies investigating the presence and distribution of pTDP-43 aggregates within motor nerves are still lacking. Aim of this study is to define the TDP-43/pTDP-43 pathology in diagnostic motor nerve biopsies performed in a large cohort of patients presenting with a lower motor neuron syndrome and to assess whether this might be a discriminating tissue biomarker for ALS and non-ALS cases.

Methods:
We retrospectively evaluated 102 lower motor neuron syndrome patients referred to our centre for a diagnostic i motor nerve biopsy. Histopathologic criteria of motor neuron disease (MND) and motor neuropathy were applied by two independent evaluators, who were blind for clinical data. TDP-43 and phosphorylated TDP-43 (pTDP-43) were evaluated by immunohistochemistry (IHC), and results compared to final clinical diagnosis.

Results:
We detected significant differences between ALS and non-ALS cases in pTDP-43 expression in myelinated fibres: axonal accumulation was detected in 98.2% of ALS patients; however, intriguingly, it was also observed in 30.4% of non-ALS samples (P < 0.0001). Concomitant positive staining in Schwan cell cytoplasm was found in 70.2% of ALS patients vs 17.4% of non-ALS patients (P < 0.001). Notably, we were also able to detect pTDP-43 aggregates in ALS cases displaying normal features at standard histopathological analysis.

Conclusions:
Our findings demonstrated that a specific pTDP-43 signature is present in the peripheral nervous system of ALS patients, and might be exploited a specific, accessible tissue biomarker. The demonstration of pTDP-43 aggregates within motor nerves of living ALS patients, occurring prior to axonal degeneration, suggests that this is an early event that might contribute to disease pathogenesis.
References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Motor Neuropathy, Nerve biopsy, Motor Neuron disease, TDP43, aggregates
Introduction:
Understanding the relative importance of the phenotypic manifestations of the genetic neuropathies and their molecular underpinnings is an increasingly important task in this evolving era of targeted therapies. The aim of this study was to characterize the phenotypic and molecular profile of genetic neuropathies in the adult Irish population.

Methods:
A prospective database of 436 patients attending an Irish tertiary referral neuropathy clinic between 1st Jan 2014 and 31st Dec 2021 was analysed. Comprehensive clinical, electrophysiological and genetic characterization was performed on 198 patients with genetic neuropathies (pure neuropathy [153], multisystem [45]).

Results:
Charcot Marie Tooth (CMT) and related disorders were the most common pure inherited neuropathy (132 cases) with genetic diagnosis achieved in 102 (77%) cases. As expected, these were largely accounted for by known variants (PMP22 duplication [31], PMP22 deletion [18], GJB1 [13], MFN2 [7], MPZ [6], SH3TC2 [5], AARS [4]). However, the proportion of those with CMT2 (axonal CMT) achieving genetic diagnosis (20/36 [56%]) exceeded reports of previous studies (25%), with a significant minority (7 [35%]) accounted for by isolated segregating rare variants. Comprehensive phenotyping of those with multisystem neuropathies (including hereditary TTR amyloidosis [20], Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) [9]) assisted in eliciting genetic etiologies in 80% cases. Finally, several isolated kindreds with uncommon phenotypes driven by rare genetic variants (e.g., congenital insensitivity to pain/PRDM12) were recognized.

Conclusions:
This work supports the findings of previous studies in demonstrating that the vast majority of the more common genetic neuropathy phenotypic presentations may be explained by previously recognized genetic variants. Expert opinion adds value in explaining the genetic etiology in those with unusual phenotypes. In particular, detailed phenotyping and segregation analyses of informative kindreds may help realize the importance and extent of variation in phenotypic expression of putative pathogenic variants.

References:
Yes

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: Genetic, Epidemiology, Specialist, CMT2, Multisystem
Involvement of Poly (ADP-ribose) polymerase in Schwann cell death under high-glucose pyruvate-depleted conditions

Poster No:
43e

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Introduction:
Pyruvate functions as a glycolysis accelerator and an antioxidant under normoglycemic conditions; however, its role under hyperglycemic conditions remain unclear. We observed rapid Schwann cell death under high-glucose conditions in the absence of extracellular pyruvate, and its underlying mechanisms define the aim of this study.

Methods:
Immortalized mouse Schwann cells (IMS32) were exposed to normal (5 mM) and high glucose (>15 mM) conditions in the presence or absence of sodium pyruvate (1 mM) for up to 24 h. Cell viability and glucose metabolism under each culture condition were evaluated using MTS cell proliferation assay, Metabolomics and Extracellular Flux Analyzer. The activity of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and pyruvate dehydrogenase (PDH) was quantified using the respective assay kit.

Results:
Significant decreases in glycolytic flux, levels of some TCA cycle intermediates, including 2-oxoglutaric acid (2-OG), and mitochondrial respiration under high-glucose pyruvate-depleted conditions were observed. Supplementation with 2-OG or a poly (ADP-ribose) polymerase (PARP) inhibitor rucaparib restored glycolytic flux and intracellular ATP contents and prevented cell death under such conditions. It is interesting to note that 2-OG, but not rucaparib, improved mitochondrial respiration. Consistent with that finding, rucaparib restored the activity of GAPDH that catalyzes the first reaction of the pay-off phase of glycolysis with ATP formation, but not the activity of PDH that catalyzes the conversion of pyruvate to acetyl-CoA in mitochondria.

Conclusions:
Because GAPDH activity is suggested to be impaired by its poly ADP-ribosylation through PARP activation under high-glucose conditions, our findings suggest that rucaparib prevents the pyruvate depletion-induced cell death by sustaining ATP production via glycolysis, but not mitochondrial respiration. Exogenous pyruvate may play a pivotal role in maintaining ATP production under high-glucose conditions regardless of mitochondrial function. While this study contributes to the advancement of our understanding of Schwann cell metabolism under hyperglycemic conditions, the efficacy of pyruvate toward diabetic neuropathy awaits future analyses.

References:
No

References 1:

References 2:
References 3:

References 4:


**Keywords:** pyruvate, poly (ADP-ribose) polymerase, Schwann cells, glycolysis, mitochondrial respiration
**Cholesterol biosynthesis pathway is down regulated in late-onset CMT1B mouse model**

**Poster No:**
44e

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**Introduction:**
In most CMT1 neuropathies demyelination precedes axonal loss, which can be confounding when attempting to specifically address the mechanisms of axonal degeneration. Remarkably, the substitution of Threonine 124 by a Methionine in the myelin protein zero (MPZ) gene (P0T124M) results in an axonal neuropathy (late onset CMT1B or CMT2J) with little to no myelin damage, suggesting that the two processes are separable. To investigate axonal degeneration mechanisms in CMT1, we generated the P0T124M mouse model which fully recapitulates axonopathy observed in patients.

