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Poster No: 1 | Patisiran in patients with hATTR amyloidosis post-orthotopic liver transplant: 12-month results

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Introduction: Hereditary transthyretin-mediated (hATTR) amyloidosis is a progressive, debilitating disease. Orthotopic liver transplant (OLT) eliminates circulating variant transthyretin (TTR) to slow progression in early-stage hATTR amyloidosis. Patisiran reduces production of variant and wild-type TTR. The APOLLO study showed patisiran to halt or reverse polyneuropathy and improve quality of life in patients who had not undergone OLT.

Methods: Phase 3b open-label study (NCT03862807) to evaluate the safety, efficacy, and pharmacokinetics (PK) of patisiran in patients with hATTR amyloidosis with polyneuropathy and disease progression post-OLT. Patients received patisiran 0.3 mg/kg intravenously q3w for 12 months. Data as of March 10, 2020 are presented, with 12-month efficacy and safety to be presented.

Results: Twenty-three patients enrolled and received patisiran in the study. Median age was 58.0 years, 13 (56.5%) were male, and 15 (65.2%) had the V30M mutation. At baseline, 1 (4.3%) patient had polyneuropathy disability (PND) score I, 9 (39.1%) PND II, and 13 (56.5%) PND IIIA/B. Five patients (21.7%) had New York Heart Association (NYHA) classification I, 5 (21.7%) NYHA II, and none had NYHA III/IV at study baseline. At month 6, the mean (SEM) TTR level was 21.2 (3.7) mg/L, representing an 89.2 (2.0) percent reduction from baseline. All patients experienced at least 1 adverse event (AE) and 5 (21.7%) patients experienced at least one serious AE; majority of AEs were mild or moderate in severity. Liver function tests were stable in the majority of patients. One patient experienced transplant rejection deemed unrelated to patisiran by investigator; biopsy was consistent with inadequate immunosuppression.

Conclusions: To date, the reduction in serum TTR levels and safety profile of patisiran in patients with hATTR amyloidosis with polyneuropathy with disease progression post-OLT has been consistent with results observed in APOLLO. Patisiran has the potential to address an unmet need in this patient population.

Grant Support: Alnylam Pharmaceuticals.

Keywords: Hereditary transthyretin-mediated amyloidosis, Orthotopic liver transplant, Patisiran, Polyneuropathy, Transthyretin.

Poster No: 2 | Automation of quantifying axonal loss through MRI and deep learning in patients with peripheral neuropathies

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Introduction: Axonal loss determines the final disability in patients with peripheral neuropathies. Consequently, axonal loss results in intramuscular fat accumulation, which can be measured through MRI-based muscle fat fraction (FF). Indeed, volumetric muscle FF has been a promising biomarker in CMT1A. However, the responsiveness is yet to be improved given the inhomogeneity of muscle denervation. In this study, we developed a deep learning-based method to automate the quantification of individual muscle FF, which mitigates the laborious manual segmentations and enables the use of individual muscle FF as outcome measures in upcoming longitudinal studies to track axonal loss.

Methods: MRI data from 24 patients with peripheral neuropathies and 19 controls were manually segmented for all individual muscles in the thigh and calf locations. These data were randomly divided into two groups for either training (n_thigh = 23; n_calf = 10) or testing (n_thigh = 17; n_calf = 12). A deep learning-based 3D U-Net model was developed to automatically segment individual muscles. Dice coefficient (DC), Bland-Altman and Pearson Correlation analyses were performed to evaluate the performance of the automation.

Results: The DC values varied from 0.83 ± 0.17 to 0.98 ± 0.02 for thigh muscles; and from 0.63 ± 0.18 to 0.96 ± 0.02 for calf muscles. The 95% confidence intervals of Bland-Altman analysis and Pearson coefficient between manual FF and automatic FF were [0.49%, −0.56%] and $r^2 = 0.989$ for thigh muscles; [0.84%, −0.71%] and $r^2 = 0.971$ for calf muscles, respectively.

Conclusions: The automation of individual muscle segmentation is compromised by many challenges such as the small size and irregular

shapes of muscles. Furthermore, separating a muscle from adjacent muscles often depends on knowledge of anatomy, but not characteristics of MRI images. Our automated method achieved excellent agreement with those from manual segmentations. There were very few outliers that can be readily corrected in future refining. On-going effort is to leverage the model to track partially denervated muscles longitudinally in patients with inherited peripheral neuropathies.

Grant Support: This study is supported by grants from NIH (R01NS066927, R01NS115748), VA BLR&D (IBX003385A), and Detroit Medical Center Foundation (2018-3328).

Keywords: Axonal Loss, Inherited Neuropathies, Magnetic Resonance Imaging, Deep Learning, Muscle Fat Fraction.

Poster No: 4 | **Cross-sectional area reference values for peripheral nerve ultrasound in adults: A systematic review and meta-analysis - part I: Upper extremity nerve**

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Introduction: Measurement of the cross-sectional area (CSA) of peripheral nerves using ultrasound is useful in the evaluation of focal lesions like entrapment syndromes and inflammatory polyneuropathies. We performed a systematic review and meta-analysis of published CSA reference values for upper extremity nerves.

Methods: We included available to date nerve ultrasound studies on healthy adults and provide meta-analysis for CSA of the following nerves: median nerve at wrist, forearm, upper arm; ulnar nerve at Guyon loge, forearm, elbow, upper arm; radial nerve at upper arm. We report regression and correlation analyses for age, gender, height, weight, geographic continents and publication year.

Results: We included 74 studies with 4186 healthy volunteers (mean age 42.7 years) and 18 226 examined nerve sites. Calculated mean pooled CSA of median nerve at wrist was 8.3 mm2 [95% confidence interval (95%CI):7.9-8.7, n = 4071], at forearm 6.4 mm2 (95% CI:5.9-6.9, n = 3021), at upper arm 8.3 mm2 (95%CI:7.5-9.0, n = 1388), of ulnar nerve at Guyon loge 4.1 mm2 (95%CI:3.6-4.6, n = 1688), at forearm 5.2 mm2 (95%CI:4.8-5.7, n = 1983), at elbow 5.9 mm2 (95%CI:5.4-6.5, n = 2551), at upper arm 6.6 mm2 (95% CI:5.1-6.1, n = 1737), of radial nerve 5.1 mm2 (95%CI:4.0-6.2, n = 1787). Substantial heterogeneity across studies (I2 > 50%) was found only for radial nerve. Subgroup analysis revealed a positive effect of age for median nerve at wrist and for height and weight for different sites of ulnar nerve.

Conclusions: We provide the first meta-analysis on CSA reference values for the upper extremities with no or only low heterogeneity of reported CSA values in most nerve sites. Our data facilitate the goal of an international standardized evaluation protocol.

Keywords: nerve ultrasound, meta-analysis.

Poster No: 5 | **Cross-sectional area reference values for peripheral nerve ultrasound in adults: A systematic review and meta-analysis - part II: Lower extremity nerve**

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Introduction: Measurement of the cross-sectional area (CSA) of peripheral nerves using ultrasound is useful in the evaluation of focal lesions like entrapment syndromes and inflammatory polyneuropathies. We performed a systematic review and meta-analysis of published CSA reference values for lower extremity nerves.

Methods: We included available to date nerve ultrasound studies on healthy adults and provide meta-analysis for CSA of the following nerves: fibular nerve at fibular head, popliteal fossa; tibial nerve at popliteal fossa, malleolus; sural nerve at the level of the two heads of gastrocnemius muscle. We report regression and correlation analyses for age, gender distribution, height, weight, and geographic continents.

Results: We included 16 studies with 1001 healthy volunteers (mean age 47.9 years) and 4023 examined nerve sites. Calculated mean pooled CSA of fibular nerve at fibular head was 8.4 mm2 [95% confidence interval (95%CI):6.8-9.9 mm2, n = 1166], at popliteal fossa 7.9 mm2 (95% CI:6.6-9.2 mm2, n = 995), of tibial nerve at popliteal fossa 25.9 mm2 (95%CI:17.5-34.4 mm2,n = 771), at malleolus 10.0 mm2 (95% CI:7.7-12.4 mm2, n = 779), of sural nerve 2.4 mm2 (95%CI:1.7-3.1 mm2, n = 312). Substantial heterogeneity across studies (I2 > 50%) was found only for tibial nerve at popliteal fossa. Subgroup analysis revealed a lower CSA of tibial nerve at popliteal fossa and sural nerve in studies conducted in Europe than in America and New Zealand.

Conclusions: We provide the first meta-analysis on CSA reference values for the lower extremities with no or only low heterogeneity of reported CSA values in all nerve sites except tibial nerve at popliteal fossa. Our data facilitate the goal of an international standardized evaluation protocol.

Keywords: nerve ultrasound, meta-analysis.

Poster No: 6 | **Cross-sectional area reference values for peripheral nerve ultrasound in adults: A systematic review and meta-analysis - part III: Cervical nerve root**

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Introduction: Measurement of the cross-sectional area (CSA) of cervical nerve roots using ultrasound is useful in the evaluation of inflammatory polyneuropathies and measurement of CSA of the vagal nerve might give information about involvement of autonomic nervous system. We performed a systematic review and meta-analysis of published CSA reference values for cervical nerve roots and vagal nerve.

Methods: We included available to date nerve ultrasound studies on healthy adults and provide meta-analysis for CSA of the following nerves: cervical nerve roots C5, C6, and C7 as well as vagal nerve in carotid sheath at the carotid bifurcation level. We report regression and correlation analyses for age, gender, height, weight and geographic continents.

Results: We included 11 studies with 885 healthy volunteers (mean age 42.7 years) and 3149 examined nerve sites. Calculated mean pooled CSA of C5 root was 5.6 mm2 [95% confidence interval (95% CI):4.6-6.7 mm2, n = 911], of C6 root 8.8 mm2 (95%CI:7.4-10.3 mm2, n = 909), of C7 root 9.5 mm2 (95%CI:8.0-10.9 mm2,n = 909), of vagal nerve 2.2 mm2 (95%CI:1.5-2.9 mm2, n = 420). No heterogeneity was found across studies for any site. Subgroup analysis revealed no significant effects of age, gender, height, weight and geographic continents on CSA of any of these nerve sites.

Conclusions: We provide the first meta-analysis on CSA reference values for the cervical nerve roots and the vagal nerve with no heterogeneity of reported CSA values in all nerve sites. Our data facilitate the goal of an international standardized evaluation protocol.

Keywords: nerve ultrasound, meta-analysis.

Poster No: 7 | HELIOS-A: 9-month results from the phase 3 study of vutrisiran in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy

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Introduction: Hereditary transthyretin-mediated (hATTR) amyloidosis, also known as ATTRv amyloidosis, is a rapidly progressive and fatal disease caused by misfolded transthyretin (TTR) that accumulates as amyloid fibrils in multiple tissues and organs. Vutrisiran, an investigational RNAi therapeutic for the treatment of ATTR amyloidosis, targets liver-expressed variant and wild-type TTR.

Methods: HELIOS-A (NCT03759379) is a Phase 3, global, open-label study of vutrisiran 25 mg SC every 3 months in patients with ATTRv amyloidosis with polyneuropathy who were randomized (3:1) to vutrisiran or patisiran, a reference comparator RNAi therapeutic approved for hATTR amyloidosis with polyneuropathy based on the APOLLO study. Randomization was stratified by TTR genotype (V30M vs non-V30M) and baseline NIS score (<50 vs ≥50). The APOLLO placebo arm (N = 77) serves as an external control for the primary and most secondary endpoints. Month 9 efficacy analyses include change from baseline in mNIS +7 (primary endpoint), Norfolk QOL-DN (secondary), and 10-m walk test (10-MWT) (secondary), compared to APOLLO placebo arm.

Results: HELIOS-A enrolled 164 patients (122 [74.4%] vutrisiran, 42 [25.6%] patisiran) across 57 sites in 22 countries. Vutrisiran met the primary endpoint ($P < 0.001$) and achieved statistically significant results ($P < 0.001$) for all planned secondary endpoints (Norfolk QOL-DN and 10-MWT). The majority of patients showed improvement in neurologic impairment and quality of life (QOL) relative to baseline. Vutrisiran demonstrated an acceptable safety profile; most common adverse events (AEs) in vutrisiran-treated patients included diarrhea, pain in extremity, fall, and urinary tract infections which occurred at a similar or lower rate vs the APOLLO placebo arm.

Conclusions: The 9-month primary analysis data demonstrate that vutrisiran improves neuropathy and QOL in patients with ATTRv amyloidosis with polyneuropathy. HELIOS-A will continue to investigate the efficacy and safety of vutrisiran through the 18-month treatment and extension periods.

Grant Support: Alnylam Pharmaceuticals.

Keywords: hATTR, ATTRv, amyloidosis, polyneuropathy, vutrisiran.

Poster No: 8 | Relation of exercise and pain in patients with idiopathic distal axonal polyneuropathies

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Introduction: Regular exercise is known to improve outcome measures in patients with diabetic polyneuropathy, however, little is

known of the effects of exercises in those with idiopathic polyneuropathy (IPN). The aim of this study was to look at a how exercise habits influence a broad range of outcome measures in a well-characterized cohort of patients with idiopathic distal, symmetrical, axonal polyneuropathy.

Methods: We reviewed the records of 324 patients with a diagnosis of IPN who were enrolled in the Peripheral Neuropathy Research Registry (PNRR) and whose collected dataset included exercise information. Each patient had exercise routine data including type, frequency, and duration of activities. These components were combined to calculate an average weekly metabolic equivalents (METs) for each participant. We then divided patients into four categories based on average METs and analyzed whether exercise category had an effect on any of the patient-reported outcomes including pain, numbness, or muscular weakness. We repeated this analysis controlling for metabolic syndrome factors, including Hemoglobin A1c, systolic and diastolic blood pressure, high density lipids level, triglyceride level, and body mass index as defined by the Adult Treatment Panel III Guidelines.

Results: Patients with IPN who exercised were less likely to report painful neuropathy independent of their average METs per week ($P < 0.01$) and even after controlling for the features of metabolic syndrome ($P < 0.05$). Patients who participated in lower METs activities were significantly more likely to have neuropathic pain but no other features of peripheral neuropathy such as numbness, weakness, or balance difficulties.

Conclusions: This study suggests that exercise, independent of intensity, duration, or frequency, may benefit patients with idiopathic neuropathy. Patients who exercised were less likely to have painful neuropathy, which may mean that physical activity can be used to manage painful neuropathy symptoms alongside more traditional neuropathic pain medications.

Grant Support: The Foundation for Peripheral Neuropathy.

Keywords: idiopathic axonal polyneuropathy, exercise, METs, neuropathic pain.

Poster No: 9 | Determining the utility of the Guillain-Barré syndrome classification criteria

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Introduction: Several variants of the Guillain-Barré syndrome (GBS) and Miller Fisher syndrome (MFS) exist but their frequencies vary in different populations and do not always meet the inclusion criteria of the existing diagnostic criteria. However, the GBS classification criteria by Wakerley et al. recognize and define the clinical characteristics of each variant and in the current study, we apply this criteria to our GBS and MFS cohort with the aim of determining their utility.

Methods: Consecutive GBS and MFS patients presenting to our center between 2010 and 2020 were analyzed. Patients' clinical characteristics, electrophysiological data and anti-ganglioside antibody profiles were utilized in determining the clinical classification.

Results: A total of 132 patients with GBS and its related disorders were classified according to the new classification criteria as follows: 64 (48.5%) classic GBS, 2 (1.5%) pharyngeal-cervical-brachial (PCB) variant, 7 (5.3%) paraparetic GBS, 29 (22%) classic MFS, 3 (2.3%) acute ophthalmoparesis, 2 (1.5%) acute ataxic neuropathy, 2 (1.5%) Bickerstaff brainstem encephalitis (BBE), 17 (12.9%) GBS/MFS overlap, 4 (3%) GBS/BBE overlap, 1 (0.8%) MFS/PCB overlap and 1 (0.8%) polyneuritis cranialis. The electrodiagnosis was demyelinating in 55% of classic GBS but unclassified in 79% of classic MFS patients. Anti-GM1, anti-GD1a, anti-GalNAc-GD1a and anti-GD1b IgG ganglioside antibodies were more commonly detected in the axonal GBS subtype whereas the anti-GQ1b and anti-GT1a IgG ganglioside antibodies were more common in the classic MFS and its subtypes.

Conclusions: In our cohort of patients, the majority of patients met the criteria of either classic GBS or MFS but a variant was seen in a third of patients. These findings support the need to recognize variants of both syndromes in order to achieve a more complete case ascertainment in GBS.

References

1. Fokke C, van den Berg B, Drenthen J, Walgaard C, van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. Brain. 2014;137:33-43.

2. Wakerley BR, Uncini A, Yuki N, GBS Classification Group. Guillain-Barré and Miller Fisher syndromes: new diagnostic classification. Nat Rev Neurol. 2014;10:537-44.

3. Tan CY, Razali SNO, Goh KJ, Shahrizaila N. Diagnosis of Guillain-Barré syndrome and validation of the Brighton criteria in Malaysia. J Peripher Nerv Syst. 2020;25:256-64.

4. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol. 1990;27(Suppl):S21-4.

Keywords: Guillain-Barré syndrome, Miller Fisher syndrome, Wakerley classification, Brighton criteria, Bickerstaff brainstem encephalitis.

Poster No: 10 | Valency dictates anti-Nfasc155 IgG4 pathogenicity

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Introduction: The presence of autoantibodies targeting cell adhesion molecules at paranodes (CNTN1, Nfasc155, Caspr1) has recently been associated with subgroups of patients with chronic inflammatory demyelinating polyneuropathy (CIDP). These novel biomarkers had

important clinical benefits and helped both the diagnosis and the treatment orientation of the patients. We recently demonstrated that anti-Nfasc155 IgG4 induces paranodal disorganization and leads to conduction alterations and gait abnormalities in animal models. These data critically helped demonstrating the pathogenicity of these antibodies. Because, IgG4 are known to undergo exchange of their variable, we here investigated whether valency modulates the pathogenicity of anti-Nfasc155 IgG4.

Methods: IgG4 were purified using selective purification beads (CaptureSelect) from the plasma of two CIDP patients. Papain and IdeS digestion were performed using Pierce's Fab preparation kit (Thermofisher) and FragIT kit (Genovis) according to manufacturer's protocols. For intraneural injections, Lewis rats were anesthetized and sciatic nerve were injected with 10 μg of antibody. Passive transfer models were performed as previously described[1].

Results: To demonstrate this, we have digested anti-Nfasc155 IgG4 with papain or IdeS to generate monovalent Fab or bivalent F(ab')2, respectively. We first assured that the enzymatic cleavage did not affect the affinity of Fab and F(ab')2 for Nfasc155, then we injected the antibodies in neonatal animals to test their impact on paranode formation. Both native IgG4 and F(ab')2 antibodies potently abrogated paranode formation. By contrast, monovalent Fab antibodies did not have pathologic consequences. Also, only native IgG4 and F(ab')2 antibodies were able to induce Nfasc155 aggregation at adherens junctions.

Conclusions: Our results demonstrate that the bivalency of anti-Nfasc155 IgG4 dictates their pathogenicity. This also highlighted that strategies aiming at rendering IgG4 monovalent may be of benefits.

References

1. Manso C, Querol L, Lleixa C, et al. Anti-Neurofascin-155 IgG4 antibodies prevent paranodal complex formation in vivo. Journal of Clinical Investigation 2019; 129(6): 2222-36.

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Keywords: paranode, myelin, conduction, demyelination, antibody.

Poster No: 11 | A recurrent MORC2 mutation causes CMT2Z

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Introduction: CMT2Z is a dominantly inherited axonal neuropathy caused by mutations in MORC2. Clinical features range from proximal weakness with sensory loss to a spinal muscular atrophy-like presentation.

Methods: We evaluated three individuals from two unrelated families, including clinical electrophysiology, and a commercial genetic panel.

Results: We found a p.Ala406Val (c.1217C > T) mutation in MORC2 in all three individuals. The neuropathy began in childhood to early adulthood, with distal weakness progressing to proximal weakness. Vinblastine (for Hodgkin lymphoma) acutely worsened the weakness in one patient.

Conclusions: The identification of two additional, unrelated families with the same p.Ala406Val mutation in MORC2 and severe neuropathy demonstrates the pathogenic role of this mutation. In addition, we report the first case of vinblastine neurotoxicity in CMT2Z. Thus, it seems prudent to carefully monitor a patient with CMT for whom therapy with any vinca alkaloid is being considered.

Keywords: CMT2Z, neuropathy, Charcot-Marie-Tooth disease, vinblastine.

Poster No: 12 | Improvement of intractable common peroneal neuroma pain with a more proximal nerve block: A case report

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Introduction: Neuromas usually form after a nerve injury during its repair process; however, they can also be associated with various syndromes. Neuromas can become painful with time due to: nerve compression by scar tissue, traction injury, nerve ischemia, and peripheral and central sensitization. Conventional treatments include pharmacological modalities, desensitization mirror therapy, injections, and surgical interventions.

Methods: An 84-year-old male presented with a history of gradually worsening chronic right lateral calf pain for 5 years. The pain was unresponsive to neuropathic pain medications, opioids, injections, nerve blocks, and surgery. At the very onset, lumbar radiculopathy was ruled out with clinical examination, negative MRI of lumbar spine and EMG/NCS. Lower extremity MRI had revealed common peroneal cystic change suggestive of neuroma around fibular head and an old-healed tibial midshaft fracture indicative of previous injury. Patient subsequently underwent Right peroneal neuroplasty and exploration at fibular head, however the surgery did not improve his pain. He then underwent Right common peroneal nerve block at fibular head with ultrasound guidance which was diagnostic but provided only a few hours of pain relief. After reviewing his complicated treatment history, a common peroneal nerve block with 5 mL of 0.5% Bupivacaine was performed in the popliteal region using ultrasound guidance.

Results: Patient experienced sustained greater than 50% pain improvement with the diagnostic common peroneal nerve block at the popliteal area. Even at 4 months post the popliteal block, patient reported continual pain relief and significant improvement in his function and quality of life.

Conclusions: This is the first report of prolonged pain relief for painful peroneal neuroma with a more proximal nerve block after a distal block provided only few hours of relief. The likely reason may be widespread peripheral sensitization of the common peroneal nerve. Hence, peripheral sensitization should be considered an important pathophysiology in painful neuroma while determining interventional treatment.

Keywords: neuroma, common peroneal nerve, ultrasound, nerve block, peripheral sensitization.

Poster No: 13 | **Defective vestibular function may contribute to severe sensory ataxia in PMP22-related congenital peripheral hypomyelination**

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Introduction: Peripheral myelin protein 22 (PMP22) related neuropathies account for over 50% of inherited peripheral neuropathies (Charcot-Marie-Tooth-CMT). While a PMP22 duplication is responsible for the majority of the dominant cases, two loss-of-function pathogenic variants have been reported only in a minority of cases. The associated phenotype is consistent with a congenital, Dejerine-Sottas like, peripheral hypomyelination syndrome. This is characterized by severely reduced nerve conduction velocities (<5 m/s), enlargement of cranial nerves and spinal roots, and elevated CSF proteins. The few reported patients harboring two null PMP22 alleles present a predominant severe sensory ataxia with relative sparing of muscle strength.

Methods: In a 10-year-old girl affected by PMP22-related peripheral hypomyelination, we performed a detailed assessment to ascertain whether vestibular dysfunction could detrimentally contribute to her ataxia. The following vestibular tests were performed: vestibular evoked myogenic potentials (VEMP), acoustic reflexes, video Head Impulse test (vHIT).

Results: The molecular role of PMP22 is not fully deciphered, but its tissue and developmental upregulation during embryogenesis suggests that a threshold level might be required for the normal development of dorsal root ganglia (DRG) and for the maturation of myelin in other segments. Notably, DRG and Scarpa's (vestibular) ganglion display a similar embryological development. In our patient, the vestibular assessment demonstrated bilateral vestibular hypofunction. In particular, she had a positive head thrust test bilaterally, absent Otolith function bilaterally (absent VEMP), poor semicircular canal function (abnormal vHIT), and absent acoustic reflexes. Hearing was normal in both ears and no nystagmus was observed. These results are in keeping with studies suggesting that CMT-affected patients[1,2] might display a largely unrecognized vestibular impairment.

Conclusions: We reckon that vestibular function should be routinely investigated in patients affected by PMP22 −/− related neuropathy and other CMTs associated with sensory ataxia, as this is potentially amenable to rehabilitation.

References

1. Poretti A, Palla A, Tarnutzer AA, et al. Vestibular impairment in patients with Charcot-Marie-tooth disease. Neurology. 2013;80 (23):2099-105. doi: 10.1212/WNL.0b013e318295d72a

2. Pérez-Garrigues H, Sivera R, Vílchez JJ, Espinós C, Palau F, Sevilla T. Vestibular impairment in Charcot-Marie-Tooth disease type 4C. J Neurol Neurosurg Psychiatry. 2014;85(7):824-7. doi: 10.1136/jnnp-2013-307421

3. Zambon AA, Pitt M, Laurà M, Polke JM, Reilly MM, Muntoni F. A novel homozygous variant extending the peripheral myelin protein 22 by 9 amino acids causes early-onset Charcot-Marie-Tooth disease with predominant severe sensory ataxia. J Peripher Nerv Syst.

Keywords: PMP22, CMT, Sensory ataxia, Congenital hypomyelination, Vestibular function.

Poster No: 14 | **Personalized biopsychosocial treatment for small fiber neuropathy, a study protocol**

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Introduction: Small fiber neuropathy (SFN) is a condition dominated by invalidating neuropathic pain. Although neuropathic pain is caused by a lesion of the somatosensory system, also psychological factors, appear to play a role in the origin and maintenance of chronic pain and pain related disability. A recent qualitative study we performed, revealed that catastrophizing and negative thoughts have an impact on daily life, well-being and quality of life (QOL). The most used coping strategy was planning and adjustment, which as a consequence, resulted in a reduction of physical, work and social activities and eventually increasing disability and changing their whole life.

Methods: According insights resulting from this study, will lead to the possibility to develop a multidisciplinary therapeutic approach, necessary to treat biopsychosocial aspects of pain related disability in patients with SFN. Personalized rehabilitation based on pain education and cognitive behavioral treatment (CBT) including elements of acceptance and commitment therapy, exposure in vivo and/or mindfulness seem eligible to decrease pain disabling factors and increase the level of participation in society. To date such a rehabilitation program has not yet been applied and tested. By using a sequential replicated and randomized single-case experimental ABC-design with multiple measurements such a personalized rehabilitation program, based on the principles of cognitive behavioral therapy, will be evaluated.

Results: This is believed to reduce pain-related disabilities and improve quality of life.

Conclusions: The study protocol will be presented.

Keywords: Small fiber neuropathy, pain, treatment, protocol.

Poster No: 15 | **Effect of distal hereditary motor neuropathy on muscle structure, function, and gait patterns: Two case reports**

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Introduction: Distal Hereditary Motor Neuropathy (dHMN) is an inherited neuromuscular disorder characterized by distal muscle weakness. Here we investigate the relationship between muscle impairments and gait patterns in two individuals.
Methods: Two cases of dHMN (cases A and B) and matched healthy controls were compared. We measured lower limb strength using isokinetic dynamometry and 3D gait analysis. MRI scans were interpreted for the dHMN participants only.
Results: Case A was a 47-year-old male with no genetic diagnosis. Isokinetic dynamometry showed lower torque values for case A compared to the matched control: eccentric plantar flexion was 28.65% and concentric dorsiflexion 68.67% of control values. Ankle power generation during stance phase was 35.92% of matched control values, with reduced stride length (88.48%) and increased knee power generation in swing phase (146.26%). Case B was a 37-year-old male with BSCL2 mutation. Isokinetic dynamometry showed lower torque values for case B compared to the matched control: eccentric plantar flexion was 68.42% but concentric dorsiflexion was stronger at 153.18% of healthy control values. Ankle power generation during stance phase of gait was 59.57% of matched control values, with reduced stride length (73.39%) and he also had increased knee power generation in swing phase (274.59%). MRI scans demonstrated differing patterns of involvement between the cases, with case A showing symmetrical posterior compartment involvement, and case B showing asymmetrical, predominantly lateral compartment involvement. Thighs had normal appearance in both cases.
Conclusions: We present two dHMN cases showing greater plantarflexor muscle weakness than matched healthy controls. This was associated with reduced ankle power generation in stance but increased knee power generation in swing that may be a compensatory strategy to progress the swing leg. Variation existed between the cases, however, with differences in dorsiflexion strength and MRI findings, indicating that this is not a homogenous group of diseases.
Keywords: DHMN, MRI, Gait analysis, Dynamometer, Rehabilitation.

Poster No: 16 | **Novel variant in DNMT1 responsible for an overlapping cerebellar and sensory neuropathy phenotype**

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Introduction: Hereditary sensory neuropathy (HSN) 1E is a neurodegenerative disorder caused by pathogenic variants in DNA methyltransferase 1 (DNMT1). It is characterized by sensorineural deafness, sensory neuropathy and cognitive decline. Variants in DNMT1 are also associated with autosomal dominant cerebellar ataxia, deafness and narcolepsy.
Methods: A 42 year old man complained of imbalance and lancinating pains in the feet. He developed progressive deafness in his mid-20s and had sustained numerous paucisymptomatic injuries including a fractured tibia since his late teens. Mild cognitive decline and apathy were reported.
Results: Examination revealed abnormalities of eye movements, distal sensory loss to all modalities and areflexia without weakness. He was unable to tandem walk and had lower limb ataxia. Cognitive testing demonstrated predominantly dysexecutive mild cognitive impairment. Cochlear implant was performed at 44 years with improvement in hearing and day-to-day function. Nerve conduction studies demonstrated a length-dependent large and small fiber sensory axonal neuropathy with superimposed bilateral carpal tunnel lesions. MRI brain demonstrated biparietal and cerebellar atrophy. Audiometry prior to cochlear implantation showed bilateral high frequency sensorineural hearing loss, with hearing impairment above 4 kHz. Whole exome sequencing detected a heterozygous missense variant in DNMT1, c.1289G > A, p.Cys430Tyr. Segregation analysis confirmed it occurred de novo and in-silico parameters suggest that it is likely damaging. This variant affects a highly conserved nucleotide and amino acid, has not been reported in any of the large exome/genome databases and is classified as pathogenic using the American College of Medical Genetics (ACMG) variant classification system.
Conclusions: We describe a novel variant in DNMT1 and confirm that an overlapping HSN1E-cerebellar phenotype can occur. Only one report of cochlear implant in HSN1E has been described to date but our case adds to that literature, suggesting that cochlear implant can be successful in these patients.
Keywords: Inherited neuropathies, Hereditary sensory neuropathy type 1, DNMT1, Cognition, Cerebellar ataxia.

Poster No: 17 | **Quantitative assessment of muscle echogenicity in Charcot-Marie-Tooth disease type 1A by automatic thresholding methods**

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Introduction: In Charcot-Marie-Tooth disease type 1A (CMT1A), it is well-recognized that the lack of biomarkers to detect small changes in the disease severity or treatment responsiveness is one of the reasons for CMT1A clinical trial failure. This study aims to investigate the utility of automatic thresholding methods for quantitative muscle echogenicity assessment as a marker of disease severity in CMT1A.

Methods: Muscle ultrasound was performed in 15 CMT1A patients and 7 healthy controls. Muscle echogenicity of six limb muscles (abductor pollicis brevis, first dorsal interosseous, biceps brachii, tibialis anterior, gastrocnemius and vastus lateralis) in each subject was assessed by 16 automatic thresholding methods (Default, Huang, Intermodes, Iso Data, Max Entropy, Mean, Min Error, Minimum, Moments, Otsu, Percentile, Renyi Entropy, Shanbhag, Triangle and Yen) and conventional gray-scale analysis. Echogenicity of each method in CMT1A patients was compared with that in controls. A correlation between the echogenicity and CMT neuropathy score (CMTNS) was also analyzed in CMT1A patients.

Results: Results: Significant differences in mean echogenicity of the 6 muscles between CMT1A patients and controls were found both in gray-scale analysis ($P < 0.01$) and 11 of the 16 automatic thresholding methods (Default, Iso Data, Li, Max Entropy, Mean, Moments, Otsu Renyi Entropy, Shanbhag, Triangle, and Yen; $P < 0.05$ in each method). In CMT1A patients, mean echogenicity of the 6 muscles was positively correlated with CMTNS in 8 of the 16 automatic thresholding methods (Default ($\rho = 0.66$, $P < 0.008$), Huang ($\rho = 0.73$, $P = 0.002$), Iso Data ($\rho = 0.68$ $P = 0.005$), Li ($\rho = 0.71$, $P = 0.003$), Moments ($\rho = 0.74$, $P = 0.002$), Otsu ($\rho = 0.76$, $P = 0.001$), Renyi Entropy ($\rho = 0.55$, $P = 0.03$), and Shanbhag ($\rho = 0.76$, $P = 0.001$)), but not in gray-scale analysis ($\rho = 0.34$, $P = 0.21$).

Conclusions: Automatic thresholding methods can detect the difference in muscle echogenicity between CMT1A patients and controls. This method has potential as a surrogate marker of disease progression in CMT1A.

Keywords: Charcot-Marie-Tooth disease, muscle ultrasonography, muscle echogenicity, automatic thresholding method, biomarker.

Poster No: 18 | Inter-rater agreement in sciatic nerve segmentations in high-resolution 3D steady-state MRI images

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Introduction: Diabetic polyneuropathy (DPN) is a dysfunction of the peripheral nerves that is extremely prevalent in diabetes, associated with symptoms such as sensory impairment, neuropathic pain and allodynia. Magnetic resonance imaging (MRI) of the sciatic nerve at the thigh is emerging as a non-invasive biomarker assessing nerve damage in DPN. Such measures require manual segmentation, which is extremely onerous and time consuming. Deep learning approaches offer scope for automated segmentation of soft tissues. This study looks at producing training data for such algorithms by manually segmenting sciatic nerve images and calculating variability between segmentations.

Methods: Six balanced steady-state free precession (bSSFP) 7 T images of the knee from healthy individuals were acquired. Three segmenters (two trained medical students and one neurologist) segmented the sciatic nerve at the level of the thigh manually using ITK-SNAP software. Inter-rater variability was calculated between different segmenters and the "consensus" segmentation. These were calculated using Dice Coefficient, Intersection over Union (IoU) and Volume similarities using MATLAB code.

Results: Good similarity was achieved shown by the high dice coefficient between segmenters (0.79 ± 0.03), and between the consensus segmentation and segmenters (0.87 ± 0.03). Intersection over union figures were similarly high (0.66 ± 0.04), (0.77 ± 0.05), with the latter comparing the consensus segmentation and segmenters. We also assessed volume similarity (93.8% ± 2.79).

Conclusions: Despite the complex, highly variable nature of the sciatic nerve, a high degree of coherence was reached between segmenters, even including those with less experience of sciatic nerve anatomy. This study shows that this setup can be used to produce gold standard segmentations to be used in training deep learning architectures. The study could be improved by also calculating intra-rater variability, and assessing whether the low inter-rater variability is also maintained with nerves in DPN.

Keywords: polyneuropathy, sciatic, segmentation, MRI, diabetes.

Poster No: 20 | Progress toward integrated mouse models of neuronal and glial membrane injury in anti-GM1 antibody-mediated neuropathy

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Introduction: Anti-ganglioside antibodies (AGAbs), particularly anti-GM1 antibodies, are hypothesized to be involved in the pathogenesis of both the axonal and demyelinating variants of Guillain-Barré syndrome (GBS). It is established that binding of AGAbs causes complement activation, resulting in injury to the motor nerve terminal and the node of Ranvier (NoR) via calpain mediated pathways, as demonstrated by animal studies. However, current animal models are unable to differentiate whether binding to neuronal or glial membranes is responsible for tissue injury and functional disruption, as GM1 is expressed in both membranes.

Methods: To address this issue, mice with restricted expression of complex gangliosides to either the neuronal membrane (GalNAc-T-/--Tg[neuronal]) or glial membrane (GalNAc-T-/--Tg[glial]) were generated, allowing us to target each membrane independently with the same anti-GM1 antibody. The resulting nerve terminal and nodal injury was characterized, and it was found to differ depending on what membrane is targeted.

Results: Injury to the neuronal membrane in GalNAc-T-/--Tg(neuronal) mice results functionally, in diaphragm paralysis due to conduction block, with disruption to sodium channels at the NoR and disruption of axonal architecture as measured by a loss of neurofilament. In contrast, injury to the glial membrane in GalNAc-T-/--Tg(glial) mice causes a loss of ankyrinB immunostaining, an anchoring protein at the paranode, and consequently results in severe impairment to the axo-glial junction. Axon integrity was not affected acutely

(up to 6 hours) in GalNAc-T-/--Tg(glial) mice, however, axonal integrity is currently being examined in longer time-frame studies.

Conclusions: Overall, the implications of these results may suggest that the axonal and demyelinating variants of GBS should be considered discretely in terms of developing therapeutic strategies. In future studies, these transgenic mice will help differentiate between the distinct features of the axonal and demyelinating variants of GBS and will be valuable tools to trial targeted therapeutics.

References

1. Yao D, McGonigal R, Barrie JA, et al. Neuronal expression of GalNAc transferase is sufficient to prevent the age-related neurodegenerative phenotype of. 2014.

Grant Support: Wellcome trust.

Keywords: GBS, axo-glial junction, anti-ganglioside antibodies, mouse models.

Poster No: 21 | Different patterns of sensory nerve involvement in chronic inflammatory demyelinating polyneuropathy subtypes

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Introduction: Among the subtypes of chronic inflammatory demyelinating polyneuropathy (CIDP), different immune-pathophysiology has been proposed. The present study aimed to investigate patterns of sensory nerve conduction studies in CIDP clinical subtypes.

Methods: A total of 137 CIDP patients were screened and classified into clinical subtypes, such as typical CIDP (n = 67), multifocal acquired demyelinating sensory and motor neuropathy (MADSAM; n = 27). Sensory nerve action potentials (SNAP) were recorded in the median, ulnar, superficial radial, and sural nerves.

Results: SNAP amplitudes ($P < 0.05$) and nerve conduction velocities ($P < 0.01$) in the median nerve and conduction velocities ($P < 0.05$) in the ulnar nerve were decreased in typical CIDP, than in those with MADSAM, whereas those in the radial and sural nerves were comparable in the both subtypes. Decreased median and normal sural SNAP amplitudes were conspicuous in typical CIDP ($P < 0.01$), compared with MADSAM, suggesting predominant distal nerve terminal involvement. Conversely, MADSAM patients preferentially showed conduction abnormalities in the nerve trunks.

Conclusions: Distal nerves are preferentially affected in typical CIDP, compared with MADSAM. These findings support the hypothesis that in typical CIDP antibody-mediated demyelination in the nerve terminals, where the blood-nerve barrier is anatomically deficient, is the major immono-pathomechanism, whereas MADSAM affect the nerve trunks largely due to cell-mediated demyelination.

Keywords: chronic inflammatory demyelinating polyneuropathy, sensory nerve, nerve conduction study, distal nerve, blood-nerve barrier.

Poster No: 22 | Familial Amyloid Polyneuropathy: Experience in Myanmar

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Introduction: Familial amyloid polyneuropathy is a rare systemic disorder.

Methods: Case report.

Results: A 37-year-old Myanmar gentleman with onset of symptom at 29-year-old, presenting with chronic diarrhea, tingling and numbness sensation on extremities for 7 years. He started to have progressive weakness of both lower limbs followed by upper limbs at 31-year-old. His condition worsened and he became wheel chair bound on 36 years of age. Two of his family members had history of peripheral neuropathy and passed away at their age 30s. On examination, he had flaccid quadriparesis, severe muscle atrophy, severe sensory loss on all extremities and marked orthostatic hypotension. He also had corneal opacity in both eyes and diffuse thyroid swelling. Electrophysiological study revealed symmetrical sensorimotor axonal polyneuropathy. Sural nerve biopsy showed deposition of amorphous eosinophilic deposition and positive Congo red stain. He had Mobitz Type I heart block with normal echocardiogram. Serum protein electrophoresis and immunoglobulins were normal. Hypothyroidism on his thyroid test. Genetic study result showed Val30Met mutation in transthyretin gene analysis. He was treated with combined Doxycycline 100 mg twice daily and Ursodeoxycholic acid 300 mg twice daily for one year and supportive treatment. He had reduced frequency of diarrhea and improving appetite during treatment for one year. He passed away at the age of 39 years.

Conclusions: Familial Amyloid Polyneuropathy is common in Europe and few case reports in Asian population. This patient had a confirmed genetic mutation at Val30Met for transthyretin gene with widespread systemic involvement of the disease including peripheral nervous system, autonomic nervous systems, thyroid, ophthalmology and cardiac system. The diagnosis was delayed about 7 years. Combined Doxycycline and Ursodeoxycholic acid were well tolerated and no remarkable side effects.

References

1. Kato-Motozaki Y, Ono K, Shima K, et al: Epidemiology of familial amyloid polyneuropathy in Japan: Identification of a novel endemic focus. J Neurol Sci. 2008;270:133-140.

2. Obici L, Cortese A, Lozza A, et al. Doxycycline plus tauroursodeoxycholic acid for transthyretin amyloidosis: a phase II study. Amyloid. 2012;19(Suppl. 1):34-36.

Keywords: Familial Amyloid Polyneuropathy, Axonal polyneuropathy, Systemic disorder, Positive family history, Doxycycline and Ursodeoxycholic acid.

Poster No: 23 | **Pre-clinical studies in induced pluripotent stem cell (iPSC) lines with SORD mutations linked to a recessive neuropathy**

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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 took fibroblast samples from patients and reprogrammed them into induced-pluripotent stem cells (iPSCs). We are using these cells to perform assays to evaluate different therapeutic strategies for SORD related neuropathy.

Methods: Fibroblasts were transduced using a Sendai Virus Reprogramming kit to express reprogramming factors. Immunocytochemistry for Oct4, NANOG, and SSEA3 was performed to confirm pluripotency of cells. RNA was tested to confirm exogenous genes were no longer present and karyotyping was performed. Intracellular sorbitol levels were measured via UPLC-MS/MS. Supernatant NFL levels were measured via ELISA assay.

Results: Immunocytochemistry (ICC), RNA analysis, Sanger sequencing and karyotyping results showed that we have successfully generated iPSCs from fibroblasts for 3 patients with biallelic SORD mutations. We then differentiated these cells into motor neurons in 2D culture to carry out characterization studies and therapy screenings. We are using motor neurons to study the difference in sorbitol levels between patient samples and control cells. RNA-seq was performed to gain a better understanding of disease mechanisms and pathways. We are investigating the osmotic properties of the SORD motor neurons compared to control lines. We are also studying the use of supernatant neurofilament light chain (NFL) measurements to assess its use as a potential biomarker for this form of CMT. Future plans include developing genetic therapies such as ASOs as well as using small molecules to target pathways involved in sorbitol metabolism.

Conclusions: Our results show that we were able to reprogram patient fibroblasts into iPSC lines and then differentiate those lines into motor neurons for our ongoing studies. The ongoing pre-clinical studies of small molecule and genetic therapies will demonstrate target engagement, biomarker availability and lead to translational applications in clinical trials.

Keywords: Charcot-Marie-Tooth Disease, Motor Neuron, SORD, Neuropathy, iPSC.

Poster No: 24 | **Diagnostic performance of next generation sequencing in a French cohort of patients with spinal muscular atrophy**

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Introduction: Spinal muscular atrophy (SMA) negative for the SMN1 deletion/mutation has not been precisely characterized, neither clinically nor genetically, and the diagnostic yield of new generation sequencing (NGS) techniques is unknown.

Methods: Previous multicentric efforts have been performed in France to retrospectively study patients with distal hereditary motor neuropathies (dHMN). Here, we conduct a multicenter retrospective study of patients with SMA negative for the SMN1 mutation from 10 different French neuromuscular centers, who have undergone NGS panel screening for hereditary neuropathies or, in informative families, wide exome sequencing (WES).

Results: Up to the 31st of January 2021, 42 patients (50% males) from 35 different families have been included. Fifteen patients (35.7%) presented a scapuloperoneal phenotype (SP-SMA) with marked scapular winging, distal lower limb weakness and proximal involvement of the upper limbs. Fourteen patients (33.3%) showed proximo-distal involvement (PD-SMA), with a proximal predominance of muscle weakness observed at clinical presentation. Finally, thirteen patients (31%) presented exclusive proximal weakness (SMA phenotype). In 16 cases (38.1%), a genetic diagnosis was achieved: TRPV4 ($n = 6$), DYNC1H1 ($n = 4$), BICD2 ($n = 2$), VRK, HSPB1, VCP, and ASAH1 ($n = 1$). Interestingly, a patient with a SP-SMA presented an autosomal dominant pathogenic variant in the HSPB1 gene, expanding the clinical spectrum associated with HSPB1 mutations. Although the diagnostic performance of genetic studies in SMA (2/13 patients, 15.4%) and PD-SMA (4/14 patients, 26.7%) remains low and comparable to that reported for dHMN, the diagnostic yield was better for SP-SMA patients (10/15, 66.7%), with TRPV4 gene mutations being the most prevalent (6/10 patients, 60%).

Conclusions: The diagnostic performance of NGS techniques in SMA SMN1-negative remains low, emphasizing the need to gather these rare patients to better characterize their phenotypes which could in turn lead to the identification of possible common genes.

References

1. Beijer D, Baets J. The expanding genetic landscape of hereditary motor neuropathies. Brain. 2020; Online ahead of print.
2. Peeters K, Chamova T, Jordanova A. Clinical and genetic diversity of SMN1-negative proximal spinal muscular atrophies. Brain. 2014;137:2879-2896.
3. Echaniz-Laguna A, Geuens T, Petiot P, et al. Axonal neuropathies due to mutations in small heat shock proteins: clinical, genetic, and functional insights into novel mutations. Hum Mutat. 2017;38:556-568.
4. Echaniz-Laguna A, Dubourg O, Carlier P, et al. Phenotypic spectrum and incidence of TRPV4 mutations in patients with inherited axonal neuropathy. Neurology. 2014;82:1919-1926.

Keywords: Spinal muscular atrophy, next generation sequencing.