**Methods:**
We performed an unbiased large scale proteomic assay in sciatic nerves from 2-month-old P0T124M (beginning of axonal defects) mice.

**Results:**
Principal component analysis (PCA) revealed prominent changes in P0T124M as compared to WT. Confirming our previous electrophysiological (reduction of amplitudes but normal nerve conduction velocities) and morphological (increase of degenerative axons without compact myelin alteration) observations, Diseases and Functions analysis showed in P0T124M an increase of proteins related to neurodegeneration and a decrease of proteins involved in neuronal survival but no markers of myelin defect. DAVID gene enrichment and Ingenuity Pathway analysis (IPA) highlighted a deregulation of lipid metabolic processes, especially related to cholesterol biosynthesis. The expression of almost all the enzymes involved in this pathway was significantly decreased in P0T124M nerves. The analysis of total cholesterol levels confirmed the dramatic reduction in P0T124M nerves. Moreover, Caveolin1, involved in cholesterol trafficking and the major lipid raft (LR) protein in Schwann cells, is decreased in P0T124M.

**Conclusions:**
Because cholesterol alteration has dramatic effect on myelin studying its precise role in nervous system in-vivo is complex. In P0T124M, cholesterol content is severely decreased but myelin sheath is well compacted. This unique situation will allow us to address questions concerning the role of cholesterol in axonal function, lipid homeostasis and as a LR signaling molecule in axo-glia communication.

**References:**
No
References 1:

References 2:

References 3:

References 4:

Grant Support: Charcot-Marie-Tooth association, Telethon association

Keywords: Charcot-Marie-Tooth, Axonopathy, Cholesterol, Lipid raft, Axo-glia communication
Effects of oral immunosuppressive drugs in long term maintenance treatment of chronic inflammatory demyelinating polyradiculoneuropathy.

**Poster No:**
45e

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**Introduction:**
To determine the role of oral immunosuppressive drugs in maintaining remission in CIDP patients being tapered off from standard treatment options (mainly steroids) in terms of reduction in the frequency of relapse (INCAT disability score ≥ 1) and reduction in dose and/or withdrawal of steroids.

**Methods:**
The retrospective study of six months duration was carried out in a tertiary care hospital, Pakistan. All the patients diagnosed with CIDP on electrophysiological basis arriving at the neurology outpatient clinic from January 2015 to June 2020 were included.

**Results:**
Out of total thirteen patients, Azathioprine was used in nine, Mycophenolate Mofetil in two and Cyclosporine in two patients, with remission maintained in eight, one and zero patients respectively. Duration of immunosuppressants ranged from 3 to 24 months. Poor response was observed in patients with monoclonal paraproteinemia (n=2) or prior exposure to other oral immunosuppressants. Various small case series show similar benefits of oral immunosuppressants similar to our study.

**Conclusions:**
The study describes preliminary experience of potential role of cheaper and more convenient oral immunosuppressants (especially Azathioprine) as long term maintenance treatment of chronic inflammatory demyelinating polyradiculopathy and guides for large scale local observational and interventional studies.

**References:**
No

**References 1:**

**References 2:**

**References 3:**

**References 4:**

**Grant Support:**

**Keywords:** CIDP, chronic inflammatory demyelinating polyneuropathy, immunosuppressive drugs
Assessment of Cranial Nerve Involvement in Individuals with ATTR Ile107Val Amyloidosis

Poster No:
46e

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Institutions:
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Introduction:
Cranial nerve involvement is uncommon in hereditary amyloidosis, especially in Val30Met (p.Val50Met), the most common and well-studied variant globally. Ile107Val (p.Ile127Val) is a rare variant; however, case reports have demonstrated repeated involvement of cranial nerves, especially IX, X and XII, suggesting that this manifestation may be part of the phenotype of this variant. Cranial nerve involvement can contribute to diagnostic confusion with motor neuron disease and impact the quality of life and morbidity of the disease. It may present complications such as more significant weight loss associated with dysgeusia and risk of aspiration pneumonia due to dysphagia.

Methods:
This study aimed to evaluate the involvement of cranial nerves (V, VII, IX, X, and XII) in individuals with amyloidosis Ile107Val. The medical records of individuals with Ile107Val amyloidosis followed at a center for neuromuscular diseases between August 2017 and October 2021 were analyzed. Information from the neurological examination, assessment of forced vital capacity, and symptoms such as dysphagia, dysgeusia, and dysphonia were obtained.

Results:
The evaluation of the medical records of 14 individuals identified that 50% complained of dysphagia, 57% of dysgeusia, 43% of tongue atrophy, 43% dysphonia, 36% facial paresis, 29% masseter weakness, and 21% had forced vital capacity less than 50% of predicted with an indication for the use of non-invasive ventilation.

Conclusions:
Although this is a small, isolated-center sample, this work reinforces the involvement of cranial nerves as part of the clinical spectrum of this variant and emphasizes the importance of evaluating cranial nerves in the follow-up of individuals with Ile107Val amyloidosis. Recognizing these manifestations can favor an early diagnosis and reduce complications during the individuals' follow-up.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: amyloidosis, Ile107Val, Cranial nerve
Study of Motor Neurone Disease in No.2 Military Hospital (500) Bedded, Yangon, Myanmar: Single center experience

Poster No:
47e

Authors:
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Introduction:
Motor neurone disease (MND) is rapidly progressive neurodegenerative disease. In Myanmar, the neurophysiology and neuroimaging had developed within one decade. Therefore, the diagnosis of motor neurone disease is more accurate and ensure mimic syndromes are excluded.

Methods:
It was the cross-sectional descriptive study of motor neurone disease between August, 2017 and June, 2021 at neurology department of No.2 Military Hospital (500-bedded), Yangon.

Results:
Among 31 patients of motor neurone disease, mean age was 44.83 ± 15.60 years while 21 patients were male and 9 patients were female. According to the subtype, 23 (75%) patients had amyotrophic lateral sclerosis (ALS), 3 (10%) patients had monomelic amyotrophy, 2 (6%) patients had spinal muscular atrophy, 2 (6%) patients had progressive bulbar palsy and 1 (3%) patient had progressive muscular atrophy. Among the 23 patients of amyotrophic lateral sclerosis, mean age was 48.41 ± 11.59 years while the youngest patient was 31 years and the oldest one was 77 years. In ALS group, 12 patients were male and 9 patients were female. The average delay between onset of symptoms and diagnosis was 11 months in patients with amyotrophic lateral sclerosis. During study period, 13 patients of amyotrophic lateral sclerosis were died of aspiration pneumonia and respiratory failure while 5 patients were lost to follow up. The average life expectancy after symptoms onset was 3.5 year in ALS. Only two patients were received oral Riluzole during study period.

Conclusions:
The diagnosis of motor neurone disease remains challenging and end of life care service is limited in developing country.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:
Keywords: Motor neurone disease, Amyotrophic lateral sclerosis
Protein Interactors Of PMP22 – Shedding Light On The Molecular Role Of PMP22 In Health And Disease

Poster No:
48e

Authors:
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Institutions:
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Introduction:
Charcot-Marie-Tooth disease (CMT) 1A is the most common hereditary peripheral neuropathy with a prevalence of 1/5000. The disease is caused by a 1.5-fold increase in Peripheral Myelin Protein 22kDa (PMP22) gene dosage, affecting mainly the Schwann cells of the peripheral nervous system. Little is known about the biological role of PMP22 leading to the primary molecular pathomechanisms underlying CMT1A. By identifying protein-protein interactions of PMP22 we aim to expand the knowledge about its function and thereby improve treatment options, as no causative treatment for CMT1A has been established to date.

Methods:
Co-Immunoprecipitation (Co-IP) of PMP22 was performed from rat sciatic nerve lysates, followed by mass spectrometry and protein analysis. Additionally, a pull-down assay of PMP22 from HEK293T cells was carried out using the ALFA affinity tag.

Results:
The Co-IP from rat sciatic nerve lysates revealed multiple proteins that interact with PMP22. Most of these proteins fall into three prominent groups: cytoskeleton associated proteins, energy metabolism regulating proteins and proteins involved in endocytosis. Using the CMT rat model we observed altered expression of several interaction candidates on mRNA and protein levels in CMT1A. In addition, an actin fractionation assay showed alterations of actin dynamics in peripheral nerves from CMT rats. In vitro, we were able to demonstrate an acute impact of exogenously overexpressed PMP22 on cellular growth signaling, as well as interaction of PMP22 with several candidates resulting from the Co-IP for which an involvement in growth signaling cascades is known.

Conclusions:
Our results suggest molecular links between PMP22 and cellular processes that have previously been implicated in the function of PMP22 and the pathophysiology of CMT1A. We currently perform an in-depth analysis of the functional interaction of PMP22 with cytoskeletal dynamics and cellular growth signaling, and further aim to elucidate the structural details of the interactions that facilitate PMP22 (dys)function.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: PMP22, Schwann cell, CMT, Protein Interactions
A patient with peripheral neuropathy causing by LAMA2 mutations and anti-MAG antibody

**Poster No:**
49e

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**Introduction:**
We report a forty-eight year old man of peripheral neuropathy causing by LAMA2 mutations and anti-MAG antibody.

**Methods:**
We collected the clinical data of the patient.

**Results:**
We report a forty-eight year old man with motor difficulty and pricking and numbness of lower limbs for three years. The symptom was worse on the right side. He was born to consanguineous parents. Development milestone was achieved well. There was no known family history of neuropathy. CK was elevated to 1237U/L. Immunofixation electrophoresis detected paraprotein of IgM-lambda. Anti-MAG antibody of serum was positive. Electrophysiological studies revealed sensorimotor demyelinating polyneuropathy with axonal involvement. Sensory nerve action potentials were absent in both upper and lower limbs. Brachial plexus MRI revealed subtle elevated signal abnormalities. Nerve biopsy showed myelinated fibers were moderately decreased. The clinical features supporting a peripheral neuropathy. Genetic testing was done for hereditary sensory-motor neuropathy. The patient was found to have autosomal recessively inherited homozygous LAMA2 mutations (c.2749+1G>A). This mutation was graded PS1 according to ACMG.

**Conclusions:**
This case proved that peripheral neuropathy could be the dominant symptom of LAMA2 mutations, which is usually associated with congenital muscular dystrophy and limb girdle muscular dystrophy. It is rare but do present that the patient got both a hereditary and acquired peripheral neuropathy.

**References:**
No

**References 1:**

**References 2:**

**References 3:**

**References 4:**

**Grant Support:**

**Keywords:** LAMA2, MAG, peripheral neuropathy
Genome-wide Association Study for Chronic Axonal Polyneuropathy in the General Population

Poster No:
50e

Authors:
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Introduction:
To determine the contribution of common genetic variants in chronic axonal polyneuropathy in the general population, as clinical risk factors do not fully explain the disease susceptibility.

Methods:
This study was performed using two population-based cohort studies. Polyneuropathy diagnosis was based on screening in the Rotterdam Study and on ICD-10 codes in the UK Biobank. We determined the heritability of the sural sensory nerve amplitude and performed genome-wide association studies of chronic axonal polyneuropathy and sural sensory nerve amplitude. Furthermore, we zoomed in on variants in and surrounding 100 autosomal genes known to cause polyneuropathy based on literature and expert knowledge (candidate genes), and we performed a gene-based analysis. Analyses were adjusted for age, sex and population stratification.

Results:
Chronic axonal polyneuropathy was present in 2,357 of the 458,567 participants and 54.3% of the total population was female. Heritability of sural sensory nerve amplitude was 49% (p=0.067). No variants (p<5.0x10⁻⁸) or genes (p<2.7x10⁻⁶) reached genome-wide significance for its association with polyneuropathy. Zooming in on variants in and surrounding the candidate genes in the GWAS (p<3.9x10⁻⁶) and on these genes in the gene-based analysis (p<5.0x10⁻⁴) did neither yield significant results.