Poster No: 25 | **B6 levels do not correlate with severity of neuropathy in idiopathic axonal peripheral neuropathy**

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Introduction: Pyridoxine (vitamin B6) toxicity is known to cause a predominantly sensory, length-dependent, axonal polyneuropathy with symptoms of burning, numbness, sensory ataxia, areflexia, and gait issues. There is debate regarding the threshold for these neurological symptoms to occur. The aim of this study was to see how increased B6 levels impact a range of outcome measures in a well-characterized cohort of patients with idiopathic distal, symmetrical, axonal polyneuropathy (IPN).
Methods: We screened patients enrolled in the Peripheral Neuropathy Research Registry (PNRR) and included 246 patients who had a complete dataset including a B6 value from within three years of enrollment. Patients with B6 deficiency (0-4.9 mcg/L) were excluded. We analyzed the linear and logistic effect of B6 level on Nerve Conduction Study results (peroneal and sural), exam findings (ie, muscular strength, reflexes), and patient-reported neuropathy symptoms (ie, numbness, pain). We controlled for age in all analyses.
Results: Vitamin B6 level had no significant impact on neuropathy signs and symptoms in this group of IPN patients. There was no linear effect of B6 level on peroneal or sural velocities or amplitudes, or pinprick border. Logistic regression showed no effect of increasing B6 level on exam features including ankle and toe strength, vibration sense, deep tendon reflexes, or gait. There were also no differences in patient-reported numbness or pain intensity.
Conclusions: This study suggests that elevated B6 levels, even in the 100-200 mg/L range, are not associated with significantly worse neuropathy signs or symptoms. Although this suggests that usual B6 supplementation is insufficient to cause worsening neuropathy, this study does not directly answer whether stopping them will have a beneficial effect. In our sample, very few patients had B6 levels >300 mg/L, so testing IPN patients' B6 levels may be left to the discretion of the physician as the incidence of extremely high B6 levels, even in patients taking supplementation, is low.
Grant Support: The Foundation for Peripheral Neuropathy.
Keywords: idiopathic axonal polyneuropathy, vitamin B6, neuropathic pain.

Poster No: 26 | **Experimental mouse models toward differentiating primary and secondary axonal degeneration**

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Introduction: In both axonal and demyelinating variants of Guillain-Barré syndrome (GBS), the extent of axon degeneration is associated with the severity of clinical outcome. As such, it is critical to understand the underlying mechanisms of axon fate leading to either recovery, or axon loss, be it primary or secondary.
Methods: To address this issue, we generated transgenic mice that express GM1 ganglioside exclusively in neurons or glia, thus allowing us to very specifically target and injure these membranes with a single anti-GM1 antibody and source of complement. We used acute (4 hours) and extended (20 hours) ex vivo nerve-muscle preparations from these mice to study the effect of neuronal or glial injury on distal nerve axonal integrity (ie, loss of neurofilament immunolabeling) over time.
Results: In an acute ex vivo injury paradigm there is a loss of axonal integrity when the neuronal membrane is targeted in GalNAcT−/−−Tg(neuronal) tissue. Conversely axonal integrity is largely maintained when the perisynaptic Schwann cells (pSC) and paranodal membranes are decorated/injured by antibody and complement products in GalNAcT−/−−Tg(glial). However, at the node of Ranvier, using multiple immunostaining markers for axo-glial junction components, we observe structural disruption in both GalNAcT−/−−Tg(neuronal) and GalNAcT−/−−Tg(glial) mice. When this model is extended in GalNAcT−/−−Tg(glial) tissue, a loss of axonal integrity develops compared to control tissue. We found this did not correlate to injury of pSC overlying the nerve terminal, and is likely associated with paranodal disruption.
Conclusions: These data indicate that targeting nodal glial membranes with anti-GM1 antibody results in paranodal demyelination with delayed loss of axonal integrity, the mechanism of which is under investigation. Unraveling the consequence of paranodal Schwann cell membrane injury on axonal function, and vice versa, is a crucial step in understanding disease mechanism and could ultimately influence variant-specific therapeutics, currently a major area in GBS clinical research.
Grant Support: Wellcome Trust, GBS/CIDP Foundation International.
Keywords: axon degeneration, secondary bystander, node of Ranvier, ganglioside, paranodal demyelination.

Poster No: 27 | **Population Pharmacokinetic/pharmacodynamic (PK/PD) modeling of ION-682884, an antisense oligonucleotide in development for transthyretin amyloidosis**

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Introduction: Hereditary transthyretin amyloidosis (hATTR) is a rare, progressive fatal disease caused by pathogenic variants in the transthyretin (TTR) gene. ION-682884 is a triantennary N-acetyl galactosamine (GalNAc3)-conjugated antisense oligonucleotide targeting TTR mRNA and thereby inhibits the production of both variant and wild-type TTR protein. ION-682884 is currently in development for

patients with TTR amyloidosis. The objective of this study was to characterize the PK/PD of ION-682884 and to evaluate the impact of covariates on exposure and response by using population PKPD modeling.

Methods: Plasma ION-682884 concentration and serum TTR protein data were obtained from a Phase 1 clinical trial in healthy volunteers evaluating multiple dose cohorts of 45, 60, and 90 mg every 4 weeks and a single dose cohort of 120 mg, administered subcutaneously.

Results: ION-682884 PK was well described by a 2-compartment model with linear clearance (CL) and absorption rate (ka). Significant covariates included lean body mass on CL and body weight on intercompartmental clearance (Q), peripheral volume (V2), and ka. Interoccasion variability was included on ka to account for injection site differences; ka was 35.6% greater with injection into abdomen vs arm. The mean terminal elimination half-life was 30.1 days. TTR was well described by an indirect response model with inhibition of TTR production rate by ION-682884. Maximum fractional inhibition (Imax) was 0.972 (0.6% CV) and the 50% inhibitory concentration (IC50) was 0.036 ng/mL (18.7% CV). Simulations showed subjects with lower weight had higher PK exposure (AUC, Cmax) and subjects receiving injection into abdomen had higher Cmax (~19%) vs arm; however, differences in exposure did not significantly impact response (median > 85% TTR reduction for evaluated doses).

Conclusions: The developed population PKPD model well characterized the exposure-response relationship of ION-682884. The model supports monthly dosing and suggests weight and injection site covariates have minimal clinical relevance given the high potency of ION-682884.

Keywords: TTR, PKPD, ASO, amyloidosis.

Poster No: 28 | Ethoxyquin prevents bortezomib neurotoxicity in vitro and in a mouse model of chemotherapy induced peripheral neuropathy

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Introduction: Proteasome inhibitor, bortezomib (BTZ), is a chemotherapy drug commonly used to treat multiple myeloma and mantle cell lymphoma. Similar to other chemotherapy drugs, it causes chemotherapy induced peripheral neuropathy (CIPN), a serious, painful, and dose-limiting complication. There are currently no effective therapies that prevent CIPN. Recently we had identified ethoxyquin as a broad neuroprotective compound that prevents neurotoxicity of paclitaxel and cisplatin. In this study, we asked if ethoxyquin is able to prevent bortezomib induced distal axonal degeneration in vitro and in vivo.

Methods: An in vitro model of bortezomib induced neurotoxicity was established with dorsal root ganglion neurons and then cultures were treated with or without EQ. In vivo, bortezomib (0.8 mg/kg twice a week for 4 weeks) was administered by tail vein injections to adult A/J mice and ethoxyquin (75 μg/kg/day) was administered by intraperitoneal injections.

Results: In vitro, bortezomib caused a dose-dependent neurotoxicity in sensory neuronal cells that was associated with inhibition of the proteasome pathway and activation of caspase 3/8 activity. The bortezomib induced neurotoxicity was prevented by co-administration of ethoxyquin. In our in vivo experiments, the key manifestations of mouse peripheral neuropathy models, including loss of intra epidermal nerve fibers (IENF), thermal hyperalgesia, and reduction in sensory evoked responses were observed in Bortezomib group, but mice receiving Bortezomib and ethoxyquin did not show loss of IENF, thermal hyperalgesia or reduction in sensory evoked responses.

Conclusions: These studies suggest that ethoxyquin and its analogues are potential neuroprotective compounds that can be developed to prevent peripheral neuropathy caused by bortezomib.

Keywords: chemotherapy, peripheral neuropathy, Bortezomib, Ethoxyquin, CIPN.

Poster No: 29 | MAP4K4 Inhibition Prevents Axonal Degeneration caused by Chemotherapy

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Introduction: Although anticancer drugs have different mechanisms of action, many are associated with chemotherapy-induced peripheral neuropathy (CIPN), a debilitating, painful and dose-limiting side effect that affects treatment regimens and result in significant morbidity. In order to identify potential therapeutic targets that can be used to prevent neurotoxicity of different chemotherapy drugs, we examined the effect of several different kinase inhibitors on axon degeneration in sensory neuronal cells caused by paclitaxel, cisplatin and bortezomib, three chemotherapy drugs with very different mechanisms of action.

Methods: We used embryonic rat dorsal root ganglion neuronal cultures and administered several different kinase inhibitors together with these chemotherapy drugs and carried out an ATP assay to measure axonal degeneration induced by these chemotherapy drugs.

Results: Rock inhibitor Glycyl-H-1125 prevented axonal degeneration caused by paclitaxel and cisplatin but did not provide neuroprotection against bortezomib neurotoxicity. Spectrum selective tyrosine kinase inhibitor MGCD265 (glesatinib), irreversible epidermal growth factor receptor EKB-569 (pelitinib) and multikinase inhibitor KW-2449 prevented axon degeneration caused by paclitaxel. However, several DLK/LZK inhibitors did not provide neuroprotection against any of the three chemotherapeutic drugs. In contrast to these observations, PF-06260933, a MAP4K4 inhibitor prevented axonal degeneration caused by paclitaxel, cisplatin and bortezomib.

Conclusions: Although in vivo confirmation of these observations is needed for further validation of the in vitro studies, these findings

suggest that axon degeneration cascades initiated by paclitaxel, cisplatin and bortezomib converge on MAP4K4 and that inhibitors of MAP4K4 are potential therapeutic targets to prevent CIPN.

Keywords: chemotherapy, peripheral neuropathy, paclitaxel, cisplatin, bortezomib.

Poster No: 30 | **Digitizing the manual plaster casting process to produce ankle-foot orthoses**

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Introduction: Ankle-foot orthoses (AFOs) are commonly prescribed for patients with walking difficulties, such as foot drop associated with Charcot-Marie-Tooth disease (CMT). Traditional fabrication methods for AFOs involve the use of plaster to create and modify lower limb positive casts to improve comfort and control the fit of the final device. With no studies that describe these plaster modifications, investigations into the digital fabrication of AFOs highlight that virtual modifications are the weakest link. Thus, this study aims to digitize and map the actions of the orthotist during the modification process to understand ideal AFO modifications and inform translation to digital fabrication.

Methods: Pre- and post-modified plaster casts of children's lower limbs (n = 50) from a single orthotist at a pediatric orthotics department were 3D scanned, registered and compared under an approved ethics protocol. Mesh-to-mesh distance, defined as the difference between the pre- and post-modification casts in a normal direction, was compared with participant characteristics.

Results: Participants ranged from ages 1 to 18 years (mean 8.6, SD 3.5) with 62% male, who were prescribed fixed (60%) or hinged (32%) AFOs. Intra-rater reliability for mesh registration was found to be excellent (ICC = 0.99). The mean mesh-to-mesh distance across the cohort was 2.62 mm (SD 0.41 mm). Positive mesh-to-mesh distance showed an excellent correlation with participant height (rs = 0.68, $P < 0.05$), and moderate correlation with age (rs = 0.68, $P < 0.05$). Plaster modifications were mapped three dimensionally and combined universally applied with participant specific.

Conclusions: This study presents the first investigation into digitizing and mapping orthotist behavior during plaster cast modification for the fabrication of orthoses. Our study highlights the nuanced approach required for virtual modifications that may be condition and deformity specific. These differences are important when considering digital fabrication for AFOs in CMT, as they will likely not be the same as other conditions.

Grant Support: Thrasher Research Fund Early Career Award Program.

Keywords: Ankle-foot orthoses, Orthotic devices, Digital map.

Poster No: 31 | **Baseline variation in commonly used inflammatory neuropathy clinical outcome measures**

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Introduction: Background: Reliable, clinically responsive outcome measures are essential for guiding Immunoglobulin (Ig) therapy in inflammatory neuropathy. The PeriNOMS initiative has developed a range of disease specific outcome measures with statistically sound minimal important clinical difference (MCID) to detect change (I-RODS MCID: +/−4; grip strength MCID: +/-8 kPa). Score stability in well-treated disease is another important clinometric characteristic but variation is acknowledged. Aims: To appreciate random variability of grip strength, I-RODS and MRC-SS on repeated assessment in clinically stable CIDP/MMN patients and explore subclinical identification of trending.

Methods: We retrospectively analyzed clinical outcome measurements prospectively recorded in a single-center neurosciences department neuropathy Ig database between 2009 and 2020. We used first score on maintenance dosing regimen as baseline, and any increase in dose (g/kg/month) as indicative of meaningful clinical deterioration. We calculated mean and SD change(Δ) in actual score and percentage for grip strength (/90 kPa), I-RODS (logit scale) and MRC-SS (/70) over a period of clinical stability as judged by consultant review.

Results: 108/404 patients had sufficient periods of clinical stability for analysis. 85 CIDP (23F, age mean 63.4 years, median 65 years), 23 MMN (5F, age mean 58.3 years, median 57 years). RODS: 540 timepoints, 0.4-83.9 months (median:20.3); Grip: 908 timepoints, 0.5-981 months (median:23.2); 87 timepoints, 1.4-52.7 months (median:10.6). For CIDP: ΔRODS: ΔRODS: mean:+0.78(0.78%), SD:7.85(7.85%). ΔRight grip: mean:+0.39 kPa(0.43%), SD:5.60 (6.21%). ΔLeft grip: mean:+0.47 kPa(0.53%), SD:5.76(6.40%). ΔMRC-SS: mean:+0.54(0.78%), SD:4.84(6.91%). For MMN: ΔRODS: ΔRODS: median:0(0%), mean:+0.55(1.15%), SD:3.52(7.32%). ΔRight grip: mean:-1 kPa(−1.11%), SD:6.06(6.73%). ΔLeft grip: mean:+0.006 kPa (0.006%), SD:6.61(7.35%). ΔMRC-SS: mean:+0.87(1.24%), SD:2.17 (3.10%). Analysis on trend identification is ongoing.

Conclusions: Appreciation of the magnitude of normal variation is important in clinical practice. Early identification of significant trends will influence dosing decisions and help in differentiating noise from signal.

Keywords: CIDP, MMN, RODS, Grip, MRC-SS.

Poster No: 32 | **CIDP patient serum triggers complement activation and functional deficits in motoneurons blocked by anti-C1s therapeutic**

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Introduction: Chronic autoimmune demyelinating neuropathies are a group of rare disorders with complex and incompletely understood pathophysiology, in part due to limited availability of experimental models recapitulating human disease. Several lines of evidence suggest that complement activation could play a key role in chronic inflammatory demyelinating polyneuropathy (CIDP), but no complement inhibitors are approved for use in this or related conditions, such as multifocal motor neuropathy (MMN).
Methods: In this study, we examined the effects of TNT005, a mAb that inhibits activated C1s within the complement classical pathway, using a novel human-on-a-chip (HoaC) electrical conduction model consisting of a microelectrode array with directed axonal outgrowth.
Results: Serum samples from CIDP and MMN patients were found to contain anti-GM1 IgM and IgG antibodies which bound to the plasma membranes of human primary Schwann cells and human induced pluripotent stem cell (iPSC)-derived motoneurons. Further, patient autoantibody binding activated the complement pathway, resulting in the detection of C3b and C5b-9 deposits on the cells via immunocytochemistry. Subsequently, treating the HoaC model with patient sera triggered changes in motoneuron spontaneous action potential frequency and conduction velocity. TNT005 rescued the diseased-serum-induced complement deposition and functional deficits, while treatment with an isotype control antibody provided no rescue.
Conclusions: These data demonstrate that functional deficits triggered by factors in patient serum can be reversed by complement inhibition in a human-relevant CIDP/MMN model, opening the door for therapeutic inhibition of the classical complement pathway in these and other autoimmune neuropathies.
Keywords: neuromuscular junction, multifocal motor neuropathy, CIDP, human, electrophysiology.

Poster No: 33 | **CMT with conduction slowing and nephropathy - consider a dip in the OPD**

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Introduction: Mutations in the INF-2 gene are the commonest cause of autosomal dominant nephrotic syndrome. A proportion of patients have a combination of Focal Segmental Glomerulosclerosis and Dominant Intermediate CMT type E. We describe two cases from our cohort.
Methods: The first patient, a 19-year-old male had normal early milestones but developed balance impairment and difficulty running aged 3. Following progressive foot deformity surgery was required at age 10. Hand weakness evolved by 11, followed by scoliosis at 13 requiring surgical intervention at 15. Clinically, there was a length dependent pattern of distal muscle atrophy and weakness with sensory loss including impaired vibration perception, absent reflexes and scoliosis. At age 12, neurophysiology demonstrated absent SAPs, reduced CMAP amplitudes and MCV of 10-18 m/s. Dipstick proteinuria was identified in OPD. A previously described(1) de novo p.Cys104Tyr variant in INF-2 was found on a 100 000 gene panel. Cohort review identified another patient who required cadaveric transplant for renal failure in her 20's, thought to have been precipitated by scarlet fever. Her CMT was onset age 11 requiring multiple foot surgeries, tendon transfers and scoliosis management. The p.Val102Asp INF-2 mutation was identified on a next generation sequencing panel, previously described associated with pathologically demonstrated thrombotic microangiopathy and glomerulosclerosis.(2)
Results: We describe two patients who have CMT with renal involvement due to mutations in the INF-2 gene. One of these had slowed conduction velocities in the demyelinating range.
Conclusions: In the literature, the latest described onset of CMT is 28 years, of proteinuria in patients with CMT is 6 months to 55 years, and severity of renal involvement is widely variable. We advocate urine dipstick testing in all genetically undiagnosed CMT patients who have conduction slowing.
References
1. Bacquet J, Stojkovic T, Boyer A, et al. Molecular diagnosis of inherited peripheral neuropathies by targeted next-generation sequencing: Molecular spectrum delineation. BMJ Open. 2018;8 (10):1-14.
2. Challis RC, Ring T, Xu Y, et al. Thrombotic microangiopathy in inverted formin 2-mediated renal disease. J Am Soc Nephrol. 2017;28 (4):1084-91.
Grant Support: N/A.
Keywords: INF-2, Conduction slowing, Nephropathy.

Poster No: 34 | **Health utilities in chronic inflammatory demyelinating polyneuropathy**

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Introduction: The aim of this project is to determine how patients with CIDP value their current health states and to identify the main

factors that impact on their overall health. We accomplished this by establishing health utilities, a surrogate measure of patient preference, in a large cohort of patients with CIDP, and further identifying the main determinants that influence them.

Methods: This is a cross sectional study evaluating patients with a confirmed diagnosis of CIDP. Recruited patients completed a survey answering basic demographic and clinical data, as well as disease specific disability scales. Patients also completed the EQ5D-5 L (EuroQoL Five-Dimension Five-Level) and SF-6D (Short-Form Six-Dimension) quality of life questionnaires, from which we derived health utility scores (HUS). A multivariable linear regression model was done to identify determinants of the EQ-5D-5L and SF-6D HUS. Additionally, patients were categorized based on disease severity using R-ODS scale quantiles, and mean HUS were estimated for each quantile.

Results: Among the 318 patients recruited, 309 patients completed the EQ-5D-5L and 314 patients the SF-6D. Mean EQ-5D-FL HUS were as follows: first R-ODS quantile 0.2 ± 0.24, second R-ODS quantile 0.44 ± 0.22, third R-ODS quantile 0.61 ± 0.18, fourth R-ODS quantile 0.83 ± 0.11. Mean SF-6D HUS were as follows first R-ODS quantile 0.53 ± 0.11, second R-ODS quantile 0.59 ± 0.1, third R-ODS quantile 0.66 ± 0.08, fourth R-ODS quantile 0.74 ± 0.07. The main drivers of worse HUS were being on disability, dissatisfaction with treatment, any symptoms (stable or worsening) or a point increase in INCAT score.

Conclusions: We provide estimates of HUS for CIDP patients, that can be used in health economic studies. Patients with worse disease severity had lower HUS. Any symptoms, being on disability, treatment dissatisfaction, or point increase on INCAT scale were shown to have the highest impact on HUS.

Keywords: CIDP, Health Utilities Scores, Inflammatory Neuropathy, Health economics, Patient preference.

Poster No: 35 | A low amyloidogenic E61K transthyretin mutation could cause late-onset familial amyloid polyneuropathy

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Introduction: Transthyretin (TTR)-type familial amyloid polyneuropathy (FAP) typically exhibits sensory dominant polyneuropathy and autonomic neuropathy. However, the molecular pathogenesis of the neuropathy still remains unclear. In the present study, we characterize the features of FAP TTR E61K. This FAP was late-onset one with sensory dominant polyneuropathy, autonomic neuropathy, and cardiac amyloidosis. Interestingly, no amyloid deposits were observed in the endoneurium of the nerve specimens examined. Therefore, we investigated the amyloidogenic properties of E61K TTR in vitro. Furthermore, we examined the neurotoxicity of E61K TTR using DRG neuron cultures as well as the sural nerve specimens.

Methods: Recombinant wild TTR, V30M TTR and E61K TTR protein was incubated at 37°C for 72 hours, and the amyloid fibril formation was examined using Thioflavin T binding assay. The neurotoxicity of E61K TTR was explored by neurite outgrowth assay using cultured primary rat DRG neurons. Furthermore, we studied the sural nerve of our patient by TTR immunohistochemistry, TUNEL and electron microscopy.

Results: Amyloid fibril formation by E61K TTR was less than that by V30M TTR, and similar to that by WT TTR. E61K TTR did not have an inhibitory effect on neurite outgrowth from adult rat DRG neurons, but V30M TTR did. TTR was not detected extracellularly, but was observed in endoneurial cells. A number of apoptotic cells were observed in the endoneurium of the nerve by TUNEL. Chromatin condensation was found in the nucleus of non-myelinating Schwann cells by electron microscopy.

Conclusions: These findings indicate that E61K TTR is low amyloidogenic in vitro and in vivo. However, TTR amyloid in the DRG may cause sensory impairments in FAP because the DRG has no blood-nerve barrier. Moreover, TTR aggregates within the cells and Schwann cell apoptosis may contribute to the neurodegeneration.

Keywords: amyloid, DRG, familial amyloid polyneuropathy, Schwann cell apoptosis, transthyretin.

Poster No: 36 | Quality of life, disability and weekly dosage indicate remission in CIDP patients treated with subcutaneous immunoglobulin

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Introduction: The purpose of this trial was to identify factors predicting remission during standardized tapering off subcutaneous immunoglobulin (SCIG) in patients with chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods: Patients with CIDP receiving a stable SCIG dosage followed a standardized tapering off regimen of SCIG: 90%, 75%, 50%, 25% and 0% of initial dose, every 12th week, pending no deterioration occurred. If patients tolerated complete tapering off without relapse, they were followed for further 12 weeks. Patients were evaluated clinically every 6-12th week. Overall disability score (ODSS), Quality of Life (EQ-5D-5L), sensory score, muscle strength, pain, dexterity and walk performance was evaluated.

Results: Fifty-five patients were included. Twenty participants (36%) did not relapse during tapering off SCIG treatment. Comparing baseline values of all participants we found the following risk factors for a relapse: At baseline, the relative risk (RR) of relapse was predicted by a SCIG dosage (>25 g/week) (RR 3.0; range 1.5-6.4), a ODSS (arm >1) (RR 2.0; range 1.2-7.4), an EQ-5D-5L (VAS <70) (RR 3.3; range 1.4-8.7) and an EQ-5D-5L (index value <0.8) (RR 2.2; range 1.1-4.3).

Age, gender, duration of CIDP or duration of SCIG treatment did not influence the risk of relapse. Comparing clinical evaluations from baseline, the final visit, and the last visit before final (LVBF), we found no change from baseline to LVBF, but only between LVBF and final visit.

Conclusions: Low quality of life, affected arm disability and high weekly dosage of SCIG at baseline predicted relapse during tapering off SCIG. In contrast, risk of relapse was not related to age, gender, duration of CIDP or SCIG treatment. Regular evaluations during tapering off treatment could not predict relapse. Our findings can help identifying patients receiving SCIG who are in remission.

Grant Support: Danish Regions.

Keywords: CIDP, SCIG, Quality of Life.

Poster No: 37 | SPTAN1 related disorders: expanding the spectrum beyond peripheral neuropathies

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Introduction: The SPTAN1 gene displays an intriguing phenotypical spectrum, already established to include early-onset epileptic syndromes, intellectual disability and Hereditary Motor Neuropathy (HMN). Reports of SPTAN1 variants in Hereditary Spastic Paraplegia (HSP) patients have been made, with either compound heterozygous or dominant inheritance patterns. The alpha-II-spectrin protein is known to be of critical importance during neuronal development and homeostasis but coupling the several observed mutations to its cellular functions remains a challenge.

Methods: We systematically re-evaluated international NGS databases (Solve-RD, Genesis) to identify additional SPTAN1 variants in Rare Disease (RD) patients. All variants were confirmed through Sanger Sequencing and segregation analysis was performed where possible. Phenotypic data was uniformly collected through a questionnaire to elucidate phenotypic traits associated with variants.

Results: In addition to the already established phenotypes, we identify a recurrent, dominantly inherited p.Arg19Trp variant to be associated with Hereditary Spastic Paraplegia (HSP), confirming SPTAN1 as a cause for HSP. Furthermore, we identify several de novo missense variants as a cause of ataxic syndromes with or without seizures and intellectual disability, of which one p.Lys2083del mutation is shared across four different patients. Of special interest, we find the phenotypical spectrum to be associated with SPTAN1 nonsense mutations to expand beyond HMN: recent findings include one de novo inherited frameshift variant associated with axonal sensorimotor neuropathy and developmental disorder, as well as a potential novel link with distal myopathies.

Conclusions: SPTAN1 displays an unusually large phenotypical spectrum, possibly associated with its wide range of cellular functions. Clear-cut genotype-phenotype correlations cannot be established as of yet. We therefore set out to functionally characterize several variants associated with different phenotypes, in search of underlying divergent pathomechanisms.

Grant Support: This work was supported by Solve-RD, a Horizon 2020 EU funded Project.

Keywords: SPTAN1, phenotypical spectrum, inherited neuropathies, axonal transport.

Poster No: 38 | Imaging axonal calcium changes in mouse models of Guillain-Barré syndrome ex vivo

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Introduction: Guillain-Barré syndrome (GBS) is caused in some cases by peripheral nerve injury induced by autoantibodies against gangliosides. Autoantibodies activate the complement cascade, allowing excessive calcium to enter intracellular compartments via terminal complement pores, thereby activating the protease, calpain and mediating injury. Our aim was to develop a method to detect and quantitate changes in intra-axonal calcium ex vivo in axonal and demyelinating models of GBS and compare the extent and time course of calcium fluxes between the two.

Methods: Thy1-TNXXL mice, expressing a genetically encoded FRET-based calcium indicator (TNXXL) in axons, were crossed with GalNAcT−/−−Tg(neuronal) or GalNAcT−/−−Tg(glial) mice to produce mice which express axonal TNNXL and have complex ganglioside expression restricted to either neuronal (Thy1-TNXXL/Neuronal) or Schwann cell (Thy1-TNXXL/Glial) membranes. Nerve-muscle preparations were incubated with anti-GM1 antibody followed by a source of complement. This injury primarily affects the NMJ in Thy1-TNXXL/Neuronal mice and the paranode in Thy1-TNXXL/Glial mice. Changes in axonal calcium were measured over a 4-hour time period.

Results: In Thy1-TNXXL/Neuronal mice, a significant increase in axonal calcium levels vs control (antibody only treated) mice occurs at the NMJ within 70 minutes following complement addition. Calcium remains high throughout the imaging period. At sites proximal to the injury (single axon, small, medium and large bundles), calcium also rose, though did not reach significance vs controls. Preliminary studies in Thy1-TNXXL/glial mice suggest no major changes in calcium within this imaging period.

Conclusions: Here, we demonstrate the ability to detect changes in axonal calcium after acute injury to the motor nerve terminal

mediated by anti-ganglioside antibody and complement. We have shown that calcium influx can extend retrogradely from the distal axon to sites where direct injury has not occurred. This will be a useful tool in the future to elucidate differences in axonal calcium signaling between axonal and demyelinating forms of GBS.

Grant Support: Wellcome Trust grant number 202789.

Keywords: Calcium, Axon, Guillain-Barré syndrome, Complement, Live imaging.

Poster No: 39 | Generating a TRPV4 neuropathy patient database to facilitate clinical trial readiness

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Introduction: Dominant mutations of the calcium-permeable cation channel TRPV4 (transient receptor potential vanilloid 4) can cause Charcot-Marie-Tooth (CMT) disease type 2C and forms of distal spinal muscular atrophy (dSMA), which share features of variably severe arm and leg weakness, frequent vocal fold weakness, and scapular winging. Disease-causing mutations in TRPV4 result in gain of ion channel function in vitro and in vivo, suggesting that existing, orally-bioavailable small molecule TRPV4 antagonists could ameliorate disease in patients. However, the rarity and clinical heterogeneity of TRPV4 channelopathies represent significant challenges to designing a clinical trial.

Methods: To more fully define the clinical spectrum and natural history of TRPV4 neuropathy, we have initiated a TRPV4 neuropathy patient database through the Inherited Neuropathy Consortium patient registry.

Results: Analysis of the 30 existing patients in the database demonstrates frequent weakness of proximal arm and leg muscles, distinct from the pattern seen in most patients with CMT. Pain and subjective sensory loss are infrequent, although sensory involvement is often detected clinically. Longitudinal data demonstrates heterogeneity in severity and disease progression. As standard clinical CMT metrics may not fully capture the spectrum and progression of TRPV4 neuropathy, we have designed a TRPV4-neuropathy specific patient questionnaire to supplement the clinical information in the database. We have also begun biochemical characterization of novel and potentially pathogenic TRPV4 variants to further define the genetics of TRPV4 neuropathy.

Conclusions: Careful delineation of progressive vs non-progressive patients within our cohort will allow investigation and subsequent validation of TRPV4 neuropathy biomarkers, such as neurofilament levels, which could be used to evaluate efficacy of TRPV4 antagonist drugs in patients. Together these studies will define the clinical and genetic spectrum of TRPV4 neuropathy and increase readiness for a future clinical trial.

Grant Support: K08 NS102509.

Keywords: Charcot-Marie-Tooth Disease, Spinal muscular atrophy, TRPV4, Natural history.

Poster No: 40 | Lack of skin cell-secreted neurotrophic factors results in a small fiber neuropathy

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Introduction: Small fiber neuropathy is a disorder in which only the small unmyelinated sensory fibers are affected. In skin conditions such as RDEB, there is degeneration of the distal part of these fibers secondary to chronic skin injury, followed by a failure of these fibers to regenerate, even when the skin injury has receded. Sensory nervous system regeneration is dependent of neurotrophic factors by targets of innervation such as skin, depend on NGF or GDNF to regenerate during adulthood. Keratinocytes and fibroblasts are known to express these factors to guide axonal regrowth after injury.

Methods: Patients with SFN secondary to RDEB and their matched controls were used to collect biopsies from the sites of injury 2 or 10 days after. qRT-PCR to evaluate the increase in mRNA expression of NTF. Then we quantified NGF and GDNF protein level using ELISA. Primary keratinocytes from patients and controls and produced an in vitro scratch injury to induce secretion of growth factors. Rat sensory neurons to test the functionality of these growth factors secreted by human keratinocytes in vitro.

Results: We observed a growth factor response following skin injury in control subjects (NGF and GDNF transcripts and protein were increased), which was not seen in SFN secondary to RDEB patients. Control keratinocytes 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 conditioned medium from control human keratinocytes showed increased neurite outgrowth compared to neurons grown with SFN.

Conclusions: Patients with SFN secondary to RDEB do not respond secreting growth factors following skin injury as control subjects do. Keratinocytes from healthy donors secrete functionally active NGF and GDNF following in vitro injury, probably to promote regeneration of injured intraepidermal axons. However, keratinocytes from our patients fail to secrete neurotrophic factors.

References

1. von Bischhoffshausen, Sofia, et al. Recessive dystrophic epidermolysis bullosa results in painful small fiber neuropathy. Brain 2017;140(5):1238-1251.

2. Martinez NW, Sánchez A, Diaz P, et al. Metformin protects from oxaliplatin induced peripheral neuropathy in rats. Neurobiol Pain 2020;8:100048.

Keywords: small fiber neuropathy, sensory, trophic factor, pain.

Poster No: 41 | **Decreased distribution of microvessels in sweat glands in diabetic skin biopsy**

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Introduction: Microvascular disease is common in diabetes (DM) and is associated with complications including peripheral neuropathy (PN).
Methods: Using immunohistochemical and stereological techniques, we compared the differences in the distribution of microvessels in superficial dermis and sweat glands in distal leg skin biopsies of healthy control (HC) and age/gender matched DM subjects.
Results: Vessel density (% positive CD31) in superficial dermis and sweat gland were determined using unbiased stereological area fraction fractionator. Compared to the HC subjects, the CD31+ area fraction was significantly reduced in DM subjects (5.23% ± 0.49% vs 3.59% ± 0.33%, $P = 0.03$. Similarly, the CD31+ area in sweat glands was 24.8% ± 3.48% vs 10.8% ± 3.34%, $P = 0.016$. Together, our data show that CD31 positive blood vessels was were reduced by 31% in the superficial dermis and by 56% in sweat glands.
Conclusions: These results suggest that vascular damage plays a role in small fiber loss whether sensory or pseudomotor nerves. The microvascular supplying sweat glands are more severely damaged than that supplying superficial dermis. Skin biopsy is an effective tool to assess microvascular injury in diabetes.
Keywords: skin biopsy, microvascular disease, diabetes, CD31, sweat glands.

Poster No: 42 | **Current Interventions for diabetic peripheral neuropathy: Do they reduce fall risk? A systematic review**

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Introduction: Diabetic peripheral neuropathy (DPN) is the most common complication of diabetes, occurring in 50% of diabetics. People with DPN are 15 times more likely to report injury following a fall and feel significantly less safe during standing and walking. Balance training and fall prevention are essential elements of any rehabilitation program for people with DPN. The objective of this review is to identify rehabilitation interventions with the highest impact on fall-related outcomes, particularly those proven to predict fall risk.
Methods: We conducted a systematic review of studies investigating the effects of active rehabilitation interventions on fall-related outcomes in people with DPN. Our search revealed eleven studies fitting our inclusion criteria. Fall risk was identified using fall risk cut-off scores validated in healthy older adults.
Results: Only one active rehabilitation intervention study assessed falls throughout the intervention and prospectively for a period of 6 months. Eleven studies assessed changes in fall risk outcomes from pre- to post-intervention. Fall risk outcome scores fell below their respective fall risk cut offs in the majority of studies. According to established cut-off scores, only two studies resulted in reduced fall risk.
Conclusions: Active rehabilitation interventions have been found to improve walking speed, strength, and other static balance tests, however, their effect on fall risk and prospective fall rates remain unclear. Most of the participants included in these studies were not at risk of falls prior to the intervention, therefore, it is difficult to truly determine whether these interventions are capable of reducing fall risk. In addition, few studies have prospectively examined the long-term effects of these interventions on balance control and fall rates.
Keywords: Diabetic peripheral neuropathy, Falls, Rehabilitation.

Poster No: 43 | **Clinical and genetic profile of patients with autosomal recessive forms of Charcot-Marie-Tooth disease in Brazil**

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Introduction: Charcot-Marie-Tooth disease (CMT) is the term used to refer to a heterogenous group of disorders in which the neuropathy is the main or sole feature of the disease. Its estimated prevalence ranges from 1:2500 to 1:10.000. Autosomal recessive forms of Charcot-Marie-Tooth (AR-CMT) are rarer and usually account for less than 10% of the cases in most epidemiological studies.
Methods: From February 2015 to December 2020, we conducted a retrospective observational study of 500 patients who met clinical and neurophysiological criteria for CMT. Data were obtained from EMR and all subjects had their blood samples collected for genetic investigation. MLPA technique to access duplication/deletion mutations of PMP22 and Sanger sequencing of GJB1 were performed in advance for all suspected cases of demyelinating CMT. Unsolved demyelinating cases and all axonal CMT were evaluated by a targeted gene panel sequencing (71 genes). Mutations were classified according to the 2015 ACMG Standards and Guidelines for the interpretation of sequence variants and cases with pathogenic of likely pathogenic mutations were considered as genetically confirmed.
Results: Among 500 subjects with suspected diagnosis of CMT, a molecular diagnosis was achieved in 378 (75.6%) of them. Twenty eight patients with definitive diagnosis had AR-CMT (7.4%) and the most common subtypes in our series were related to GDAP1 (4/28), SBF2 (4/28), PRX (3/28), and SH3TC2 (3/28). Mutations in DHKTD1, DNAJB2, FGD4, FIG4, HINT, IGHMDP2, LMNA, NDRG1, NEFL and

PLEKHG5 were also found. Most patients had the onset of symptoms in the first decade of life (26/28). Eight patients with AR-CMT have abnormal pulmonary function tests.

Conclusions: This study provides further data about frequency of AR-CMT subtypes in a Brazilian clinical-based population and could help to address the genetic testing work up, demonstrating that NGS-panels could be a reasonable approach. It also draws attention to the importance of assessing lung function in AR-CMT.

References

1. Skre H. Genetic and clinical aspects of Charcot-Marie-Tooth's disease. Clin Genet. 1974;6(2):98-118.

2. Dubourg O, Azzedine H, Verny C, et al. Autosomal-recessive forms of demyelinating Charcot-Marie-Tooth disease. Neuromolecular Med. 2006;8(1-2):75-86.

3. Murphy SM, Laura M, Fawcett K, et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. J Neurol Neurosurg Psychiatry. 2012;83(7):706-10.

4. Fridman V, Bundy B, Reilly MM, et al. CMT subtypes and disease burden in patients enrolled in the inherited neuropathies consortium natural history study: a cross-sectional analysis. J Neurol Neurosurg Psychiatry. 2015;86.

Keywords: Charcot-Marie-Tooth Disease, Hereditary motor and sensory neuropathy, Inherited neuropathies.

Poster No: 44 | Ultra-high dose of human immunoglobulin in patient with multifocal motor neuropathy resistant to treatment

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Introduction: Multifocal motor neuropathy (MMN) is a chronic progressive immune-mediated neuropathy, characterized by progressive asymmetric weakness, mainly involving upper limbs with evidence of motor conduction block. The treatment of choice is immunoglobulin (Ig) with poor or no response to immunosuppressants. In the long-term, most patients require maintenance intravenous Ig (IVIg) or subcutaneous IG (SCIg) to prevent clinical worsening.

Methods: We describe one patient with MMN who became resistant to standard treatment but markedly improved using ultra-high IVIG doses (UHIVIg).

Results: A 36-year-old woman, with a 4 years history of MMN, anti GM1 (+) presented bilateral asymmetric weakness and wasting on hands and right stepagge gait (ONLS: 4). She received IVIg 2 g/kg/month (100 g) per 2 months followed by a maintenance dose of IVIg of 1 g/kg/month. Her strength improved (ONLS: 2) and she was switched to SCIg 2 g/kg/month (100 g) remaining stable for 32 months. After 3 years despite stable SCIg treatment she developed marked worsening of muscle strength without sensory symptoms (ONLS: 5, MRC: 40, handgrip left 0kpa right 0kpa, RODS: 16). She was switched to IVIG 2 g/kg/month per 4 months without improvement. A trial of prednisone 1 mg/kg during 6 weeks followed by Rituximab 375 mg/m2 in four consecutive weeks were not effective. Due to lack of response, severe disability and low QRISK score (6%) we started UHIVIg 4 g/kg/month (200 g) followed by 5 g/Kg/month for 2 months (250 g) fractionated in 2 cycles every 15 days. The patient progressively improved her strength MRC:54 hand grip left: 5Kpa Right: 30Kpa, RODS: 41 and ONLS: 4 (Figure 2). No IVIg-related adverse events occurred after UHIVig.

Conclusions: UHIVIg is a useful therapy in aggressive MMN with severe disability that became refractory to standard Ig treatment. Low QRISK score may be useful to identify patients with lower risk of thromboembolic complications.

Keywords: neuropathy, inmune, inflammatory, immunoglobulin, resistant.

Poster No: 45 | Ophthalmological involvement in wild-type transthyretin amyloidosis

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Introduction: Ophthalmological abnormalities have been reported in hereditary transthyretin amyloidosis but it remains unknown whether they might be present in transthyretin wild-type amyloidosis (ATTRwt).

Methods: Fourteen ATTRwt patients (all men, mean age 75 ± 7 years) underwent full ophthalmological examination, including intraocular pressure quantification, optical coherence tomography (OCT, obtaining cross-sectional images of retina and choroid), OCT-angiography (obtaining images of the vascularization of retina, choroid and optic nerve) and in vivo corneal confocal microscopy (CCM, obtaining a high magnification imaging of the cornea with evaluation of the corneal subbasal nerve plexus). Of the 14 patients, three had diabetes and one an IgMk monoclonal gammopathy of undetermined significance. Seventeen age-matched healthy subjects (mean age 71 ± 6 years) were enrolled as controls.

Results: The visual acuity was significantly reduced in ATTRwt patients compared to controls ($P < 0.0001$). Four ATTRwt patients were affected by glaucoma, two of whom newly diagnosed. Twelve patients had cataract or had undergone cataract surgery. Three patients had mild vitreal opacities, while eight patients had epithelial/endothelial corneal deposits. Ten patients presented with abnormal findings of the retinal pigment epithelium at OCT, with advanced macular degeneration in two patients. CCM showed significantly reduced number of fibers ($P < 0.0001$), with reduced nerve fiber length ($P = 0.0004$) and impaired branching ($P = 0.01$). OCT-angiography evidenced a significant impairment of the retinal vascular density, both of radial peripapillary capillary plexus and macular vascular plexuses ($P \leq 0.01$).

Conclusions: Ophthalmological abnormalities were common in our sample of ATTRwt patients, particularly affecting the retinal pigment epithelium, the intraocular pressure and the corneal small-fibers. Although age and comorbidities may have influenced the results, and no amyloid-specific staining was applied to the in-vivo detected deposits, the prevalence and severity of the pathological findings seems to suggest a relevant pathogenic role of ATTRwt. Extensive ophthalmological examination should be included in the clinical work-up of ATTRwt patients.

Keywords: Amyloidosis, Ophthalmology, Small fibers, Transthyretin, Wild type.

Poster No: 46 | Efficacy of two AAV serotypes to target Schwann cells after intrathecal and intravenous delivery

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Introduction: Lumbar intrathecal injection of lentiviral vectors driven by the Schwann cells specific Myelin Protein Zero promoter results in widespread and long-lasting expression in Schwann cells. In order to develop a more translatable approach we compared two AAV serotypes and two different routes of delivery for efficient Schwann cells transduction.

Methods: AAV9 and AAVrh10 carrying either the Egfp or GJB1 genes were injected either intrathecally or intravenously in wild type and Gjb1-null mice, respectively. EGFP and Cx32 expression were quantified in lumbar roots and sciatic nerves by immunofluorescence stainingnand by immunoblot analysis. Vector genome copy numbers (VCNs) were determined in different tissues.

Results: VCNs were higher in AAVrh10 injected mice in all tissues and after both intravenous and intrathecal. EGFP was detected in lumbar roots and sciatic nerves of WT animals in both AAV9 and AAVrh10 injected mice while expression levels were similar between the two serotypes as indicated by both immunoblot and immunostaining analysis. Virally delivered Cx32 was detected in paranodal areas of lumbar roots and sciatic nerves of Gjb1-null mice. Expression levels of Cx32 were similar between the two serotypes as indicated by both immunoblot and immunostaining analysis. Comparison of the intrathecally and intravenously injected groups revealed overall similar EGFP and Cx32 expression in PNS tissues between the two routes of administration, although much higher vector amounts were injected intravenously.

Conclusions: We conclude that AAV9, which may provide a better ratio of infectious particles/viral genomes than AAVrh10, and intrathecal delivery, provide the optimal approach for delivering genetic therapies and expression in Schwann cells throughout the PNS to treat demyelinating peripheral neuropathies. AAVrh10 provides a similar efficacy for targeting Schwann cells.

Grant Support: Muscular Dystrophy Association and Charcot-Marie-Tooth Association (MDA603003 to KAK).

Keywords: Schwann cells, AAV9, AAVrh10, intravenous, intrathecal.

Poster No: 47 | Validation of the Italian version of the CMT-FOM

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Introduction: The Charcot-Marie-Tooth Functional Outcome Measure (CMT-FOM) is an outcome measure developed to assess disability in adults with CMT. The instrument has been shown to have test-retest reliability, internal consistency and convergent validity and can be used in adults from 18 years to quantitate functional impairment in CMT neuropathy. We are developing and validating the Italian version of the CMT-FOM (CMT-FOM Italian) with a regular and complete process of transcultural adaptation.

Methods: The scale will be translated and culturally adapted into Italian by two experts in CMT and neuromuscular disorders (NMD). The two translations will be reviewed by a panel of experts in CMT and NMD and a patient representative from ACMT-Rete. The agreed provisional version will be back-translated into English by a professional translator. The definitive Italian version will be developed during a consensus teleconference by the same panel. A series of well characterized CMT patients will be assessed using the finalized translated scale; a subset will have a second test administration after 2 weeks.

Results: Three centers will be involved. The aim is to enroll 15 patients. The full validation is ongoing.

Conclusions: The CMT-FOM Italian will be employed in clinical studies in the Italian population and data will be comparable to that obtained from English speaking version. Supported by NIH grant NS109403-02 to DNH.

References

1. Eichinger K, Burns J, Cornett K, et al. The Charcot-Marie-Tooth functional outcome measure (CMT-FOM) Neurology. 2018;91(15): e1381-e1384. doi: 10.1212/WNL.0000000000006323

2. Zuccarino R, Prada V, Moroni I, et al. Validation of ehe Italian version of the Charcot-Marie-Tooth disease pediatric scale. J Peripher Nerv Syst. 2020.