Conclusions:
We did not find common variants associated with chronic axonal polyneuropathy in the general population. Larger studies are needed to determine if genetic susceptibility based on both common and rare genetic variants affect the risk for chronic axonal polyneuropathy in the general population.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support: Prinses Beatrix Spierfonds (W.OR17-10)

Keywords: GWAS, genetics, common variants, chronic axonal polyneuropathy, neuropathy
Diagnostic Yield of Nerve Biopsy in the Evaluation of Peripheral Neuropathies

Poster No:
51e

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Introduction:
With progress in neurogenetics and neuroinflammation, the indications for nerve biopsies in the diagnostic evaluation of peripheral neuropathies have reduced. In the current study, we aimed to evaluate the diagnostic yield of nerve biopsies in patients with peripheral neuropathies.

Methods:
We performed a retrospective review of nerve biopsy reports from April 1998 to June 2021 of patients with peripheral neuropathies presenting to the Neuropathology Department at University of Malaya Medical Centre, Kuala Lumpur, Malaysia. The diagnostic value of the biopsies were determined based on the criteria by Midroni and Bilbao as follows: contributive (essential and helpful), non-contributive and inadequate.

Results:
A total of 108 nerve biopsies were reported. 64 (59.3%) were males and the mean age was 51.6 years, ranging from 13 to 86 years. The most common indications for performing a biopsy were peripheral neuropathy of unknown aetiology (42, 38.9%), followed by vasculitis (34, 31.5%) and amyloidosis (13, 12.0%). 94 (87.0%) were sural nerve biopsies. In 63 (58.3%) biopsies, the diagnostic value was contributive. Of this, 30 (27.8%) were essential and 33 (30.6%) were helpful. In contrast, 40 (37.0%) biopsies were non-contributive and 5 (4.6%) were inadequate. In the majority of cases, the nerve biopsy did not further the diagnosis (68, 63.0%). The greatest diagnostic yield for nerve biopsies were in determining the diagnosis of vasculitis (21, 19.4%) and amyloidosis (12, 11.1%).

Conclusions:
There is limited value in the diagnostic yield of nerve biopsy in the evaluation of patients with peripheral neuropathy, except in vasculitis and amyloidosis.

References:
Yes

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Amyloidosis, Nerve biopsy, Peripheral neuropathy, Sural nerve, Vasculitis
LOTS in the Needle Examination

Poster No:
52e

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Introduction:
Tay Sachs disease is a lethal neurodegenerative lysosomal storage disease. Patients typically present in childhood with hypotonia and developmental regression/delay, but can present in adolescence and, rarely, adulthood. The disease is caused by deficient B-hexosaminidase A activity due to recessive pathogenic variants in HEXA. We present a case of a male with late onset Tay Sachs disease, presenting as an adult onset motor neuronopathy.

Methods:
N/A

Results:
A 42 year old right-handed man presented with progressive proximal lower limb weakness which began in his early thirties. Prior to this he was an active man, with normal milestones and without any known family history of neuromuscular disease. Examination was significant for wasting of the thighs with scanty fasciculations and Gower's manoeuvre. There was mild weakness distally in the upper limbs, with proximal lower limb weakness. Reflexes were absent at the ankles bilaterally. CK was elevated 1374 (<190). Initial clinical impression was of a possible limb girdle muscular dystrophy (LGMD); however, whole exome sequencing (WES) with analysis of LGMD genes was negative. Subsequent nerve conduction studies were normal, but electromyography (EMG) showed complex repetitive discharges, fasciculation potentials, fibrillations and profuse and large amplitude positive sharp waves, favouring denervation as opposed to myopathy. SMN1 testing was normal and reanalysis of the WES data in light of the new clinical information revealed a homozygous pathogenic variant in HEXA c.805G>A (p.Gly269Ser). Hexosaminidase A levels were reduced 9 nmol/ml per hour in plasma (50 -250).

Conclusions:
This case highlights the importance of a detailed clinical and neurophysiological phenotype when analysing WES data. Tay Sachs disease should be considered in the differential for adult onset motor neuronopathy, albeit a rare cause.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: Tay Sachs, Neurophysiology
The patient journey towards a diagnosis of hereditary transthyretin amyloidosis – an Irish perspective

Poster No: 53e

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Introduction: Hereditary transthyretin amyloidosis (hATTR) is an inherited, multi-system disease which causes deposition of transthyretin amyloid fibrils in a variety of body tissues. Due to the variety of systems affected there can be a wide variability in symptom manifestation. This, along with a lack of awareness among healthcare professionals, can lead to significant delays in diagnosis. With emergence of disease modifying treatment, prompt diagnosis is of increasing importance to prevent both morbidity and mortality. In Ireland the T60A variant is the most commonly encountered mutation, with a carrier rate in North West Donegal previously estimated at 1.1%. We wished to study our patient population with regards to their journey towards a diagnosis of hATTR.

Methods: Retrospective analysis of patients with a confirmed diagnosis of hATTR attending a dedicated neuropathy clinic.

Results: To date 16 of 24 patient records have been analysed. 9 of these (56%) were male. Mean age at diagnosis was 62 years. 14 patients (87.5%) carried the T60A variant. Six patients were receiving treatment with Patisiran (as part of an early access programme or following inclusion in treatment trials, prior to approval of reimbursement in Ireland). Average number of years from first symptom to diagnosis of hATTR was 8.3 years. First symptom in eight patients was carpal tunnel syndrome (50% of all patients), whereas three patients presented with symptoms of large fibre peripheral neuropathy. The first symptoms in three patients were of autonomic neuropathy. One patient was asymptomatic. A family history was present pre diagnosis in 9 patients (56%), with 7 (44%) having family members diagnosed subsequently.

Conclusions: Patients with hATTR often have symptoms of disease for many years and may be significantly disabled by the time of diagnosis. Improved understanding of the patient journey towards a diagnosis of hATTR may lead to improved disease recognition and earlier diagnosis.

References: No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: Hereditary Transthyretin Amyloidosis
Diagnostic Dilemma in Pediatric Charcot Marie Tooth Disease

Poster No:
54e

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Introduction:
Charcot Marie Tooth disease (CMT) in children presents with a wide range of non-specific subtle symptoms causing diagnostic delays. Objective: To study the diagnostic difficulties of CMT disease in children with and without family history.

Methods:
Retrospective chart review of 54 children with CMT followed in the neuropathy clinic at Arkansas Children's hospital.