Keywords: CMT-FOM, Charcot-Marie-Tooth, Outcome Measure, Translation, Assessment.

Poster No: 48 | AAV9 gene replacement therapy in two mutant mouse models of CMT1X demyelinating neuropathy

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Introduction: X-linked Charcot-Marie-Tooth disease (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 interact with virally delivered wild type (WT) Cx32 through dominant-negative effects. Previous lentiviral delivery of the human Cx32 gene rescued the demyelinating neuropathy in T55I mutant mouse model (ER retained) but not in R75W and N175D mutants (Golgi retained).

Methods: In order to study the efficacy of AAV9 to rescue the demyelinating neuropathy in CMT1X models with Golgi-retained Cx32 mutants, we delivered by intrathecal injection an AAV9 carrying the GJB1 gene under the myelin protein zero promoter (Mpz) in 2-month-old mutant mice expressing the R75W or N175D mutations associated with CMT1X on a Gjb1-null background. Expression analysis of Cx32 was performed using immunofluorescence staining. Assessment of therapeutic effect was performed 6 months after treatment by behavioral, electrophysiological and morphological studies.

Results: Following intrathecal delivery of the human GJB1 gene, we could detect the virally delivered WT Cx32 correctly localized in the non-compact myelin areas while mutants were localized in the perinuclear compartment of myelinating Schwann cells. AAV9-Mpz. GJB1 treated R75W/Gjb1-null and N175D/Gjb1-null mice showed improved motor performance, along with lower ratios of abnormally myelinated fibers and reduced numbers of inflammatory cells in all tissues examined compared to mock-treated animals. Motor nerve conduction velocities were also improved in both lines following intrathecal delivery of the viral vector.

Conclusions: This study provides additional proof of principle for a clinically translatable gene therapy to treat CMT1X even in the presence of endogenously expressed Golgi-retained Cx32 mutants, using a clinically translatable vector, AAV9.

Grant Support: Muscular Dystrophy Association and CMT Association (Grant MDA 603003 to KAK).

Keywords: AAV9, connexin 32, Schwann cells, Intrathecal, R75W and N175D.

Poster No: 49 | Prevalence of coexisting neurological disorders in the lower extremities

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Introduction: The purpose of this study is to examine the existence of coexisting neurological disorders in the lower extremities which includes: Tarsal Tunnel Syndrome (TTS), Lumbosacral Radiculopathy (LR), and Sensory Motor Polyneuropathy (SMN).

Methods: A 4-year retro-active analysis of electromyography (EMG) and nerve conduction studies (NCS) were performed. Using EMG NCS studies on 56 patients, the results were analyzed for single and multiple disorders. Each patient was categorized depending on their results. Analysis of the results was conducted to show the percentage of the total 56 patients studied with coexisting disorders present in 35 patients.

Results: The EMG NCS results confirmed coexisting disorders were found in 35 of the 56 patients studied (62%). This broke down to: TTS/LR (n = 21), TTS/SMN (n = 4), TTS/SMN/LR (n = 6), and LR/SMN (n = 4). Only 38% (n = 21) did not have a coexisting disorder. This broke down to: TTS (n = 13), LR (n = 3), and SMN (n = 5). The z score calculation for 2 populations proportions showed $z = 1.7421$ and $P = 0.08186$. The result is not significant at $P < 0.05$. SD is 7.

Conclusions: There appears to be no significant difference between single and coexisting neurological disorders. Although, this study does reveal that coexisting disorders do exist in respect to TTS, LR, and/or SMN. Further, there can be 2 or 3 coexisting disorders present. The presence of TTS, LR, and SMN will combine to what I will call the "Rohacz Triad". Most of these nerve conditions occur within the span of sciatic nerve origination and its descent to the termination of the tibial nerve. I would suggest EMG NCS be performed routinely. This will help ensure proper treatment and more successful outcomes.

Keywords: tarsal tunnel syndrom, coexisting neurological disorders, Sensory Motor Polyneuropathy, Radiculopathy, lower extremities.

Poster No: 50 | An unusual complication of Guillain Barre syndrome: Posterior reversible encephalopathy syndrome (PRES)

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Introduction: Guillain Barre Syndrome (GBS) is an acute polyneuropathy which most patients have normal consciousness. If patients with Guillain Barre Syndrome develop reduction in level of consciousness, the explanation of this phenomenon should be sought. Posterior reversible encephalopathy syndrome (PRES) is an uncommon neurological condition which could present with various manifestations such as encephalopathy, seizure, headache or visual

disturbance and it could occur as a complication from many causes such as severe hypertension, blood pressure fluctuations or renal failure but rarely from Guillain Barre Syndrome.

Methods: Case report. Describing clinical features, findings from nerve conduction study, cerebrospinal fluid (CSF) exam and Magnetic Resonance Imaging (MRI) of the brain.

Results: A twenty-one year-old man presented with bilateral facial palsy, dysarthria, numbness of both arms, bilateral headache, nausea, vomiting and subsequently developed bilateral arm weakness. One day after admission in the first hospital, he developed generalized motor weakness (motor power grade 0 all extremities) and respiratory failure. Two days after admission he was referred to our institute. His first vital signs showed blood pressure level of 180/113 mmHg. Nerve conduction study result showed diffuse inexcitation and the CSF study was compatible with albuminocytologic dissociation profile. One day after admission in our institute his consciousness rapidly deteriorated to comatose state. Brain MRI done at two days later showed patchy T2 hyperintensity lesions in bilateral parieto-occital regions predominantly on the left side. Follow up brain MRI seventeen days later showed interval regression of bilateral parieto-occipital lesions compatible with posterior reversible encephalopathy syndrome (PRES).

Conclusions: When encountering a patient with newly developed acute polyneuropathy with significantly reduced level of consciousness, Guillain Barre Syndrome with posterior reversible encephalopathy syndrome should be in the list of differential diagnosis. Brain MRI is a valuable investigation in confirming the diagnosis.

Grant Support: None.

Keywords: Guillain Barre Syndrome.

Poster No: 51 | A case series of patients with TTR-FAP observed in Moscow, Russia

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Introduction: TTR family amyloid polyneuropathy (TTR-FAP) is a progressive systemic disease in which the peripheral and autonomic nervous systems are most commonly affected. Early detection of TTR-FAP is extremely important, given that pathogenetic therapy is currently available.

Methods: From 2018 to 2020, 140 patients with chronic polyneuropathies of unknown etiology were screened for TTR-FAP at our site. Screening was carried out using DNA sequencing for TTR gene.

Results: A TTR mutation was detected in 6 cases (4%): 5 men (83%) and 1 woman (17%), the average age was 59 years [41; 72]. The mutation c.148G > A (Val50Met) was found in 4 cases (67%), in one patient the mutation c.220G > C (Glu74Gln) and in another one the mutation c.157 T > C (Phe53Leu) were detected. The median time from onset to diagnosis was 2.8 years. All patients had polyneuropathic symptoms. 4 patients (67%) had mild polyneuropathy and did not use a cane to walk outdoors; and autonomic disorders, among which was diarrhea (n = 5; 83%) and orthostatic hypotension (n = 3; 50%). Nerve conduction studies showed axonal (50%) and demyelinating (50%) polyneuropathy. Ultrasound of the peripheral nerves revealed an increase in the cross-sectional area in 3 patients (50%) with the average score on the Ultrasound Pattern Sum Score [Grimm; 2015] of 10 points. Half of the patients were diagnosed with concomitant heart disease (arrhythmia) and kidney disease (proteinuria). 4 patients underwent sural nerve biopsy, only 2 of them had morphological signs of amyloidosis. When examining 19 patients' relatives, mutations in the TTR gene were detected in 6 people (32%), 3 had a polyneuropathy, 3 turned out to be asymptomatic carriers.

Conclusions: In an unspecified polyneuropathy with autonomic disorders, concomitant cardiac and renal pathology, screening for TTR-FAP should be performed. In 50% observed TTR-FAP cases, there was a clinical, neurophysiological and sonographic picture of chronic inflammatory demyelinating polyneuropathy.

Keywords: TTR amyloidosis, Nerve conduction studies, Nerve ultrasound, autonomic disorder, polyneuropathy.

Poster No: 52 | Biallelic Replication Factor C subunit 1 (RFC1) repeat expansion mutation is highly frequent in sensory Chronic Idiopathic Axonal Polyneuropathy

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Introduction: Chronic axonal polyneuropathy is a common occurrence in middle-aged and elderly populations, often labeled as idiopathic after thorough and unsuccessful investigations. A peculiar Replication Factor C subunit 1 (RFC1) intronic repeat expansion mutation has recently been associated with Cerebellar Ataxia, Neuropathy, Vestibular Areflexia Syndrome (CANVAS), a rare disease often presenting as sensory neuropathy at onset. We aimed to investigate the prevalence of RFC1 repeat expansion mutation in Chronic Idiopathic Axonal Polyneuropathy (CIAP) population.

Methods: We reviewed clinical and pathology records of 594 consecutive patients referred for sural nerve biopsy to our Center from January 2007 to December 2016. Clinical, instrumental and pathological features were collected. Prevalence of RFC1 mutations expansion was tested in three groups according to the degree of motor to sensory involvement on evaluation (pure sensory, predominantly sensory and mixed sensorimotor CIAP).

Results: 234 CIAP patients were ultimately included out of 248 identified CIAP cases. RFC1 biallelic intronic AAGGG repeat expansion was common in patients with pure sensory CIAP (21/40, 53%) and predominantly sensory CIAP (10/56, 18%) compared to sensorimotor cases (3/138, 2%). Clinically, RFC1-positive subjects presented frank signs of sensory ataxia associated to mild autonomic disturbances.

Apart from the characteristic retention of deep tendon reflexes, no other peculiar CANVAS clinical features were observed. Nerve conduction studies were suggestive for a diffuse severe axonal neuro(no) pathy. Scant regenerative changes on pathology were suggestive for neuronopathy, with a greater involvement of large myelinated fiber compared to small myelinated and unmyelinated fibers.

Conclusions: Slowly progressive sensory axonal neuropathy is often associated with biallelic RFC1 repeat expansion mutation. Lack of the full-fledged CANVAS clinical presentation should not avert the clinician from appropriate genetic testing.

Grant Support: This work was partially sponsored by Akcea. The funder did not take any part in the definition of the study model, analysis, writing or in the decision to publish.

Keywords: Chronic Idiopathic Axonal Polyneuropathy, Replication Factor c subunit 1, Cerebellar Ataxia, Neuropathy, Vestibular Areflexia Syndrome, Inherited neuropathies.

Poster No: 53 | Neurological complications and pathogenetic therapy for chronic nitrous oxide intoxication ("laughing gas")

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Introduction: Neurological complications in nitrous oxide abuse develop due to a deficiency of vitamin B12, the activity of which is blocked by N2O. We studied the characteristics and course of neurological disorders in patients using "laughing gas" to determine key diagnostic markers of vitamin B12 deficiency.

Methods: The study included 12 patients (10 men and two women) aged 18 to 45 years (average age 29 years) with a diagnosis of B12-deficient myelopolyneuropathy induced by regular use of nitrous oxide.

Results: The most common neurological complication of nitrous oxide abuse for more than 1 month was a generalized lesion of the peripheral nerves with acute or subacute distal symmetric sensory or sensorimotor axonal polyneuropathy. In the clinical picture, sensory complaints and disorders prevailed. Paresis developed in half of the cases. A typical neuroimaging symptom characteristic of funicular myelosis was rarely detected (16.7%). A decrease in B12 vitamin level could most reliably be diagnosed only indirectly, by the presence of hyperhomocysteinemia (91.7% of cases). In all cases that were followed-up, prolonged therapy with cyanocobalamin led to partial (n = 5; 62.5%) or complete (n = 3; 37.5%) regression of neurological symptoms.

Conclusions: Caution regarding the use of nitrous oxide should be in all cases of predominantly sensory polyneuropathy with acute or subacute development in young and middle-aged people. A thorough history taking (targeted survey on the fact of nitrous oxide consumption) and diagnostics (testing the level of homocysteine, if possible methylmalonic acid) allow you to not miss a deficiency of vitamin B12, the treatment of the consequences of which with timely verification and adequate correction is quite effective. It is recommended that the level of homocysteine in the blood to be regularly monitored during the treatment (in order to achieve its normalization).

Keywords: nitrous oxide, "laughing gas", funicular myelosis, vitamin B12, homocysteine.

Poster No: 54 | A prospective natural history study of CMT4J - genetic and phenotypic characterization

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Introduction: Charcot-Marie-Tooth disease type 4J (CMT4J) is a rare, autosomal recessive peripheral neuropathy resulting from mutations in the FIG4 gene. Pediatric-onset is often characterized by rapid progression of muscle weakness and atrophy, culminating in loss of ambulation, respiratory compromise, and premature death. Adult-onset can present with a more variable disease course. This prospective study aims to investigate CMT4J natural history, and concurrently to identify markers of disease progression as potential therapeutic trial endpoints.

Methods: The prospective, longitudinal, multi-center natural history study will enroll up to 30 subjects with genetically-confirmed CMT4J. Visits are scheduled every 6 months for a period of 5 years, and include assessments of CMT-specific patient outcomes, sensorimotor neurological examination, laboratory testing including neurofilament light chain levels, pulmonary function testing, nerve conduction velocity, and lower extremity muscle MRI for documentation of fat fraction. In response to COVID-19, the study has been amended to allow remote data collection until study sites re-open.

Results: This is the largest prospective CMT4J study with current enrollment of 11 pediatric and 4 adult subjects with biallelic FIG4 mutations. Baseline data and test results from up to 3 in-person visits have been collected for all 11 pediatric and 1 adult study subjects. Virtually all subjects presented with a sensorimotor demyelinating peripheral neuropathy, most often symmetric. 3/12 study subjects demonstrated cognitive impairment. Interestingly, the ESR was elevated in 7/11 pediatric subjects, range 23-42 mm/hr, ages 4-17 years. Central reads on CMTFOM, CMTPeds, CMTNS, NCV and MRI studies are in progress to map CMT4J progression timelines.

Conclusions: The baseline CMT4J phenotype demonstrates variable sensorimotor neuropathy with abnormal cognition in a minority of patients. ESR levels may suggest an inflammatory component in pediatric-onset disease. Patient data collected across testing modalities and over multiple visits is expected to provide a robust and quantitative dataset supporting clinical trial outcomes.

Keywords: CMT4J, Observational, Prospective, Longitudinal, Muscle MRI.

Poster No: 55 | **M2 macrophages regulate axon regeneration by surrounding the growing axons to stimulate uPAR in the injured axons by secreting uPA**

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Introduction: Although it has been suggested that M2 macrophages (M2MPs) were involved in regenerative processes after peripheral nerve injury (PNI), their precise role after PNI remains elusive. The current study aimed to identify the cellular and molecular functions of M2MPs in axon regeneration after PNI.
Methods: The spatiotemporal distribution of M2MPs after PNI was evaluated by an immunolabeling study of crushed rat sciatic nerves. To evaluate the role of M2MPs in axon regeneration and functional recovery after PNI, the density of M2MPs in the region of Wallerian degeneration was increased or decreased by the graft of M2MPs or the injection of M2MPs apoptosis drug. To identify the axon stimulating molecule secreted from M2MPs, transcriptome analysis was performed, and a candidate molecule was manipulated in dorsal root ganglion(DRG) neuron culture and rat sciatic nerve injury model.
Results: M2MPs accumulated around the tips of the regenerating axons and moved distally over time to match their location to that of the growing axons. M2MPs could directly promote axon regeneration, and the increase or decrease in the density of M2MPs in the region of Wallerian degeneration promoted or inhibited axon regeneration, respectively. Importantly, the graft of M2MPs significantly improved functional recovery after PNI. Further, the study of DRG neuron culture revealed that only pre-injured neurons were sensitive to humoral factors from M2MPs for neurite outgrowth. In vitro and in vivo studies identified that plasminogen activator (uPA) secreted from M2MPs directly stimulated uPA receptor (uPAR) upregulated in injured axons to promote axon regeneration.
Conclusions: These findings indicate that M2MPs play a pivotal role in axon regeneration after PNI and that uPA-uPAR is a molecular axis of the effect of M2MPs on axon regeneration, providing a basis for the development of a new therapy for PNI.
Grant Support: Grant-in-Aid for Scientific Research (17K11527), the Japan Agency for Medical Research and Development (JP20gm6210004), the General Insurance Association of Japan (2017-2020), the Kobayashi Foundation, and the SEI Group CSR Foundation.
Keywords: M2 macrophage, urokinase plasminogen activator, axon regeneration.

Poster No: 56 | **CMT-COVID survey**

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Introduction: Coronavirus disease 2019 (COVID-19) is a pandemic and public health emergency caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Our study evaluated the impact of the COVID-19 on patients with Charcot-Marie-Tooth (CMT), the most common genetic neuromuscular disorder.
Methods: A simple online questionnaire for CMT patients diagnosed with COVID-19 was developed to investigate how much the COVID-19 impacted the community of CMT and consequences on the progression of CMT. The survey was distributed via e-mail through the INC Contact Registry and with the support of the Italian Association (ACMT-Rete) through the web-based Contact Registry, the Italian CMT Registry, ACMT-Rete members newsletter and social networks.
Results: 152 individuals completed the survey. Approximately 62% of completers were female, and the average age was 49.96 (SD 12,65, range 22-76 years). 13.8% of the respondents had COVID and 2% (n = 3) of them were health workers. Symptoms of COVID-19 were typically mild and none went to the ICU. The full data analysis is ongoing.
Conclusions: These results are ongoing but currently do not show a clear increase risk of COVID in people with CMT.
References
1. Du W, Yu J, Wang H, et al. Clinical characteristics of COVID-19 inchildren compared with adults in Shandong Province, China. Infection. 2020:1-8. doi: 10.1007/s15010-020-01427-2
2. Gou FX, Zhang XS, Yao JX, et al. Epidemiological characteristics of COVID-19 in Gansu province [in Chinese]. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41:E032. doi: 10.3760/cma.j.cn112338- 20 200 229-00216
3. Jeng MJ. COVID-19 in children: current status. J Chin Med Assoc. 2020. doi: 10.1097/JCMA.0000000000000323
4. Prada V, Hamedani M, Genovese F, et al. People with Charcot-Marie-Tooth disease and COVID-19: impaired physical conditions due to the lockdown. An International cross-sectional survey Ann Phys.
Keywords: COVID-19, Charcot-Marie-Tooth, CMT, Survey.

Poster No: 57 | **Novel PLEKHG5 mutations associated with intermediate CMT disease presenting with conduction blocks and leukoencephalopathy**

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Introduction: Biallelic variants in PLEKHG5 have been reported in 15 families associated with different clinical phenotypes including spinal muscular atrophy (SMA), hereditary motor neuropathies (HMN) and intermediate Charcot-Marie-Tooth disease (CMT). We report two additional families with 3 novel PLEKHG5 mutations presenting with intermediate CMT and atypical clinical and neurophysiological findings.
Methods: Four patients from two unrelated families originated from two different geographical areas were clinically examined and subjected to para-clinical and genetics investigations. Clinical data and ancillary tests were retrospectively retrieved and reanalyzed.
Results: Patients presented predominant distal weakness with none or mild sensory involvement. All patients remained ambulant at last examination (22-36 years). Nerve conduction studies revealed in all patients intermediate motor nerve conduction velocities, reduced sensory amplitudes and multiple conduction blocks in upper limbs, outside of typical nerve compression sites. CK levels were strikingly elevated (1611-3867 U/L). CSF proteinorrachia was mildly elevated in two patients. Diffuse bilateral white matter lesions were detected in one patient. Genetic analysis revealed three novel recessive frameshift variants c.1835_1860del and c.2308del (family 1) and c.104del (family 2).
Conclusions: PLEKHG5-associated disease ranges from pure motor phenotypes with predominantly proximal involvement to intermediate CMT with predominant distal motor involvement and mild sensory symptoms. Leukoencephalopathy, elevated CK levels and conduction blocks associated with intermediate velocities in NCS may be part of the phenotype and may raise the suspicion toward this disease.

1. Maystadt I, Rezsöhazy R, Barkats M, et al. The nuclear factor κB-activator gene PLEKHG5 is mutated in a form of autosomal recessive lower motor neuron disease with childhood onset. Am J Hum Genet. 2007.
2. Azzedine H, Zavadakova P, Planté-Bordeneuve V, et al. pLEKHG5 deficiency leads to an intermediate form of autosomal-recessive charcot-marie-tooth disease. Hum Mol Genet. 2013;22:4224-4232.
3. Kim HJ, Hong Y Bin, Park JM, et al. Mutations in the PLEKHG5 gene is relevant with autosomal recessive intermediate Charcot-Marie-Tooth disease. Orphanet J Rare Dis. 2013.
4. Chen Z, Maroofian R, Başak AN, et al. Novel variants broaden the phenotypic spectrum of PLEKHG5- associated neuropathies. Eur J Neurol. 2020:ene.14649.

Keywords: PLEKHG5, Intermediate CMT, Conduction block, Leukoencephalopathy, Proteinorrachia.

Poster No: 58 | Safety of IVIG administration in patients with CIDP. Data from a large randomized efficacy and safety study: The ProCID study

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Introduction: The ProCID study, a prospective, double-blind, randomized, parallel group, multi-center phase III study, investigated the efficacy and safety of Panzyga in patients with active CIDP starting with a loading dose of 2.0 g/kg followed by 7 maintenance doses (1).
Methods: Patients were randomized to either low (0.5 g/kg), standard (1.0 g/kg) or high (2.0 g/kg) maintenance dosing every 3 weeks (total duration: 24 weeks). Dosing was done by actual body weight with no upper limit per day. Patients had to stop or reduce their previous CIDP treatment (87% received corticosteroids) and needed to show deterioration prior to enrollment.
Results: A total of 142 patients were enrolled. The mean IVIg amount/day was 76.5 g (range 10.6 g to 128 g). Starting with the first infusion, the infusion rate could be increased stepwise to a maximum of 12 mg/kg/min. All infusions were given over 2 consecutive days (= 1 infusion-cycle; patients receiving low or standard dosing, were infused with saline solution on the second day to keep blinding). In 971/982 infusion cycles (98.8%), the maximum infusion speed was reached at least once. In only 8 of 142 patients the highest possible infusion rate was not reached or infusion had to be interrupted and rate reduced due to adverse reaction (AR) occurring at the maximum infusion rate. Only 11 patients (7.75%) received premedication. The most common adverse reactions were headache, pyrexia, and dermatitis, with headache being the only AR overall showing a dose dependent effect with an incidence of 2.9%, 14.5% and 23.7% in the 0.5, 1.0 and 2.0 g/kg group, respectively. The most serious adverse reaction related to IVIg administration was vomiting and headache (1 patient). In one patient, allergic dermatitis (related to study drug) led to study discontinuation.
Conclusions: The ProCID study showed that Panyzga infusions were well tolerated at high doses and high infusion rates, even in IVIg naïve CIDP patients.

References

1. Cornblath DR. et al, A randomized, multi-center phase III study of 3 different doses of intravenous immunoglobulin 10% in patients with chronic inflammatory demyelinating polyradiculoneuropathy (ProCID trial): Study design and protocol. Journal. 2018.

Grant Support: This study was sponsored by Octapharma PPG.
Keywords: IVIG, Safety, CIDP, infusion rate, Dosing.