Results:
Our study population consists of 48% females. CMT type 1A was the most common type (55%). In patients with family history of CMT disease, symptoms were first noted at a mean age of 3.7 years, and concerns were expressed to a primary care provider at a mean age of 5 years. Mean ages at the time of clinical diagnosis and genetic diagnosis were 7.2 years and 8 years respectively. In patients without a family history of CMT disease, symptoms were first noted at a mean age of 5.6 years, and concerns were expressed to a primary care provider at a mean age of 6.7 years. Mean ages at the time of clinical diagnosis and genetic diagnosis were 9.3 years and 10.3 years respectively. The most common initial symptoms were abnormal gait (46%), frequent falling (44.4%) and feet pain (33.3%). Majority of the patients were initially referred to orthopedics (40%), followed by genetics (24%) and physical medicine and rehabilitation (20%). Final diagnosis of CMT disease was made by neurology (71%) in majority of our patients followed by physical medicine and rehabilitation.

Conclusions:
There is delay of about 4 years between symptom onset and diagnosis in children with family history and the delay is about 5 years in children without family history. Symptoms were recognized at an earlier age in children with family history. Though pediatric neurology was eventually involved in the care and diagnosis, initial referral was not made to neurology in majority of the children delaying the diagnosis.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** children, CMT, diagnosis
POEMS syndrome associated with anti-myelin associated glycoprotein neuropathy

Poster No:
55e

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Institutions:
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Introduction:
POEMS syndrome is a rare condition characterized by polyneuropathy, organomegaly, endocrinopathy, IgG-λ or IgA-λ type monoclonal protein monoclonal gammopathy, and skin lesions. Anti-myelin-associated glycoprotein(anti-MAG) neuropathy is a chronic, progressive and demyelination neuropathy, presenting as predominant sensory ataxia with or without mild muscle weakness. The anti-MAG neuropathy often occurs in the context of IgM monoclonal gammopathy, the most common of which are Waldenstrom's macroglobulinemia (WM) and monoclonal gammopathy of undetermined significance (MGUS). Here, we reported a rare case with POEMS syndrome concurrent with anti-MAG neuropathy.

Methods:
Patient data were obtained from the department of Neurology and the department of Haematology in our hospital

Results:
A 60-year-old man presented numbness and weakness in the extremities for 11 months, skin pigmentation and edema in the lower extremities for 6 months, and bloating and dyspnea for 1 month. He was found polyneuropathy, elevation of vascular endothelial growth factor, IgM-kappa type monoclonal protein, organomegaly (splenomegaly, hepatomegaly, and lymphadenopathy), endocrinopathy (adrenal, thyroid, gonadal, parathyroid), skin pigmentation, extravascular volume overload, weight loss and thrombotic diatheses. Nerve conduction studies confirmed demyelination and axonal degeneration. Anti-MAG antibody was positive in his serum and cerebral spinal fluid. POEMS syndrome concurrent with anti-MAG neuropathy was diagnosed. Therapy of high dose of methylprednisolone in combination of cyclophosphamide was not effective. However, edema and muscle strength improved treating by rituximab.

Conclusions:
POEMS syndrome associated with anti-MAG neuropathy is rare. The treatment is very challenging. This case showed us the therapeutic strategies for this disease.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: POEMS, anti-myelin-associated-glycoprotein, neuropathy, antibody, therapy
Prevalence estimation of transthyretin familial amyloid polyneuropathy in China based on genetic databases

Poster No:
56e

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Introduction:
Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a rare hereditary disease caused by single amino-acid changes in the transthyretin gene. Its global prevalence is traditionally estimated as 5,000 to 10,000. However, it might be underestimated and the exact prevalence of ATTR in China mainland remains unknown.

Methods:
GnomAD database and two Chinese population-based genomic sequencing databases, a public population-based genomic sequencing database named ChinaMAP and a commercial genomic sequencing database named Amcare lab gene database, were integrated to estimate the possible prevalence of TTR-FAP in world population and mainland Chinese population. The variants were divided into the five categories: affects function, probably affects function, uncertain significance, probably does not affect the function and does not affect function variants. Affects function and probably affects function were defined as pathological mutation variants. Prevalence estimation was calculated as pathological variant alleles/Total alleles in the database.

Results:
Five variants, including 441 alleles, were defined as pathological variants in gnomAD. The prevalence of TTR-FAP in the world population is thus 3.7/10,000. Two alleles were defined as pathological variants in the ChinaMAP database and 29 alleles in the Amcare lab exome database. Thus, the estimated prevalence interval of TTR-FAP in mainland China is 1.89/10,000-2.62/1,000 based on the exome database.

Conclusions:
The lower limit of prevalence interval in China mainland is 20-fold higher than that in America and Caucasians concluded by traditional epidemiological methods. In addition, together with the estimated prevalence of 3.7/10,000 in the world population, it shows that the previous prevalence was seriously underestimated concluded from traditional methods. Therefore, raising awareness of the disease is essential for recognizing TTR-FAP in its early stage.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** Transthyretin familial amyloid polyneuropathy, prevalence, genomic sequencing databases
Anti-AGO1 antibodies identify an immunomodulatory treatment-responsive sub-group of sensory neuronopathy

Poster No: 57e

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Institutions: 1University of Lyon / Saint-Étienne, Saint-Étienne (Saint-Priest-en-Jarez), France, 2University Hospital Saint-Étienne, Saint-Étienne, France, 3Université de Lyon, Lyon, France, 4University of Lyon, Lyon, France, 5Hospices Civils de Lyon, Lyon, France, 6) INSTITUT NEUROMYOGÈNE, INSERM U1217/ CNRS UMR 5310, Lyon, France

Introduction: Autoantibodies (Abs) improve diagnosis and treatment of idiopathic neurological disorders. Recently, Abs against Argonaute proteins (AGO) have been suggested as autoimmunity biomarkers in peripheral and central nervous system disorders, most frequently sensory neuronopathy (SNN) [1]. Here, we aim to reveal 1) the prevalence, 2) titers and IgG subclasses, 3) specific clinical pattern, and 4) treatment response of AGO Abs-associated SNN.

Methods: AGO1 Abs were screened by ELISA in 132 SNN, 301 non-SNN neuropathies, 274 autoimmune diseases (AID), and 116 healthy controls (HC). Seropositive cases were tested for IgG subclasses, and Abs titer. Conformational epitopes were detected by comparative denaturing/stabilizing ELISA.