Poster No: 59 | Definition of a new ICF core-set for the upper limbs of hereditary neuropathies

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Introduction: The International Classification of Functioning, Disability, and Health (ICF) is currently fundamental for health and functional status assessment, planning and monitoring of treatment and outcome measurements. However, it has been scarcely applied to Charcot Marie Tooth (CMT) Neuropathy. Therefore, no standardized ICF Core-Set is available to define hand dysfunction in CMT. The definition of an ICF Brief Core-Set specific for the upper limbs (UL) in hereditary neuropathies will support medical care of patients allowing standardized reporting and measurement.
Methods: A panel of 25 health professionals (16 neurologists, 6 physiotherapists, 3 physiatrists) has been recruited to participate in an online Delphi survey to identify the properly ICF code. During the first phase they chose the main chapters, in phase 2 selected the main codes and in phase 3 individuated the 30 codes of a Brief Core-Set, useful to describe the neuropathy disease at the UL level.
Results: The brief core-set defined by the experts included the following codes: like touch, proprioception and pain for the sensory system; range of movement; activities of the daily living, such as eating, writing, doing housework; presence of environmental factors and structure of the upper extremities and of the hands.
Conclusions: In conclusion, this is the first ICF Brief Core-Set for the UL in hereditary neuropathies, created by a panel of experts thanks to an online Delphi survey. This could be a strong and useful tool to characterize the patients and to relate them with their disabilities. Next step will be the validation on the patients, comparing the results with a golden standard scale, such as the CMTES.
Grant Support: ULNA project is supported by AFM-Telethon; Grant #20821 ULNA group: I. Poggi, L. Mori, *M. Grandis*, C. Gemelli, L. Gentile, A. Tisano, M. Russo, C. Pisciotta, G. Schirinzi, S. Fenu, F. Manganelli, S. Tozza, G. Aceto, D. Dellaventura, T. Cavallaro, A. Pere.
Keywords: Charcot-Marie-Tooth Disease, International Classification of Functioning, Brief Core-set, Inherited Neuropathies, hATTR neuropathies.

Poster No: 60 | Gait and balance impairments in individuals with Charcot-Marie-Tooth disease using wearable sensors

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Introduction: Charcot-Marie-Tooth disease (CMT) disrupts balance and gait due to damage to motor and sensory peripheral nerves. Postural sway parameters are markedly impaired in individuals with CMT (1). The Opal sensors (APDM Inc) are wearable inertial sensors that can be used in clinic to evaluate posture and gait in a rapid, sensitive and easily administered way.
Methods: Postural sway and temporal spatial gait analysis were evaluated on patients with known genetic causes of CMT using Opal sensors and Mobility Lab. Sensors were placed on both feet and the waist. Postural sway data was recorded for 30 seconds on patients standing with feet apart, eyes opened (EO) and closed (EC). The measured parameters included total sway area; 95% of confidence of the ellipse area; root mean square sway; path length. The Romberg index, a measure of visual dependency, was calculated. Temporal spatial measures of gait were collected during functional assessments (TUG, 6MWT and 10MWT). These parameters of gait and balance were correlated with the CMTESv2 and CMT-FOM.
Results: All 13 patients (10 CMT1A, 3 CMT1B) demonstrated abnormalities in all balance and gait parameters analyzed. The Romberg index showed a marked visual dependency, with sway indices particularly evident in the EC paradigm. The 6MWT showed the most temporal spatial gait abnormalities. All parameters correlated significantly with both the CMTESv2 and CMT-FOM ($P < 0.05$).
Conclusions: Our preliminary data suggest that Opal sensors are a feasible instrument to use during clinic visits to evaluate gait and balance. Measured parameters proved useful to understand the biomechanics of balance and gait in CMT. Patients with more severe disease defined by the CMTESv2 and CMT-FOM, demonstrated more severe impairment of the sway area and abnormalities of all parameters in gait. Further studies are underway within the Inherited Neuropathy Consortium to test the validity, sensitivity and responsiveness of this tool.
References
1. Tozza S, Aceto MG, Pisciotta C, et al. Postural instability in Charcot-Marie-Tooth 1A disease. Gait Posture. 2016;49:353-357. doi: 10.1016/j.gaitpost.2016.07.183
Grant Support: This consortium Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01).
Keywords: Charcot-Marie-Tooth disease, Gait, Balance, Sensors, Outcome measures.

Poster No: 61 | Quantitative magnetic resonance neurography in myelin protein zero-mutated CMT patients

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Introduction: Quantitative magnetic resonance neurography (qMRN) has been developed to assess the peripheral nervous system involvement in acquired and hereditary neuropathies. Significant differences in several MRI nerve metrics have been found in previous studies between Charcot Marie Tooth type 1A (CMT1A) patients and controls. The objective of this study was to quantitatively evaluate the nerve involvement pattern in Myelin protein zero (MPZ)-mutated patients, and to find clinical correlations between MRI metrics and clinical parameters.

Methods: qMRN was used to extract the 3D nerve volume, proton density (PD) and magnetization transfer ratio (MTR) in the sciatic and tibial nerves of 10 MPZ-mutated, 10 CMT1A patients and 9 healthy controls. Disease severity assessment with CMTNSv2, CMTES, ONLS scores and MRC muscle strength was performed in all patients along with an electrophysiological examination.

Results: MPZ-mutated patients displayed a different nerve involvement pattern than CMT1A. Nerve volume in MPZ-mutated patients was reduced compared to CMT1A and did not differed compared to controls. PD and MTR were similar to healthy subjects in the sciatic nerve but significantly lower in the tibial nerve. Nerve volume was correlated with all functional scores in CMT1A but not in MPZ-mutated patients. However, tibial nerve volume in MPZ-mutated patients was inversely correlated with the dorsal foot flexion strength. Sciatic nerve PD and MTR were also inversely correlated with motor impairment in the lower limbs.

Conclusions: We analyzed in vivo the structural and morphological nerve impairment in MPZ-mutated patients using qMRN and reported significant differences compared to CMT1A and controls. This is of primary interest as one of the main problems regarding the new clinical trials in CMT patients is the lack of sensitive biomarkers to assess potential therapeutic effects. This specific MPZ-mutated patient nerve involvement pattern will be of primary interest in future follow-up studies as qMRN provide several quantitative metrics that correlates with disability.

Keywords: Neurography, MRI, CMT1B, MPZ-mutation, Quantitative.

Poster No: 62 | **Intravenous immunoglobulin treatment patterns in chronic inflammatory demyelinating polyradiculoneuropathy patients: A US claims database analysis**

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Introduction: Immunoglobulin therapy has been shown to be effective in improving impairment and disability scores for patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), a slow progressing or relapsing immune-mediated neuropathy. Intravenous immunoglobulin (IVIG) is recommended as a first-line therapy option. This study aimed to describe real-world treatment patterns among patients with CIDP initiating IVIG treatment.

Methods: This retrospective cohort study used health insurance claims data between 2008 and 2018 from the IBM MarketScan Research Databases. Adult patients (≥18 years old) with CIDP without prior immunoglobulin treatment were identified, and patients subsequently initiating IVIG were included in the analysis. We described timing and frequency of dosing, switching to other immunoglobulin treatments, discontinuation of the index IVIG, and initiation of other CIDP treatments.

Results: Of 32 090 immunoglobulin-naïve patients with CIDP identified, 3975 patients initiated IVIG and were included in this analysis. Few patients had previous non-immunoglobulin CIDP therapy, except for high-dose corticosteroids (34%). Patients received a median of 1 IVIG dose (Q1,Q3: 1.3) during the 14-day loading period. After the loading period, the median interim between doses was 21 days (Q1,Q3: 7.28) and median treatment duration was 129 days (Q1,Q3: 85271). Most (68%) patients arrived at steady-state dose with index IVIG treatment; of those, 27% discontinued the index IVIG and 6% switched immunoglobulin treatment by year 1 of follow-up. Most patients who discontinued did so by the fourth treatment month, and fewer patients discontinued after the eighth treatment month.

Conclusions: Observed IVIG treatment patterns in immunoglobulin-naïve patients with CIDP were consistent with clinical practice, including treatment frequency and discontinuation patterns. Many patients discontinued treatment by the eighth month; after which less discontinuation occurred. Most patients who initiated IVIG treatment had no prior CIDP treatment. Shire US Inc., a Takeda company, funded this study. Baxalta US Inc., a Takeda company, funded writing support.

Keywords: intravenous immunoglobulin, chronic inflammatory demyelinating polyradiculoneuropathy, real-world data.

Poster No: 63 | **Intravenous immunoglobulin initiation in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): A retrospective claims-based cohort study**

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Introduction: CIDP is a debilitating and slowly progressing or relapsing immune-mediated neuropathy. Intravenous immunoglobulin (IVIG) is recommended as first-line therapy for CIDP. The clinical profile of patients with CIDP newly initiating IVIG is not well characterized. This retrospective claims-based cohort study aimed to identify and describe characteristics of US patients with CIDP initiating IVIG treatment.

Methods: Adult immunoglobulin-naïve patients with CIDP from 2008-2018 were identified via diagnosis coding using the IBM

MarketScan Research Databases (full cohort). Clinical and demographic characteristics of new IVIG users were described overall and by initial IVIG product. Logistic regression and propensity score methods were used to evaluate probability of receiving available IVIG treatments based on baseline characteristics.

Results: New IVIG users (n = 3975, mean age 57 years) had similar demographics compared with the full cohort (n = 32 090, mean age 57 years). Almost all (99%) new IVIG use was started in an ambulatory setting. Forty-one percent of new IVIG users had prior non-immunoglobulin CIDP treatments (35% high-dose corticosteroids). New IVIG users tended to have greater comorbidity/symptom burden (weakness and/or difficulty walking [61% vs 35%], neuropathic or chronic pain [80% vs 64%], diabetes [33% vs 29%], hypertension [62% vs 52%], hypothyroidism [21% vs 18%], rheumatoid arthritis [19% vs 14%], and other autoimmune disorders [7% vs 3%]) and were more likely to have had diagnostic/laboratory testing than the full cohort. Clinical and demographic characteristics tended to be similar among patients by initial IVIG product; differences in initial IVIG product selection varied by year and geographic region.

Conclusions: Patients with CIDP initiating IVIG have a heavy burden of symptoms, comorbidities, and diagnostic/laboratory testing. The characteristics of US patients initiating different IVIG products are well balanced, suggesting that IVIG products are generally used interchangeably. Shire US Inc., a Takeda company, funded this study. Baxalta US Inc., a Takeda company, funded writing support.

Keywords: intravenous immunoglobulin, chronic inflammatory demyelinating polyradiculoneuropathy, real-world data.

Poster No: 64 | **Individual responses in grip strength to alterations in serum immunoglobulin G trough levels in patients with multifocal motor neuropathy on IVIG**

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Introduction: The association between serum immunoglobulin G trough (IgGtrough) levels and the efficacy of intravenous immunoglobulin (IVIG) in multifocal motor neuropathy (MMN) is not well understood. In this retrospective analysis, we examined grip strength (GS) response to alterations in serum IgGtrough in patients with MMN participating in a phase 3 trial (NCT00666263) of IVIG 10%.

Methods: Male and female adults with MMN on stable IVIG therapy were randomized (1:1) to two sequences of five 12-week treatment periods of IVIG 10% or placebo: IVIG-IVIG-IVIG-placebo-IVIG (S1, n = 22); IVIG-placebo-IVIG-IVIG-IVIG (S2, n = 22). Periods 1, 3, and 5 (IVIG) were open-label; periods 2 and 4 (IVIG or placebo) were double-blinded. IgGtrough and GS were measured at the beginning and end of each period, respectively. In this retrospective analysis, GS during IVIG vs placebo was compared by analysis of variance, and the association between IgGtrough and GS evaluated by linear regression.

Results: Twelve women and 32 men (mean [SD] age: 51.6 [10.3] y) were included. A rapid, significant decline in GS occurred in the more affected hand after switching from IVIG to placebo (mean [SD] change: −28.7% [25.7%] for S1; −27.1% [41.1%] for S2; least square means of percent change in GS between IVIG and placebo: 35.13%; $P = 0.005$). Directional changes in IgGtrough and GS were similar in most patients at the individual level, but no significant correlations between percent change in GS vs IgGtrough or percent change in IgGtrough occurred at the group level. Similar findings were observed for the less affected hand.

Conclusions: GS response to alterations in serum IgGtrough levels was patient specific. These findings highlight the importance of maintaining stable serum immunoglobulin G levels on an individual patient basis in MMN. Shire US Inc., a Takeda company, funded this study. Baxalta US Inc., a Takeda company, funded medical writing support.

Keywords: intravenous immunoglobulin, immunoglobulin G, multifocal motor neuropathy.

Poster No: 65 | **Long-term safety of facilitated subcutaneous immunoglobulin: Insights from a postauthorization safety study in primary immunodeficiency diseases (PID)**

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Introduction: Facilitated subcutaneous immunoglobulin (fSCIG), a dual-vial unit of immunoglobulin G (IgG) 10% and recombinant human hyaluronidase (rHuPH20), is approved in the United States (US) for adults with PID and is in phase 3 development for treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). rHuPH20 locally increases subcutaneous tissue permeability by temporarily depolymerizing hyaluronan, allowing for administration of larger IgG volumes. An ongoing postauthorization safety study (PASS; NCT02593188) is acquiring real-world data on the long-term safety of fSCIG in patients with PID.

Methods: This prospective, noninterventional, uncontrolled, multicenter PASS started November 2015 in the US in patients ≥16 years with PID receiving fSCIG at the treating physician's discretion, per routine clinical practice. Adverse event (AE) data were collected from enrollment through study completion/discontinuation (up to approximately 3 years), and anti-rHuPH20 antibody titers were evaluated. An interim

analysis (data cutoff: May 2, 2019) assessed fSCIG safety, dose, and infusion parameters.

Results: Enrollment was completed (n = 264; mean age 54.7 years; 79.2% female), with 81 patients still undergoing follow-up. Patients received fSCIG for a mean (SD) duration of 10.4 (3.6) months, with infusions most commonly administered every 4 weeks. No serious AEs related to fSCIG were reported. Over 98% of infusions were received without rate reduction, interruption, or discontinuation due to AEs. Causally related nonserious local and systemic AEs occurred in 10.2% (n = 27, 0.35 events/patient-year, 0.05 events/infusion) and 14.0% (n = 37, 0.72 events/patient-year, 0.10 events/infusion) of patients, respectively. No neutralizing rHuPH20 antibodies were detected in patients with immunogenicity data (n = 194).

Conclusions: These real-world data confirm the tolerability of fSCIG in patients with PID. The infusion characteristics and attributes of fSCIG may be beneficial for diseases that require high doses of IgG, such as CIDP, in which intravenous IgG has been the standard of care until now. Baxalta US Inc., a Takeda company, funded this study and writing support.

Keywords: facilitated subcutaneous immunoglobulin, real-world data, safety study, chronic inflammatory demyelinating polyradiculoneuropathy.

Poster No: 66 | RFC1 expansions are a common cause of idiopathic sensory neuropathy

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Introduction: After extensive evaluation, one third of patients affected by polyneuropathy remain undiagnosed and are labeled as chronic idiopathic axonal polyneuropathy (CIAP), which refers to a sensory or sensory-motor, axonal, slowly progressive neuropathy of unknown origin. Since a sensory neuropathy/neuronopathy is identified in all patients with genetically confirmed RFC1 CANVAS we speculated that RFC1 expansions could underlie a fraction of idiopathic sensory neuropathies, also diagnosed as CIAP.

Methods: We retrospectively identified 225 patients diagnosed with CIAP (125 sensory neuropathy, 100 sensory-motor neuropathy) from our general neuropathy clinics in Italy and the UK. All patients underwent full neurological evaluation and a blood sample was collected for RFC1 testing.

Results: Biallelic RFC1 expansions were identified in 43 patients (34%) with sensory neuropathy, and in none with sensory-motor neuropathy. Forty-two per cent of RFC1 positive patients had isolated sensory neuropathy or sensory neuropathy with chronic cough, while vestibular and/or cerebellar involvement, often subclinical, were identified at examination in 58%. Although the sensory ganglia are the primary pathological target of the disease, the sensory impairment was typically worse distally and symmetric, while gait and limb ataxia were absent in two third of cases. Sensory amplitudes were either globally absent (26%), reduced in a length-dependent (30%) or non-length dependent pattern (44%). One fourth of RFC1 positive patients had previously received an alternative diagnosis including Sjögren's syndrome, sensory chronic inflammatory demyelinating polyneuropathy (CIDP) and paraneoplastic neuropathy and 3 cases had been treated with immune therapies.

Conclusions: After the exclusion of the common acquired causes, RFC1 expansions should be considered in all cases with isolated sensory, but not sensory-motor, CIAP.

References

1. Cortese A. et al. Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia. Nat Genet. 2019;Springer US, 51(4):649-658. doi: 10.1038/s41588-019-0372-4

2. Cortese A. et al. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome due to RFC1 repeat expansion. Brain: J Neurol. 2020;143 (2):480-490. doi: 10.1093/brain/awz418

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Keywords: Sensory neuropathies, Ataxia, RFC1, Idiopathic axonal polyneuropathies, Inherited neuropathies.

Poster No: 67 | Axillary nerve palsy - a case presentation

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Introduction: Axillary nerve palsy is a rare finding, representing only 3-6% of all injuries concerning the brachial plexus. The vast majority of causes generating axillary nerve palsy are traumatic.

Methods: We herein present the case of a 16 years old patient with an acute weakness for flexion, abduction, and external rotation of the shoulder, without trauma.

Results: The EMG examination revealed an isolated axillary nerve lesion. Laboratory showed high LDH and alkaline phosphatase. The patient was referred to an ultrasound examination that showed a hypoechogenic axilary nerve and in the upper portion of the arm a inhomogenous tumor with hypervascularisation, MRI revealed a tumor of the humerus diaphysis of 75/47 mm with contrast enhancement that invades supraspinatus and deltoid muscles suggestive for sarcoma. The patient underwent a biopsy and started radiation therapy.

Conclusions: Considering the fact that a nontraumatic isolated axillary nerve lesion is a rare finding, the EMG examination is mandatory in order to exclude other lesions including those of the brachial plexus or cervical radiculopathies and also imaging plays a very important role in determining the etiology.

Keywords: axillary nerve, EMG.

Poster No: 68 | Novice vs expert: Intra- and inter-rater reliability of ultrasonographic measurements of the median nerve cross-sectional area of Filipinos

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Introduction: When complemented with traditional history taking and physical examination, physician-performed peripheral nerve sonography can be a powerful point-of-care diagnostic tool to evaluate patient pathology. To better implement this tool into standard practice, integration of ultrasonography into medical education may prove beneficial, particularly with image acquisition and interpretation. The primary objective of this study was to assess the intra- and inter-rater reliability of novice and expert measurements of the cross-sectional area (CSA) of the median nerve (MN) at the carpal tunnel inlet (CTI) and carpal tunnel outlet (CTO) among Filipinos.

Methods: A medical student with no peripheral nerve ultrasonography experience (novice) obtained serial bilateral measurements of the MN CSA at the CTI and CTO, with a single ultrasound machine with a linear array transducer, musculoskeletal setting, and electronic caliper function over the course of four months. Measurements were compared with those of an expert with more than 25 years of ultrasonographic experience. The latter was considered the reference standard. Both the novice and expert were blinded to each other's measurements.

Results: The Kendall's Coefficients of Concordance of intra-rater reliability measurements of MN CSA at the Left CTI, Right CTI, Left CTO, and Right CTO were 0.906, 0.857, 0.920, and 0.8065 for the novice; and 0.846, 0.872, 0.905, and 0.905 for the expert, respectively ($P < 0.0001$). The Kendall's Coefficients of Concordance of inter-rater reliability between novice and expert measurements of MN CSA at the Left CTI, Right CTI, Left CTO, and Right CTO were 0.878 ($P < 0.01$), 0.822 ($P < 0.01$), 0.595 ($P = 0.193$), and 0.679 ($P = 0.068$), respectively.

Conclusions: There were strong degrees of intra-rater reliabilities, and moderate to strong degrees of inter-rater reliabilities in ultrasonographic measurements of MN CSA using ultrasonography. Ultrasound of the median nerve CSA can therefore be efficiently taught to a novice, and result in measurements consistent with an expert operator.

Keywords: Ultrasonography, Median Nerve, Ultrasonography in Medical Education, Intra-rater reliability, Inter-rater reliability.

Poster No: 69 | The neurophysiological lesson from the Italian CIDP database

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Introduction: Electrophysiological diagnosis of CIDP may be challenging. Thus, with the aim of providing some practical advice in electrophysiological approach to a patient with suspected CIDP we evaluated electrophysiological data from the Italian CIDP Database.

Methods: We analyzed 419/499 patients fulfilling and 80/499 not fulfilling the EFNS/PNS electrophysiological CIDP criteria. In fulfilling patients we calculated the rate of each demyelinating feature, the rate of demyelinating features per nerve and the diagnostic rate for upper and lower limb nerves, and, using a ROC curve analysis, the diagnostic accuracy of each nerve and demyelinating feature, in typical and in atypical CIDP subtypes. Moreover, we compared the electrophysiological data of fulfilling patients with those of not-fulfilling patients and by a logistic regression analysis we estimated the diagnostic odds ratio (OR).

Results: In fulfilling patients the ulnar nerve had the highest rate of demyelinating features and the highest diagnostic accuracy in CIDP population except for DADS in which peroneal nerves were the most informative. In not-fulfilling patients a lower number of nerves and temporal dispersion (TD) measurements had been performed compared to fulfilling patients, showing an OR of 1.41 and 1.28 for a correct diagnosis for any tested motor nerve and TD measurement. By testing ulnar nerves and then peroneal nerves bilaterally, the electrophysiological diagnosis of CIDP is achieved in the majority of cases. Adding tibial nerves for DADS phenotype and median nerves for all other CIDP subtypes improves the electrophysiological diagnostic chance, on the contrary further extension of neurophysiological examination probably does not.

Conclusions: Electrophysiological approach to a patient suspected of CIDP should take into account the clinical phenotype. An adequate extension of the examination and an accurate interpretation of neurophysiological results are crucial not to miss the diagnosis of CIDP. Obviously, all demyelinating characteristics must be carefully considered and TD should never be neglected.

Keywords: CIDP, neurophysiology, diagnostic criteria, nerve conduction.

Poster No: 70 | Biological, electrophysiological and MRI biomarkers to evaluate disability in CIDP patients

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Introduction: Numerous biomarkers have been developed to evaluate disability in chronic inflammatory demyelinating polyradiculoneuropathies (CIDP). Our objective was to evaluate a large variety of biomarkers regarding their respective sensitivity to disability.

Methods: Disability was evaluated with the Rasch-built Overall Disability Scale (RODS) in 29 CIDP patients (median age 60 yo, median disease duration 48 months). Nerve conduction studies were bilaterally performed on median, ulnar, tibial, fibular and sural nerves. Motor unit index (MUNIX) was evaluated in the abductor pollicis brevis, abductor digiti mini and anterior tibialis muscles. Quantitative MRI was performed for the lower-limb muscles (thigh and lower-leg) and the sciatic and tibial nerves on the non-dominant side. Neurofilaments light chains, cytokines (Il-1β, IL-6, IL-8, IL-17a, IFN-γ, TNF-α, IL-10, IL-2), chemokines (IP-10, MCP-1, Eotaxin) and vascular markers (VCAM-1, ICAM-1, VEGF) were quantified through multiplex analysis (MesoScale Discovery). Correlations between biomarkers and disability was assessed with the Spearman test. Multiple linear regressions were performed to determine the independent contribution of each potential factor.