Results: AGO1 Abs occurred in 44 patients, comprising significantly more SNN [17/132 (12.9%)] than non-SNN neuropathies [11/301 (3.7%); p = 0.001], AID [16/274 (5.8%); p = 0.02], or HC [0/116; p < 0.0001]. Abs titer ranged from 100-100,000. IgG subclass was mainly IgG1. AGO1 Abs were detected in 5/59 (8.5%) SNN patients without any autoimmune context. Conformational epitopes were recognized in 11/17 AGO1 Abs-positive SNN (65%). AGO1 Abs-positive SNN was more severe (SNN score: 12.2 vs. 11.0, p = 0.004; global areflexia: 13/17 [76%] vs. 29/75 [39%], p = 0.01; # abolished sensory nerve action potentials: 2.6 vs. 1.8, p = 0.046) and responded more frequently to immunomodulatory treatments (decrease of mRS ≥1 upon treatment: 7/13 [54%] vs. 6/37 [16%], p = 0.02) than AGO1 Abs-negative SNN. Multivariate logistic regression adjusted for potential confounders revealed AGO1 Abs as the only predictor of treatment response (OR 4.93, 1.10-22.24 95% CI, p = 0.03).

Conclusions: SNN is the most frequent neurological disorder with AGO1 Abs. AGO Abs-positive SNN have a specific clinical pattern and more frequently respond to immunomodulatory treatments independent of an autoimmune context. This warrants the search of AGO1 Abs in SNN in clinical practice.

References: Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Argonaute antibodies, Sensory neuronopathy, Anti-Su antibodies, Diagnosis, Treatment prediction
Diagnostic challenge: a complex regional syndrome with myokymic discharges on electrodiagnosis

Poster No:
58e

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Institutions:
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Introduction:
Complex regional syndrome (CRS) is a disorder characterized by pain, associated with sensory, autonomic, trophic, and motor abnormalities of a body region. CRS occurs usually after a minor or moderate tissue injury that begins locally and then spreads to other regions. A detailed clinical assessment is the cornerstone for the diagnosis, and electrophysiological tests help for differentiating between subtypes of CRS (the presence of nerve injury for CRS type I and without it for CRS Type II).

Methods:
We report a case of a 21-year old woman who presented with clinical manifestations of a regional motor and sensory syndrome, with evidence of myokymic discharges in electrodiagnosis. Her trauma history was positive for repetitive sprains on her left ankle in childhood, years before she consulted the Emergency Department.

Results:
The patient presented with a continuing pain disproportionate to any inciting event with hyperalgesia, edema and motor dysfunction. This clinical picture is compatible with a CRS diagnosis supported by the Budapest criteria. Nevertheless, she also had some atypical features: (1) the presence of myokymic discharges on EMG and (2) she didn't have a clear memorable event preceding symptom. The diagnostic approach initiated with the patient's chief complaint and associated symptoms, that are classically reported in CRS. Blood tests, imaging studies and electrodiagnosis were useful for ruling out other etiologies leading to a diagnosis of exclusion.

Conclusions:
This case illustrates the diagnostic challenge of a patient that presented with a motor and sensitive syndrome, without a clear recent history of trauma. After excluding radiculopathy, neuropathy, motor neuron disease and myopathy and with clinical improvement after physical therapy, the diagnosis of a CRS was made. Interestingly, electrodiagnosis showed myokymias as the only positive finding, considered an uncommon manifestation in CRS. It is relevant to emphasize the importance of beginning early physical therapy and taking into account the emotional component associated with pain.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** Cramps, Myokimia, Complex regional syndrome, EMG
Dropped head syndrome in Myasthenia gravis after a SARS-CoV-2 infection: Case Report

Poster No:
59e

Authors:
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Institutions:
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Introduction:
The current pandemic by the SARS-CoV-2 has affected the world's general population. While the predominant presentation is with respiratory disease, neurological complications are increasingly recognized. Post-infectious immune-mediated disorders such as Guillain Barré syndrome and Myasthenia Gravis (MG) have been described.

Methods:
We report a case of a patient with head ptosis and a postsynaptic myasthenic syndrome after a SARS-CoV-2 infection and a retrospective review of the literature of all the reported cases of myasthenia gravis de novo associated with SARS-CoV2 infection from march-2020 to april-2021.

Results:
Neurologic manifestations of patients infected with SARS-CoV-2 have been increasingly recognized. However, the pathophysiological mechanism is not yet known. Some authors propose that it might be a combination of the direct viral infection of nerve cells and the associated inflammatory response which can be parainfectious or post infectious 8. MG is an autoimmune disease where antibodies bind to AChR or to other postsynaptic proteins at the neuromuscular junction. Similar to what happened with Guillain-Barré syndrome, MG could also be the result of the autoimmune re-action triggered by SARS-CoV-2 infection. So far nine cases with SARS-CoV-2 infection who subsequently develop MG have been described, all with typical features including ptosis and diplopia.

Conclusions:
Further studies are required to investigate more about the relationship and the possible mechanisms that might cause MG after a SARS-CoV-2 infection. The unanswered question is whether we are facing a post-SARS-CoV-2 myasthenic syndrome or a manifestation of an unmasked MG being triggered by the infection.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:
Keywords: SARS-CoV-2, Myasthenia gravis, Dropped head, Autoimmune
Introduction:
POEMS syndrome, identified by its acronym P: polyneuropathy, O: organomegaly, E: endocrinopathy, M: M protein, S: skin changes. It is a paraneoplastic syndrome due to an underlying plasma cell neoplasm. The diagnosis of this entity is often delayed because the syndrome is rare and can be confused with other neurological disorders.

Methods:
Describe the clinical characteristics and outcomes in a series of cases of a patient with POEMS syndrome. Patients who met the diagnostic criteria for POEMS syndrome proposed by Dispenzieri were selected. These patients came from the in-patient medical consultation of different neurologists specialized in neuromuscular pathology in the period from 2005 to 2021; Likewise, a review of the Colombian literature of all published cases of patients diagnosed with POEMS syndrome was carried out. As a result, 16 cases of patients with this diagnosis were collected and reviewed.

Results:
The symptoms, clinical course, and treatment of our case series are similar to those published in the global literature. Early diagnosis and active treatment significantly modify the progression of the disease and its overall prognosis. The patients with the longest survival and the lowest disease burden were those who received adjuvant treatment with autologous stem cell transplantation.

Conclusions:
Early diagnosis and active treatment significantly modify the progression of the disease, as well as its overall prognosis. Patients with longer survival and lower disease burden were those who received adjuvant treatment with autologous stem cell transplantation. To the best of our knowledge, this is the largest case series of patients with POEMS syndrome published until now in Latin America.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:
Keywords: POEMS Syndrome, Polyneuropathy, Plasmocytoma, Castleman Disease, Paraneoplastic
Serum Neurofilament Light Chain as Biomarker of Charcot-Marie-Tooth Disease Type 1X Progression

Poster No:
61e

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Introduction:
X-linked Charcot-Marie-Tooth type 1 (CMT1X) is the second most frequent type of Charcot-Marie-Tooth (CMT) disease, which is the most common hereditary motor and sensory neuropathy. Neurofilaments are cytoskeletal neuron proteins, their light chains (NfL) are released after neuroaxonal injury. It has been suggested that NfL could be used as a biomarker for peripheral nervous diseases, including CMT, to assess disease severity and progression.

Methods:
Thirteen (n=13) CMT1X patients were enrolled in the study. Serum NfL concentrations were measured using the single-molecule array NfL assay. Disease severity was measured by clinical evaluation with CMT Neuropathy Score second version (CMTNSv2). A follow-up meeting was conducted after 3 years with repeated NfL measurements together with clinical evaluations.

Results:
Of the 13 patients enrolled in the study, 46% (6) were male, 54% (7) were female with mean age of 35.9 (± 12.3) years. Median (IQR) NfL concentration was 15.8 (31.3) pg/mL, and 16.4 (15.2) pg/mL in the follow-up measurement. Median (IQR) ∆NfL is 1.3 (11.6) pg/mL. Median (IQR) CMTNSv2 score was 17 (19), and 21 (16) in the follow-up measurement. Median (IQR) ∆CMTNSv2 was 2 (6). During the 3 year period, CMTNS score changed significantly (Z=-2.536, p=0.011), but NfL changes were not significant (Z=-1.569, p=0.117). There is very weak negative correlation between ∆NfL and ∆CMTNSv2, which is not significant (r=-0.029, p=0.929).

Conclusions:
Disease severity in CMT1X patients is with a tendency to increase. However, the NfL changes during the 3 year period were not significant, as well as correlation between disease severity and NfL changes, therefore NfL cannot be used as a biomarker of CMT1X progression for now. Repeated NfL measurements over a longer period of time, combined with disease severity evaluation might provide more information about the use of NfL in clinical practice to monitor disease progression.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

**Keywords:** Polyneuropathy, Genetic and inherited disorders
Small Fiber Neuropathy with Trisulfated Heparin Disaccharide or Fibroblast Growth Factor Receptor 3 Antibodies: A Single-Center Retrospective Study

Poster No:
62e

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Introduction:
Antibodies to trisulfated heparin disaccharide (TS-HDS) and fibroblast growth factor receptor 3 (FGFR-3) have been recently reported in small fiber neuropathy (SFN) cases. Therefore, we aimed to describe clinical features in such patients.

Methods:
We retrospectively evaluated both groups' demographic characteristics, clinical presentation, comorbidities, laboratory, biopsy, and electrophysiologic findings.

Results:
Ninety-three patients with a clinical diagnosis of small fiber neuropathy tested for these autoantibodies. In our cohort, 91.3% were women, 76.1% were white, and the median age at diagnosis was 47.5 years. Forty-six patients (49.4%) were positive for either TS-HDS or FGFR-3. Thirty-six (76%) of them were positive for the TS-HDS antibody alone. Of the seropositive group, 71.7% had non-length-dependent neuropathy, and 91.3% presented with chronic symptoms (> 3 months). The most common presenting symptoms were paresthesia/pain (93.5%), numbness (89.1%), and dry mouth/eyes (54.4%). Prior psychiatric diagnosis (69.6%), migraine (52.2%), and fibromyalgia (47.8%) were the most reported comorbidities. Elevated erythrocyte sedimentation rate and C-reactive protein were found in 32.6% and 28.3% of the patients. NCS studies demonstrated decreased sural sensory nerve action potential in 4 patients (8.7%). Skin biopsy was found abnormal in 80.4% of the patients.

Conclusions:
We showed the presence of these novel antibodies in almost half of the cases, with TS-HDS being more prevalent. In addition, we reported distinctive features of seropositive patients, which are positive and negative sensory symptoms along with sicca syndrome. The majority of the seropositive cases are non length-dependent which is indicative of ganglionopathy. Further studies involving more patients are needed to characterize this entity's features better.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

Keywords: Small fiber neuropathy, Autoantibodies, TS-HDS, FGFR-3, Ganglionopathy
Sudden increased spasticity in spinal cord injuries: the importance of assessing the peripheral nervous system

Poster No:
63e

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Introduction:
Spasticity is a disabling sequela of SCI, but also an important physiologic response to illness or other stressors. The physiatrist has a key role in recognizing, treating, and developing an effective plan focused on patient's individual goals.

Methods:
An unusual case report and its comprehensive approach.

Results:
An active 22-year-old man with T8 complete paraplegia reported sudden increase of spasticity, interfering with transfers and ADLs. No history of trauma, signs/symptoms of urinary infection or altered skin integrity. Bladder and bowel programs remained stable. Had equal neurologic level, with marked hyperreflexia, clonus and frequent extensor spasms. Labs were unremarkable. Rest was recommended (he stopped practicing wheelchair handball), oral antispasmodics dosing was increased and administration of botulinum toxin anticipated, without clinical improvement. One month later, he noticed slight swelling of the left knee. Normal knee X-ray. On ultrasound, there was obvious thickening of the left sciatic nerve involving its full length, until the subgluteal space, where an important change was also noticed in the structural organization of the subgluteal muscles (haematoma?). Hip MRI showed marked inflammatory changes of the left subgluteal space with unquestionable signs of sciatic nerve compression and left iliac and acetabulum edema. Anti-inflammatory therapy was introduced, with marked clinical improvement, which correlated with the MRI re-evaluation images (taken 2 months after starting therapy).

Conclusions:
This unusual case is presented for its diagnostic difficulties and challenging therapeutic choice. Altered spasticity is often a symptom as much as a warning sign. Quick management is crucial to achieve satisfactory results. In this case, the increased spasticity was probably due to traumatic compression of the sciatic nerve related to high impact transfers in a young athlete practising wheelchair handball.