Results: Disability was significantly related ($P < 0.05$) to the sum of the compound muscle action potential (CMAP) amplitudes ($r = 0.46$), mean distal latencies of tibial nerves ($r = -0.41$), mean CMAP duration of fibular nerves ($r = 0.54$), sum of the MUNIX ($r = 0.41$), neurofilament light chains level ($r = -0.45$), MRI fat fraction of the quadriceps ($r = -0.58$), sartorius ($r = -0.53$), semi-tendinous ($r = -0.47$) and medial gastrocnemius muscles ($r = -0.51$). In multivariate analysis, disability was correlated with the fat fraction of the quadriceps muscle ($r = -0.68$, $P = 0.015$, R2 0.41).

Conclusions: We have identified, in CIDP patients, several electrophysiological, biological and MRI biomarkers associated with disease severity. MRI fat fraction of the quadriceps muscle is an independent biomarker which can be assessed to reflect patients' disability.

Keywords: CIDP, MUNIX, Neurofilament light chain, quantitative neuromuscular MRI, Disability.

Poster No: 71 | Highly stringent proteomics to elucidate molecular mechanisms underlying neuropathic pain and axonal degeneration in painful diabetic neuropathy

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Introduction: Painful diabetic neuropathy (PDN), one of the most common and intractable complication of diabetes, is characterized by neuropathic pain and small fiber degeneration. We aim to identify the molecular pathways linking hyperexcitability and calcium overload to neuropathic pain and axonal degeneration in PDN.

Methods: High-fat diet model: Mice were either fed a regular diet (RD, 11% fat) or a high-fat diet (HFD, 42% fat) for 10 weeks. Highly stringent proteomic analyses: Lumbar DRG (L1-L6) from RD and HFD mice were extracted, flash frozen and TMT-16 plex peptide labeling was performed. In vivo calcium imaging: Using a calcium indicator

(GCaMP6) selectively expressed in L4 DRG nociceptors in RD and HFD mice, calcium transients were measured in real time in response to mechanical stimuli applied to the paw. Electron Microscopy: L4 and L5 DRG were fixed in 2.5% Glutaraldehyde in 0.1 M Sodium Cacodylate buffer.

Results: We identified 1121 unique proteins (False Discovery Rate [FDR] < 0.05) that were differentially expressed between RD and HFD including several significantly enriched pathways (mitochondrial organization and mitochondrial calcium ion transmembrane transport). In particular we found that proteins involved in fission were elevated in HFD L5 and L4 DRGs. Furthermore, HFD DRG neurons mitochondria displayed fragmented morphology as early as two weeks after diet commencement, preceding the onset of mechanical allodynia and small fiber degeneration. Moreover, calcium in vivo study demonstrated that HFD DRG nociceptors responded to a mechanical stimulus with [Ca2+]i transients of significantly higher amplitude compared to RD. Interestingly preventing calcium entry into the mitochondria by selectively deleting the Mitochondrial Calcium Uniporter (MCU) from DRG nociceptors, restored normal mitochondria morphology and dynamics, prevented axonal degeneration and reversed mechanical allodynia in PDN mice.

Conclusions: We propose that targeting calcium entry into nociceptor mitochondria is a promising therapeutic approach toward realizing novel, effective and disease-modifying treatments for patients suffering from PDN.

References

1. Jayaraj ND, et al. Reducing CXCR4-mediated nociceptor hyperexcitability reverses painful diabetic neuropathy. J Clin Invest. 2018;128:2205-2225.

2. Obrosova IG, et al. High-fat diet induced neuropathy of pre-diabetes and obesity: effects of "healthy" diet and aldose reductase inhibition. Diabetes. 2007;56:2598-2608.

3. Vargas ME, Yamagishi Y, Tessier-Lavigne M, Sagasti, A. Live imaging of calcium dynamics during axon degeneration reveals two functionally distinct phases of calcium influx. J Neurosci: Off J Soc Neur.

Keywords: neuropathic pain, mitochondria, diabetes, High fat diet, proteomics.

Poster No: 72 | Identifying changes in the gene expression profile of sensory neurons in painful diabetic neuropathy

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Introduction: The molecular mechanism underlying dorsal root ganglion (DRG) nociceptor hyperexcitabilty in painful diabetic neuropathy (PDN) is unknown. We aim to identify the gene expression changes of sensory neurons in PDN for the discovery of druggable targets.

Methods: 1.High-fat diet model: We use a well-established mouse model of PDN, where mice were either fed a regular diet (RD, 11% fat) or a high-fat diet (HFD, 42% fat) for 10 weeks. These mice recapitulate the two hallmarks of PDN that is, they exhibit mechanical allodynia and show a reduction in the intra-epidermal nerve fiber density. 2.Single-cell RNA (scRNA-seq) sequencing using the 10X platform: DRG neurons were isolated from RD and HFD mice and an unbiased approach is used to identify cell type and cell states. 3.In vivo calcium imaging: Calcium transients in the DRG were measured in real time using the Nav1.8-Cre GCaMP6 animals in response to intradermal injections in the hind paw of animals with β-alanine, a known agonist of the Mas-related G-protein coupled receptor (Mrgprd).

Results: In addition to the expected neuronal and non-neuronal clusters, scRNA-seq revealed two closely related clusters expressing Mrgprd which we refer to as non-peptidergic 1 type I (NP1T1) and non-peptidergic 1 type 2 (NP1T2) with the NP1T2 population showing a significant overexpression of Mrgprd in the HFD. From in vivo calcium imaging, we observed an increase in the percentage of neurons responding to β-alanine in HFD indicating the hyperexcitability of neurons expressing Mrgprd.

Conclusions: Mrgprd is an interesting target as the expression of this receptor influences the excitability of neurons and moreover, this receptor is expressed by neurons that innervate the outermost layers of the skin. The overexpression and the hyperexcitability of these Mrgprd neurons suggest an important role of the Mrgprd receptor in the generation and maintenance of hyperexcitability in a mouse model of PDN.

Grant Support: Supported by NIH/NINDS: 1 R01 NS104295-01 and the HEAL initiative.

Keywords: Painful diabetic neuropathy, Dorsal root ganglion, Mas-related G-protein coupled receptor, Nociceptors, Neuropathic pain.

Poster No: 73 | Transcriptome analysis of activated epidermal keratinocytes of mouse skin reveals mechanisms of degeneration of cutaneous nerves

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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 degeneration of cutaneous nerves 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.

Methods: To explore mechanisms by which keratinocytes communicate with cutaneous afferents and how this communication impacts axonal degeneration underlying neuropathic pain in PDN, we

genetically expressed stimulatory DREADD, Gq-linked G protein-coupled receptors (GPCRs-hM3Dq) into epidermal basal keratinocytes (K-14) in mice as a tool for mimicking the activation of Gq-linked GPCRs in basal keratinocytes. Following IP injection of the synthetic ligand clozapine N-oxide (CNO) for activation, back skin sections were prepared and assessed for histological characterizations, immunostaining (H&E staining, BrdU incorporation and PGP9.5 staining), and transcriptomic analysis (bulk and single-cell RNA sequencing).

Results: Histological characterization revealed a clear thickening of the epidermis due to K-14 expressing cell hyperproliferation. Additionally, we observed reduced innervation of the epidermis, indicating that activation of K-14 Gq-linked GPCRs drives nerve degeneration in the epidermis. Furthermore, transcriptional profiling of activated K-14 positive cells from the skin of K14-hM3Dq mice revealed downregulation of genes involved in neuron survival and growth, including Nerve Growth Factor, artemin, and Semaphorin 3D. Interestingly genes associated with immune cells, including neutrophil chemoattractant genes such as CXCL10, and CXCL11, were overexpressed. We are now applying IsoPlexis technology to determine EKs single-cell secretome profiling in this model.

Conclusions: Activation of basal keratinocyte Gq-linked GPCRs could represent highly "druggable" and easily accessible targets for the development of therapeutics that by modulating inflammation and reversing axonal degeneration of cutaneous nerves in PDN could ameliorate the associated neuropathic pain.

Keywords: painful neuropathy, nerve fiber degeneration, diabetes.

Poster No: 75 | The diagnostic addition of the median nerve conduction study on the flexor digitorum superficialis muscle in Charcot-Marie-Tooth disease

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Introduction: In the nerve conduction study (NCS) of Charcot-Marie-Tooth disease (CMT), compound muscle action potential (CMAP) is sometimes not evoked due to severe hand muscle atrophy, which makes difficult to confirm nerve conduction velocity (NCV). In the median nerve NCS, it might be easier to record CMAP from the more proximal muscle innervated by the median nerve than the abductor pollicis brevis muscle (APB). This study aimed to elucidate the utility of median nerve NCS on the flexor digitorum superficialis muscle (FDS) in CMT diagnosis.

Methods: 52 patients with CMT (40 of CMT1, 7 of CMT2, 2 of CMT4 and 3 of CMTX) and 6 normal controls were examined. CMAPs were recorded from APB and FDS. The stimulate sites for APB were the wrist and elbow, and those for FDS were the elbow and upper arm.

Results: In CMT1 and CMTX group, the CMAP amplitudes of FDS were significantly larger than those of APB (CMT1 3.7 ± 3.0 (APB) vs 5.4 ± 1.7 mV (FDS), CMTX 2.4 ± 3.6 vs 5.4 ± 1.7 mV, $P < 0.05$). There was a similar trend in CMT2 and CMT4 group (CMT2 5.6 ± 3.2 vs 8.7 ± 3.0 mV, CMT4 2.4 ± 3.6 vs 2.9 ± 3.0 mV). There was no significant difference in CMAP amplitudes between APB and FDS in the healthy group (9.4 ± 1.9 vs 9.4 ± 1.4 mV). In the CMT group, APB-CMAPs were not evoked in 3 cases, all of which were CMT1. In one case of them, decreased CMAP amplitude and slowed NCV were observed using FDS recording, although the abductor digiti minimi muscle (ADM)-CMAP was also unrecordable.

Conclusions: In the diagnosis of CMT, FDS recording in the median nerve NCS is useful in CMT cases with severe hand muscle atrophy.

Keywords: Charcot-Marie-Tooth disease, nerve conduction study, flexor digitorum superficialis muscle, nerve conduction velocity, median nerve.

Poster No: 76 | Role of mesenchymal stem cell derived exosomes in neuronal survival

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Introduction: Autologous nerve grafting is the gold standard for peripheral nerve repair; however, limited donor resources preclude search for new therapeutic strategies(1). Mesenchymal stem cells (MSCs) able to migrate to injured sites and promote neuronal survival, thus showing potential as cell-based therapy(2). It is believed that their positive effect is not due to differentiation but due to trophic effects(3). Among the existing hypothesis on MSCs mechanism of action, different studies report MSC-secreted vesicles paracrine effects for tissue repair(4), however, their composition and role remain to be established. The aim of this work was to analyze MSC-derived vesicles effect on neuronal survival.

Methods: Extracellular vesicles (EV) were purified from medium of MSCs cultured alone or in co-culture with sensory primary neuronal cells. After the staining with lipophilic membrane dye PKH26 and added once a week to primary neuronal cells for 6 weeks. Neurons were followed up to analyze stained EV intracellular localization and neuronal survival.

Results: Confocal microscope analysis demonstrated that EV were able to enter into neurons and to localize in cytoplasm of both cell body and neuronal processes. Moreover, EV showed a perfect co-localization with exosomal marker Cd9. Our results also showed that neurons that received MSC derived EV, both from MSCs alone or from the co-cultures, were able to survival longer.

Conclusions: As conclusion, this work demonstrates that MSCs could support the sensory neurons' survival through exosome release. Such a mechanism could be therefore exploited to design a cell free therapy to support neuronal survival. We are now investigating the putative molecules mediating such an effect.

References

1. Han Y, et al. Mesenchymal Stem Cells for Regenerative Medicine. Cells. 2019;8(8):886.

2. Fitzsimmons REB, et al. Mesenchymal stromal/stem cells in regenerative medicine and tissue engineering. Stem Cells Int. 2018. (19).
3. Bouchez G, et al., Partial recovery of dopaminergic pathway after graft of adult mesenchymal stem cells in a rat model of Parkinson's disease. Neurochem Int. 2008;52(7):1332-42.
4. Biancone L, et al., Therapeutic potential of mesenchymal stem cell-derived microvesicles. Nephrol Dial Transplant. 2012;27:3037-3042.
Keywords: MSC, extracellular vesicles, neuronal survival.

Poster No: 77 | Role of the ATF6 branch of the UPR in CMT1B neuropathy

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Introduction: Mutations in Myelin Protein Zero (MPZ) gene caused Charcot-Marie-Tooth type 1B (CMT1B) disease. It has been demonstrated that a significative percentage of P0 mutants (such as P0S63del or P0R98C) are misfolded and retained in the endoplasmic reticulum (ER), where they activate the unfolded protein response (UPR). The modulation of the UPR is emerging as a valuable therapeutic approach. We have shown that the PERK arm of the UPR can be targeted to ameliorate the CMT1B neuropathy in P0S63del mice, but the role of the other two pathways (IRE1 and ATF6) of the UPR in CMT remained largely unexplored.
Methods: To investigate the role of the ATF6 branch in CMT1B, we decided to generate S63del/ATF6 null mice; we performed behavioral tests as well as morphological, electrophysiological and biochemical analysis.
Results: As expected, we observed that the absence of ATF6 dramatically worsened the P0S63del phenotype: we found a severe hypomyelination and a worsening of electrophysiological and locomotor parameters, both in young and adult mice. Moreover, the UPR markers appeared to be increased in S63del/ATF6 null mice suggesting exacerbation of ER-stress.
Conclusions: These preliminary results suggest that the ATF6 pathway plays an adaptive role in P0S63del mice, suggesting that the activation of this pathway could be beneficial in CMT1B, and probably in other pathologies characterized by UPR activation.
Keywords: Unfolded Protein Response, CMT, ATF6, Schwann cells, myelin.

Poster No: 78 | Understanding of genetic diagnosis and management in newly diagnosed patients with Charcot Marie Tooth disease and related disorders

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Introduction: Hereditary neuropathies are the most frequent inherited neurological conditions. Of these, the most common are Charcot Marie Tooth (CMT) disease and related disorders and amyloidosis (ATTRm) due to mutations in Transthyretin (TTR). Emerging clinical trials and treatments for genetic conditions and either antenatal or preimplantation services for future family planning have prompted the need for genetic literacy. This knowledge empowers individuals to make informed decisions and to provide informed consent.
Methods: Semi-structured telephone interviews were performed to assess patients' understanding of their genetic diagnosis, the inheritance pattern, and the implications for their family and the informational needs of newly diagnosed patients attending the genetic peripheral nerve clinic in London (UK). Questions to test patients' knowledge on the genetic nature of their condition were asked before and after the clinic consultation. Furthermore aspects regarding the management of the condition were also assessed.
Results: Overall 26 patients participated. More than half of the patients (54-60%) either agreed or strongly agreed with both understanding genetic diagnosis and its implications for their families before the clinic appointment. Their understanding significantly improved after the appointment (p - value <0.001). Only 38.4% of patients had a good understanding of the inheritance pattern before the appointment and this slightly improved after the clinic consultation but not significantly (P-value 0.39). Leaflets were the preferred way to receive educational materials compared to video. Physiotherapy and maintaining mobility were rated as the most important aspects of disease management.
Conclusions: This study demonstrated the need to create educational materials to provide more clear information on inheritance patterns in order for patients to have a better understanding of their genetic diagnosis and their implications.
Keywords: Genetic neuropathies, Patients' knowledge of genetics.

Poster No: 79 | SORD-related CMT: Expanding the phenotype

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Introduction: SORD is a newly described autosomal recessive gene that is emerging as the commonest cause of recessive CMT (Charcot-Marie-Tooth disease). The typical phenotype is a length-dependent motor-predominant neuropathy. We describe five cases that expand the phenotype of SORD-related CMT.
Methods: We present five unrelated cases of CMT secondary to biallelic mutations in SORD.
Results: Three of five cases carry homozygous c.757delG (p. Ala253GlnfsTer27) mutations in SORD, the remaining two being compound heterozygous. All developed slowly progressive motor symptoms affecting initially the distal lower limbs, with onset in teenage years. None had sensory symptoms. All had motor examination findings in lower limbs consistent with length-dependent neuropathy.

Neurophysiology showed predominantly a length-dependent motor pattern, but all had reduced or borderline sensory action potentials (SAPs) in upper limbs but normal SAPs in lower limbs. Case 1:67 year-old male. Weakness progressed to his hands and he underwent bilateral tendon transfers. Examination and neurophysiology were notable for median predominant disease in upper limbs, plus pectoral wasting and scapular winging. Case 2:29 year-old male. Neurophysiology showed bilateral ulnar conduction block in the forearms with dispersion. Case 3:47 year-old male. EMG revealed proximal denervation. Cases 4 and 5: Two 18 year-old males with additional findings of brisk lower limb reflexes.

Conclusions: These cases illustrate some additional unusual features. None describe sensory symptoms, but all have reduced upper but normal lower limb SAPs. Cases 1, 2 and 3 also demonstrate elements of a non-length-dependent motor phenotype, including predilection for individual upper limb nerves. One hypothesis is that, given the role of sorbitol dehydrogenase in glucose metabolism, there may be parallels in the pathology of mononeuropathy in diabetes, and 'mononeuropathy' in CMT due to mutations in SORD. In summary, biallelic SORD mutations typically cause a slowly progressive, length-dependent motor process, but these cases suggest other emergent features.

1. Cortese, A. et al. Biallelic mutations in SORD cause a common and potentially treatable hereditary neuropathy with implications for diabetes. Nat Genet. 2020;52:473-481.

Keywords: CMT, SORD, Genetics, Phenotype.

Poster No: 80 | Inhibition of LPA1 signaling mitigates Schwann cell dedifferentiation in experimental autoimmune neuritis

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Introduction: Accumulating evidence points to a significant involvement of lysophosphatidic acid (LPA) as pleiotropic lipid messenger in the regulation of immune functions as well as Schwann cell physiology, with potential relevance for the pathophysiology of peripheral neuroinflammation. However, while the clinical efficacy of specific LPA receptor antagonists is being investigated in autoimmune diseases such as systemic sclerosis, the role of LPA signaling in inflammatory neuropathies has remained completely undefined. We have recently demonstrated that LPA is required for Schwann cell dedifferentiation and activation following mechanical nerve injury.

Methods: Given the broad expression of LPA receptors on both Schwann cells and cells of the innate and adaptive immune system, we hypothesized that inhibition of LPA signaling may ameliorate the course of disease in experimental autoimmune neuritis (EAN). Lewis rats received an orally available LPA receptor antagonist named AM095, specifically targeting the LPA1 receptor subtype. AM095 was administered via a therapeutic treatment regime from 10 until 28 days post-immunization.

Results: Lewis rats treated with AM095 displayed a significant improvement in clinical scores, most notably during the remission phase. Cellular infiltration was only discretely affected by AM095. However, immunohistochemical analysis of sciatic nerves revealed a reduction in the number of Schwann cells expressing the dedifferentiation marker Sox2 paralleled by a corresponding increase in differentiating Sox10-positive Schwann cells. In line with this, morphometric analysis of sciatic nerve semi-thin sections identified a significant increase in large-caliber myelinated axons at 28 days post-immunization. Myelin thickness was unaffected by AM095 treatment.

Conclusions: These findings suggest that interference with LPA1 signaling might constitute a novel therapeutic target for the treatment of inflammatory neuropathies, potentially affecting regenerative responses in the peripheral nerve by modulating Schwann cell differentiation.

Keywords: Schwann cell, experimental autoimmune neuritis, myelination, differentiation, inflammatory neuropathy.

Poster No: 81 | IGHMBP2: Beyond SMARD1 and CMT2S - infantile-onset disease not to miss in children and adults

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Introduction: Biallelic mutations in IGHMBP2 are thought to cause two distinct phenotypes; spinal muscular atrophy with respiratory distress type 1 (SMARD1) and Charcot-Marie-Tooth disease type 2S (CMT2S). SMARD1 is a severe, life-limiting condition characterized by diaphragmatic weakness, respiratory failure within the first six months of life and motor neuropathy. CMT2S by contrast is a childhood onset, slowly progressive axonal, sensory and motor neuropathy, without respiratory compromise or diaphragmatic paralysis. There is, however, a lesser recognized overlap phenotype, a case of which we have previously published. Now 37 years old, our patient asked us: "are there others like me?"

Methods: We conducted a literature review of IGHMBP2-related disease focusing on the overlap SMARD1/CMT2S phenotype; this included all patients with CMT2 with respiratory issues that emerged after six months of age, and either have not required mechanical respiratory support, or such support was delayed several years.

Results: Eleven cases were identified including our patient. Six carried homozygous IGHMBP2 variants with the remainder compound heterozygous. Median age at publication was 10 years (range 3-34 years) and seven (64%) were female. The median age of onset of neuromuscular weakness was 6 months (range 1-19 months). However, the median age of respiratory symptoms onset was five years (range 0.5-15 years). Seven cases eventually required mechanical respiratory support with median age of commencement nine years (range 3.5-15 years).

Conclusions: Although SMARD1 manifests with devastating respiratory symptoms and CMT2S is not generally life-limiting, there are overlap cases with delayed onset respiratory compromise. This is particularly relevant at a time when patients with SMARD1 are being recruited for clinical trials and potentially eligible patients may be missed due to delayed manifestation of respiratory symptoms.

References

1. Pitt M, et al. Severe infantile neuropathy with diaphragmatic weakness and its relationship to SMARD1. Brain. 2003;126:2682-2692.
Cottenie E, et al. Truncating and missense mutations in IGHMBP2 cause Charcot-Marie Tooth disease type 2. Am J Hum Genet. 2014;95:590-601.
3. Tomaselli PJ, et al. IGHMBP2 mutation associated with organ-specific autonomic dysfunction. Neuromuscul Disord. 2018;28: 1012-1015.

Keywords: CMT, IGHMBP2, SMARD1, CMT2S, phenotype.

Poster No: 82 | Delayed diagnosis of POEMS syndrome in the time of Covid-19

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Introduction: POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes), is a rare and often difficult to diagnose multisystem paraneoplastic syndrome seen with plasma cell dyscrasias. Afflicted patients develop subacute demyelinating distal sensorimotor neuropathy, most often seen in the lower limbs, with sensory symptoms preceding motor. Pathophysiology for this syndrome is presently unknown.

Methods: N/A.