References:
No

References 1:

References 2:

References 3:
References 4:

Grant Support:

Keywords: spinal cord injury, peripheral nerve injury, spasticity
Clinical And Molecular Characterisation Of A Scottish Charcot-Marie-Tooth Disease Cohort

Poster No: 64e

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Introduction:
Charcot-Marie-Tooth (CMT) disease is the most common hereditary neuropathy. Studies have previously characterised CMT cohorts in locations including Italy, Germany and USA. This Scottish single-centre retrospective cross-sectional study aimed to report frequency of CMT subtypes and characterise patients' clinical, genetic and electrophysiological features.

Methods:
Information was collected from medical records on National Health Service Clinical Portal from 150 molecularly characterised and 39 uncharacterised CMT patients attending a specialist clinic. Data included patient demographics, neurological examination, family history, pain, allied health professional reports, genetic reports, neurophysiology reports, and letters from other specialties. Data were analysed using descriptive statistics.

Results:
The cohort contained 150 molecularly characterised (65 male and 85 female) and 39 uncharacterised (23 male and 16 female) patients. This included 78 patients with CMT1A, 5 with CMT1B, 5 with CMT1E, 25 with CMT1X, 17 with CMT2, 3 with CMT4 and 14 with Hereditary Neuropathy with Liability to Pressure Palsies (HNPP). There was similarity between subtypes with features such as pain and weakness; however, differences were observed. In this cohort, CMT1A patients had a lower prevalence of distal muscle wasting; CMT1B patients had an earlier mean age at presentation (13.5 years) and greater prevalence of scoliosis; CMT1E patients had a later mean age at presentation; CMT1X patients had greater prevalence of tremor; HNPP patients showed lower morbidity. Of the uncharacterised patients, 37 had electrophysiology reported (24 axonal, 5 demyelinating, 5 mixed and 3 with other findings).

Conclusions:
This study provides the first data on CMT subtypes and their associated clinical and electrophysiological characteristics within a Scottish cohort. The data broadly align with similar studies across the world, and highlight the morbidity associated with the disease. It is hoped these findings will provide a representative baseline that may contribute to further CMT studies and assist clinicians in investigation and management of this prevalent disease.

References:
No

References 1:

References 2:
References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth, Genetics, Neurophysiology, Scotland
Targeting the Expression of the Sigma 2 Receptor/ TMEM97 to Find Novel Therapeutics for Neuropathic Pain

Poster No:
65e

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Introduction:
Neuropathic pain is a debilitating condition that affects nearly 20% of the American adult population. Current therapeutics have proven to lack efficacy and often lead to severe side-effects. The Sigma 2 receptor, recently identified as TMEM97, has been shown to produce analgesia in mouse neuropathic pain models through TMEM97-binding compounds. To better understand this anti-neuropathic pain effect, we sought to investigate the location of TMEM97 expression in both humans and mice.

Methods:
We used RNAscope Fluorescent Multiplex assay on fresh frozen tissue samples from both mouse and human dorsal root ganglia (DRG). Previous data has identified that TMEM97 is highly expressed in nociceptors of mice. Therefore, we used Nav 1.8 as a marker for nociceptor positive cells to test this further. For human tissue, we used the V2 kit as well as Akoya dyes to fluorescently tag the mRNA of interest. TMEM97 was expressed in channel 1 and tagged with cy3, and Nav 1.8 was expressed in channel 3 and tagged with cy5. For mouse tissue, we used the V1 kit with Opal dyes to fluorescently tag the mRNA of interest. TMEM97 was expressed in channel 3 and tagged with blue, and Nav 1.8 was expressed in channel 1 and tagged with 488 (Fluorescein).

Results:
We were able to demonstrate that TMEM97 is expressed widely in both human and mouse sensory neurons, particularly in Nav 1.8+ nociceptors.

Conclusions:
Our results further point towards the function of Nav1.8+ nociceptors as the target of TMEM97-binding compounds. Our next steps for RNAscope would be to investigate other non-neuronal markers and identify whether TMEM97 is expressed in other cells such as satellite glial cells, schwann cells, and immune cells in humans.

References:
No

References 1:

References 2:

References 3:

References 4:
Grant Support:

**Keywords:** Neuropathic pain, TMEM97, RNAscope, Translational Research, Sensory Neurons

Poster No:
66e

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Introduction:
Distal hereditary motor neuropathies (DHMN) are a group of non-fatal motor neuron diseases which cause length-dependent axonal degeneration of the lower motor neurons leading to chronic disability. We reported a novel structural variation (SV) event in a large, genetically unsolved Australian family with autosomal dominant DHMN (DHMN1: OMIM %182960). The SV involved the duplication and inversion of a 1.35 Mb sequence at chromosome 7q36.3 that was inserted into the DHMN1 locus at chromosome 7q34-q36. The DHMN1 SV duplicates the first 10-exons of the ubiquitin-protein E3 ligase gene (UBE3C) which forms a novel gene-intergenic fusion transcript (UBE3C-IF).

Methods:
PolyA RNA sequencing was used to generate global transcriptomic profiles of DHMN1 and control iPSC-derived spinal motor neurons (iPSC-sMN). Sanger sequencing and PCR were used to validate UBE3C-IF. Transgenic C. elegans expressing UBE3C-IF in GABA-ergic motor neurons were generated to model the functional consequences of UBE3C-IF in vivo.

Results:
Global transcriptome profiles did not change between DHMN1 and control iPSC-sMN. Fusion gene analysis revealed the presence of a novel gene-intergenic fusion involving the UBE3C partial copy. UBE3C-IF is transcribed from the reverse strand and incorporates a terminal pseudo-exon from sequence within the DHMN1 locus. The UBE3C-IF transcript is not degraded by nonsense-mediated decay. DHMN1 iPSC-sMN harbouring the UBE3C-IF transcript show a significant reduction of UBE3C protein levels. C. elegans expressing the UBE3C-IF transcript show neuronal synaptic transmission deficits. Furthermore, the transgenic animals are susceptible to heat stress which may implicate defective protein homeostasis in DHMN1 pathogenesis.

Conclusions:
Formation of the UBE3C-IF gene intergenic transcript is a new mechanism of axonal and motor neuron degeneration and highlights the pathogenic impact of SV in families such as DHMN1. This pioneering work demonstrates the novelty of gene-intergenic fusions as an important but understudied mechanism for motor neuron diseases that will provide essential new knowledge and inform avenues for developing treatment therapies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, iPSC, axonal degeneration, structural variation, gene-intergenic fusion