Results: A 48-year-old male with history of obesity and new onset diabetes presented to his primary care physician with chief complaint of bilateral lower extremity sensory disturbance. Due to the SARS-CoV-2 pandemic and accompanying restrictions, the patient was evaluated via telehealth. He was diagnosed with diabetic neuropathy and venous stasis. His symptoms progressed over several months. The patient experienced lower extremity weakness and subsequent gait disturbance requiring rolling walker. He eventually presented to the emergency department due to fall and was found to have bilateral severe foot drop with decreased sensation to all modalities in the feet. There was no bowel or bladder involvement. Further questioning revealed that the patient had been found to have organomegaly within the last year and new skin lesions with hyperpigmentation. Magnetic resonance imaging of the spine was performed, which showed a large enhancing lesion in the thoracic region extending into the prevertebral soft tissue and epidural area without spinal cord signal changes. The patient underwent laminectomy and corpectomy of the area; pathology of the specimens showed plasmacytoma. Laboratory testing found elevated VEGF and monoclonal IgG lambda on immunofixation. The patient fulfilled major and minor criteria for POEMS syndrome and therefore this diagnosis was made.

Conclusions: Although significant benefits of telemedicine undoubtedly exist, subtle physical exam findings which may signal critical processes are unable to be noted. POEMS syndrome should be considered in patients with progressive neuropathy and the supporting constellation of symptoms.

References

1. Brown R, Ginsberg L. POEMS syndrome: clinical update. J Neurol. 2019;266(1):268-277. doi:10.1007/s00415-018-9110-6

Keywords: POEMS Syndrome, Covid-19, Telemedicine, Plasmacytoma.

Poster No: 84 | Effects of intravenous immunoglobulins on complement deposition in anti-neurofascin-associated neuropathy

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Introduction: Autoantibodies against isoforms of the (para)nodal protein neurofascin (NF140/155/186) can be detected in 2-10% of patients with inflammatory polyneuropathies. NF-155-seropositive patients with a predominant IgG4 subclass present a severe, motor-predominant phenotype with subacute onset, tremor and poor response to intravenous immunoglobulins (IVIG). In anti-pan-NF-associated neuropathy that was reported to be associated with a fulminant clinical phenotype and IgG3 predominance, treatment response has not been thoroughly investigated. In the present study, we aim to measure complement deposition induced by autoantibody binding and the effects of IVIG.

Methods: Sera of 190 patients with CIDP or GBS were screened for anti-NF autoantibodies and subclasses by binding assays on murine teased fibers and by ELISA. Antibodies were confirmed in seropositive patients by cell-based assay. Complement binding and the effects of different concentrations of IVIG on complement deposition and complement-dependent cell lysis were analyzed via ELISA, cell-based tests and LDH-cytotoxicity assay.

Results: Six patients with autoantibodies against NF-155 and one patient with anti-pan-NF autoantibodies were identified in this study. Two patients with predominance of the IgG4 subclass did not show a complement deposition whereas four patients with predominant IgG1-3 did. Complement binding was associated with the presence of IgG subclass IgG3 > IgG1 > IgG2 > IgG4, corresponding to physiological C1q binding-capacities. IVIG led to a strong reduction of complement deposition in a dose dependent manner. Moreover, we give evidence that patient sera with high amounts of complement deposition show an increased relative cytotoxicity that can be reduced by high-dose IVIG.

Conclusions: We conclude that complement deposition in NF-associated neuropathy is IgG subclass-dependent and IVIG leads to a reduction of complement deposition and its effector functions, such as possible cytolysis of myelinating Schwann cells. The characterization

of autoantibody subclasses as well as IVIG and other options targeting the complement cascade can be considered in the therapeutic regime of severely-affected patients, especially in anti-pan-NF-associated neuropathy.

Keywords: inflammatory neuropathy, autoantibodies to (para)nodal neurfoascin, effects of IVIG, complement deposition associated with IgG subclass, reduction of complement deposition by IVIG.

Poster No: 85 | Outcome measures in CMT: Muscle MRI in CMT study

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Introduction: This study builds on our previous work which demonstrated an increase in muscle fat fraction (FF) at calf level in patients with CMT1A over 12-months.(1,2) We investigate whether muscle FF in the thigh or calf increases over 12-months in patients with the CMT due to mutations in GJB1, MFN2 or MPZ.

Methods: Sixty patients and thirty age and sex matched controls have been recruited from the inherited neuropathy cohorts at the study sites. Baseline and 12-month assessments include MRC scoring, ONLS, CMTESv2, CMT-HI and quantitative neuromuscular MRI of thighs and calves. Dixon FF was calculated at baseline and follow up. Examples are described from each group.

Results: Twelve month follow up is complete in 63/90 participants. A 32-year-old male with CMTX1 due to a GJB1 mutation had baseline CMTES of 9, increasing to 10 at 12 months, all-muscle mid-calf FF increased from 9.5% to 11.8%. Left ankle plantar flexion MRC score dropped from 5 to 4 correlating with correlating left peroneus longus FF rising from 26% to 55%. An 18-year-old male with a MFN2 mutation had a baseline CMTES of 16 and FF at mid-thigh 10.52%. At 12-months CMTES was 17 and FF rose to 14.96%, with no change at calf level due to a ceiling effect. In a 45-year-old male with CMT1B, imaging prior to this study performed at age 35 (CMTES 17), demonstrated FF at calf 20.9%, and at age 45, CMTES was 20 and calf FF 35.6%. Thigh FF increased from 2.4% to 3.81% over the 10-year period. Sciatic nerve enlargement was conspicuous at both time points.

Conclusions: Analysis of the whole cohort data is ongoing, but these three cases show encouraging results suggesting lower limb FF as measured by MRI may be a useful outcome measure in CMT1B, CMT2A and CMT1X.

References

1. Morrow JM, Sinclair JCD, Machado PM, et al. MRI biomarker assessment of neuromuscular disease progression: a prospective observational cohort study. Lancet Neurol. 2016;15(15):65-77.
2. Morrow JM, Evans MRB, Grider T, et al. Validation of MRC Center MRI calf muscle fat fraction protocol as an outcome measure in CMT1A. Neurology 2018;91(12):e1125-e1129.

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Keywords: Charcot Marie Tooth, Intramuscular fat, Fat Fraction Dixon, Outcome measure, Biomarker.

Poster No: 86 | Loss of SARM1 does not protect against axonal degeneration in a late-onset CMT1B mouse model

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Introduction: 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. P0T124M mice fully recapitulate axonopathy observed in patient and allow us to test therapeutic approaches to limit axon loss. One of the most promising "druggable" target to counteract axonal degeneration is SARM1 (sterile alpha and toll/interleukin receptor motif-containing 1).

Methods: By its NADase activity, SARM1 is believed to be the central executioner of the axonal degenerative program. The decrease of NAD+ levels and the increase of plasmatic NF-L in P0T124M mice suggest that SARM1 could be involved in axon loss in CMT2J. To test the role of SARM1 in our model, we crossbred P0T124M mice with SARM1−/− mice. We determined the consequences of SARM1 deletion to axonal damages using electrophysiological measurements, electron microscopy and genetic tools.

Results: The analysis of 12-month-old P0T124M//SARM1−/− mice, shows that SARM1 deletion does not rescue the axonopathy observed in P0T124M mice. As P0T124M mutants, P0T124M//SARM1−/− mice present a reduction of compound motor action potential amplitudes and nerve conduction velocities, as well as reduction of myelinated fibers and an increase of degenerative axons. Finally, using a Thy-YFP reporter line, we identified tips of degenerating axons (axonal swelling and fragmentation) in P0T124M//SARM1−/− nerves.

Conclusions: SARM1 deletion does not confer long-term protection from axonal degeneration in a late-onset CMT1B model. Now, it will

be crucial to determine if SARM1 deletion could represent a valuable therapeutic target to limit axonal loss in early-onset CMT disease.

Grant Support: CMT Association, Telethon.

Keywords: Charcot-Marie-Tooth, Schwann cell, Axonal degeneration, SARM1, Metabolic support.

Poster No: 87 | **Efficacy of inotersen for neuropathic impairment scores in patients with hereditary transthyretin amyloidosis with polyneuropathy**

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Introduction: Hereditary transthyretin amyloidosis (ATTRv) is a rare, systemic, life-threatening disease that often manifests as polyneuropathy (PN). Patients with ATTRv-PN experience substantially faster progression of peripheral neuropathy, as captured by the Neuropathic Impairment Score (NIS), than in other neuropathy-manifesting conditions (eg, diabetic neuropathy, Charcot-Marie-Tooth disease). The impact of inotersen, an antisense oligonucleotide that inhibits production of transthyretin, on the NIS and the subset of items specific to lower limbs (NIS-LL), was examined.

Methods: The NIS/NIS-LL, a clinician-rated measure that captures symptoms and signs of neuropathic progression, was administered to patients in the NEURO-TTR trial of inotersen, a multicenter, multinational, double-blind trial (NCT01737398) of 172 adults with ATTRv-PN. Treatment effects on mean NIS/NIS-LL totals and domains (muscle weakness, reflexes, sensation) after 65 weeks of treatment were tested using mixed-effects models for repeated measures (MMRM) for the full analysis sample, and for subgroups defined by two key clinical characteristics: genetic mutation (V30M or non-V30M) and disability stage (stage 1 [ambulatory without assistance] or stage 2 [ambulatory with assistance]).

Results: At week 65, MMRM showed statistically significant treatment effects supporting inotersen over placebo, with smaller increases (ie, less progression) in mean scores on NIS total (4.9 vs 18.3, $P < 0.0001$), NIS-LL total (2.6 vs 9.6, $P < 0.0001$), and all NIS and NIS-LL domains (all $P < 0.05$). Statistically smaller increases for patients receiving inotersen, relative to placebo, were observed within all patient subgroups for NIS total (range of mean change 3.5-5.9 for inotersen vs 15.5-24.1 for placebo, all $P < 0.002$), NIS muscle weakness (2.9-5.3 vs 9.6-18.2, all $P < 0.005$), and NIS sensation (−0.4-0.6 vs 2.0-4.8, all $P < 0.05$), as well as for NIS-LL total (2.1-3.2 vs 8.6-11.6, all $P < 0.002$) and NIS-LL muscle weakness (1.9-2.7 vs 5.9-10.2, all $P < 0.002$).

Conclusions: Neuropathic impairment progresses rapidly in patients with ATTRv-PN. The current results provide evidence that inotersen slows progression of neuropathic impairment for patients with ATTRv-PN.

Grant Support: This study was funded by Ionis Pharmaceuticals.

Keywords: Hereditary Transthyretin Amyloidosis, Polyneuropathy, Neuropathic progession, Clinical trial, Gene silencing treatment.

Poster No: 88 | **Monocarboxylate transporter 1 (MCT1) overexpression in macrophages accelerates peripheral nerve regeneration after injury in mice**

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Introduction: Peripheral nerves have the capacity for regeneration, but the rate of regeneration is so slow that many nerve injuries lead to incomplete recovery and permanent disability for patients. Nerve injuries can result from trauma, but also occur secondary to autoimmune or toxic insults such as vasculitic and chemotherapy-induced peripheral neuropathy. Macrophages play a critical role in the peripheral nerve response to injury, both for Wallerian degeneration and for contributing to regeneration, and their function has recently been shown to be dependent on intracellular metabolism. To date, the impact of manipulating macrophage metabolism on peripheral nerve regeneration has not been studied.

Methods: Monocarboxylate transporter 1 (MCT1 or SLC16a1) is the predominant lactate transporter in macrophages and alterations of this transporter impact both cellular metabolism and macrophage function. Using conditional transgenic mice, we investigated the impact of down- or up-regulation of MCT1 within macrophages on the regeneration of peripheral nerves following sciatic nerve crush.

Results: We found that downregulation of macrophage MCT1 led to delayed and incomplete peripheral nerve regeneration following nerve crush, as quantified by nerve conduction studies, myelinated nerve counts, and neuromuscular junction (NMJ) reinnervation. The delayed nerve regeneration was completely repaired by tail-vein infusions of wild-type macrophages. We also developed two mouse models that overexpress MCT1 in macrophages and found that peripheral nerves in these mice regenerate more rapidly than control mice, again quantified by nerve conduction studies and NMJ reinnervation.

Conclusions: Our study provides the first evidence that MCT1 is critical for supporting the functions of macrophages in the recovery from peripheral nerve injury. We also show that manipulating MCT1, or perhaps other metabolic targets on macrophages, could be used as a treatment to enhance recovery from peripheral nerve injuries, for with there are currently no approved medical therapies.

Grant Support: NIH R01NS086818.

Keywords: Regeneration, Metabolism, Macrophage, animal model.

Poster No: 89 | **Volumetric MRI; a promising outcome measure of muscle reinnervation**

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Introduction: The development of outcome measures that can track the recovery of reinnervated muscle would benefit the investigation of new therapies which hope to enhance peripheral nerve repair. The primary objective of this study was to assess the validity of volumetric MRI as an outcome measure of muscle reinnervation.

Methods: Over a three-year period 25 patients who underwent nerve transfer to reinnervate elbow flexor muscles were assessed using intramuscular EMG and MRI (median post-operative assessment time of 258 days, ranging from 86 days pre-operatively to 1698 days post-operatively). Muscle power (Medical Research Council [MRC] grade) and Stanmore Percentage of Normal Elbow Assessment (SPONEA) assessment was also recorded for all patients. Sub-analysis of peak volitional force (PVF), muscular fatigue and co-contraction was performed in those patients with MRC > 3. The responsiveness of each parameter was compared using Pearson or Spearman correlation. A Hierarchical Gaussian Process (HGP) was implemented to determine the ability of volumetric MRI measurements to predict the recovery of muscular function.

Results: Reinnervated muscle volume per unit BMI demonstrated good responsiveness ($R^2 = 0.73$, $P < 0.001$). Using the temporal and muscle volume per unit BMI data, a HGP model was able to predict MRC grade and SPONEA with a mean absolute error (MAE) of 0.73 and 1.7 respectively. Muscle volume per unit BMI demonstrated moderate to good positive correlations with patient reported impairments of reinnervated muscle; co-contraction ($R^2 = 0.63$, $P = 0.02$) and muscle fatigue ($R^2 = 0.64$, $P = 0.04$).

Conclusions: The findings reveal that volumetric MRI is a promising outcome measure for muscle reinnervation. This represents a critical step toward clinical trials which hope to identify regenerative therapies which evoke a meaningful clinical response.

Grant Support: This work was funded by the Royal National Orthopedic Hospital Charitable Trust to TQ, England Golf Trust to MW and a UCL Graduate Research Scholarship to MW.

Keywords: muscle reinneration, outcome measure, peripheral nerve injury, nerve regeneration, nerve transfer.

Poster No: 90 | Polyneuropathy characteristics in hATTR V122I patients: A multicenter perspective

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Introduction: HATTR is an autosomal dominant genetic disorder occurring world-wide. There have been over 120 point mutations found in the TTR gene, but the most common mutation occurring in the United States is the V142I variant, occurring in up to 3.5% of African-Americans, with incomplete penetrance. The V142I variant has previously been described as having predominantly cardiomyopathy but our centers have found polyneuropathy (PN) to be commonly present with varying phenotypes. We summarize the experience of 3 centers and provide clinical and electrodiagnostic features of PN in V142I patients.

Methods: This was a retrospective analysis of 21 patients (15 Vanderbilt, 5 Atrium Health, 1 at Thomas Jefferson University). Patients' neurological, autonomic symptoms as well as neurological examination and electrodiagnostic studies were reviewed. Cardiac evaluation and BNP levels are provided where available. Cardiac involvement was diagnosed by either abnormal echocardiogram or PYP scan.

Results: Results: Thirteen men and eight women, African American except two Caucasians, were evaluated. All patients had signs of PN with weakness in 8 patients, abnormal deep tendon reflexes in 10 patients. 12 patients had abnormal vibration, 2 patients had abnormal pinprick sensation and 8 patients reported pain.. 8 patients had GI symptoms and 2 had orthostatic hypotension. 11 patients had carpal tunnel syndrome. Nerve conduction studies were performed in 14 patients and were abnormal in 13/14 studies. Significant conduction velocity slowing was observed in 6 patients with 1 patient meeting ENFS criteria for CIDP. 2 patients had small fiber neuropathy presentation confirmed by skin biopsy. Only 9/21 patients had documented cardiac involvement, and only 2 had significant decreased ejection fractions and abnormal BNP.

Conclusions: Polyneuropathy is more commonly found in V142I patients than previously found and has a wide phenotypic variation of weakness, pain, autonomic involvement and electrodiagnostic features. Genetic testing in patients with African ancestry is important to identify patients with a treatable genetic disorder.

Grant Support: N/A.

Keywords: amyloidosis, V122I mutation, Nerve conduction studies, hATTR.

Poster No: 91 | Targeting the low density lipoprotein receptor related protein for treating pain

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Introduction: Pain in neuropathies is often associated with neuroinflammation and loss of axon integrity. Low-density lipoprotein receptor-related protein-1 (LRP1) is a cell signaling receptor highly involved in anti-inflammatory processes implicated in persistent pain. Moreover, LRP1 regulates Schwann cell-axon communication. Whether LRP1 activation modulates pain states remains unknown.

Methods: A novel peptide, SP16, derived from alpha-1-anti-trypsin, was synthesized based on the known structure-activity of LRP1. SP16 is an established LRP1 agonist that initiates LRP1-dependent sprouting in DRG neurons and has proven safe for healthy adults in Phase I and II Clinical Trials. Male and female C57BL6 mice (8 weeks; n = 5-9/group) were subcutaneously administered vehicle or SP16 (50 μg) one hour prior to stimulus/lesion. Mice were tested in three

paradigms that distinguish inflammatory pain (2.5% formalin), nociceptive pain (capsaicin; 20 μg) and neuropathic pain (partial sciatic nerve ligation; PNL). Acute and chronic pain related behaviors were measured. Cellular and molecular biomarkers of neuroinflammation in the sciatic nerve (GFAP, cd11b) after injury and in microglia cells (NF-B activation and IL1-B levels) were evaluated.

Results: In response to formalin, vehicle-treated male mice demonstrated increased paw licking in phases 1 and 2, as anticipated. However, SP16-treated mice showed significantly reduced responses in phase 1 ($P < 0.01$) and phase 2 ($P < 0.05$). When female and male mice were exposed to capsaicin, SP16, but not vehicle, reduced capsaicin-induced paw licking. Following PNL, SP16 prevented the development of tactile allodynia ($P < 0.05$). In sciatic nerve, cd11b + inflammatory cells ($P < 0.01$) and Toll-like receptor-4 (TLR4) were reduced ($P < 0.05$), whereas GFAP increased ($P < 0.001$) after SP16 treatment. LRP1 agonism significantly activated NF-kB and decreased IL1-B in microglia cells ($P < 0.01$).

Conclusions: SP16 ligand binding to LRP1 inhibits both acute and chronic pain related behaviors in mice. The underlying mechanisms include limiting neuroinflammation. These findings support use of LRP1 agonism as an innovative therapeutic paradigm designed to treat neuropathic pain.

Grant Support: Veteran Administration, 101 RX002484 to W.M.C.

Keywords: Schwann cell, neuropathic pain, neuro inflammation, acute pain, LRP1.

Poster No: 92 | Epidermal SIRT1 modulates mechanical allodynia in diabetic neuropathy

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Introduction: Diabetic neuropathy (DN) is a debilitating disorder characterized by sensory loss and pain. Although common, DN has no effective treatment. A notable pathologic finding of DN is loss of sensory apparatus in the skin, causing sensory abnormalities and pain. Given that diabetic patients frequently develop skin complications, we hypothesize that skin microenvironment is important for the pathogenesis of DN.

Methods: Our investigation focused on a skin molecule epidermal sirtuin 1 (SIRT1), which is an NAD + -dependent deacetylase known to regulate metabolism and senescence. To address the role of epidermal SIRT1 in neuroprotection against DN, we created a tamoxifen-inducible epidermal SIRT1 knockout (KO) and a doxycycline-inducible epidermal SIRT1 overexpression (OE) mouse model. The KO and control mice were placed on high-fat diets (HFDs), and were subsequently assessed by behavioral, morphologic and transcriptome analyses. SIRT1 overexpression was induced in mice after three months of HFDs.

Results: The DN phenotype was greatly exacerbated by depletion of epidermal SIRT1, as mice developed extreme mechanical allodynia after HFD. There was also evidence of large-fiber neuropathy, including loss of Meissner corpuscles, tail sensory nerve conduction defects and degeneration of large-diameter axons, while small nerve fibers and the corresponding nociception were largely intact. The phenotype could not be rescued by treatment with the NAD+ precursor nicotinamide riboside. In comparison, induction of epidermal SIRT1 overexpression alleviated the diabetic mechanical allodynia in mice. One potential mechanism of achieving epidermal SIRT1-mediated neuroprotection is increasing the expression of epidermal brain-derived neurotrophic factor (BDNF), which could preserve the morphologic and functional integrity of Meissner corpuscles.

Conclusions: Our data suggest an important role of epidermal SIRT1 in maintaining skin sensory apparatus and preventing mechanical allodynia in the setting of diabetes. The findings also highlight epidermal SIRT1 as a promising therapeutic target for DN due to easy accessibility of SIRT1 in skin keratinocytes.

Grant Support: NIH NS102468 NIH DK107007.

Keywords: Diabetic neuropathy, Sirtuin, SIRT1, BDNF, Meissner corpuscle.

Poster No: 93 | B2M related hereditary systemic amyloidosis: A case report

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Introduction: Amyloidosis refers to a group of protein misfolding diseases, pathologically characterized by extracellular amyloid fibrils producing amorphous congophilic deposist in several different tissues, with heterogeneous phenotype, depending on which tissues are affected. β2-microglobulin (B2M) is the causing agent of dialysis related amyloidosis (DRA), affecting bones and cartilages of individuals with chronic renal failure undergoing long-term dialysis, and of a hereditary amyloidosis, previously described in a French family. Unlike patients with DRA caused by sustained high plasma concentrations of wild-type B2M, those affected by hereditary amyloidosis related to B2M mutations had severe autonomic dysfunction with normal renal function and β2-microglobulin levels.

Methods: Clinical data were collected from the EMR of a 67-year-old female with hereditary systemic amyloidosis and a positive familiar history for this condition. A review of literature was conducted to identify additional reports and compare data to our results.

Results: We describe a 67 year-old female with slowly progressive gastrointestinal symptoms and peripheral neuropathy, who had onset of symptoms at 59 years and with a positive familiar history for amyloidosis characterized by autosomal dominant pattern of inheritance. The neurophysiological study demonstrated an axonal motor and sensory neuropathy. Serum biochemical measurements were normal,

including creatinine and β2-microglobulin levels. PET-CT did not show hypermetabolic lesions and tilt-test revealed signs of dysautonomia and sustained sinus tachycardia. Amyloid deposits were detected by Congo red staining of sections of formalin-fixed, wax-embedded biopsy specimens from abdominal fat pad and minor salivary gland. No pathogenic variant was identified in TTR gene sequencing. Whole exome sequencing revealed an heterozygous pathogenic variant c.286 G > A p.(Asp96Asn) in B2M gene.

Conclusions: The clinical course of the disease in our patient is in accordance with previously described cases. This report highlights the diagnostic challenge of B2M amyloidosis and the importance of investigating other forms of hereditary amyloidosis in addition to that related to TTR gene.

References

1. Valleix S, Gillmore JD, Bridoux F, et al.
2. Stoppini M, Bellotti V. Systemic amyloidosis: lessons from β2-microglobulin. J Biol Chem. 2015;290(16):9951-8.

Keywords: Hereditary systemic amyloidosis, β2-microglobulin, Inherited neuropathies.

Poster No: 94 | **A cross-sectional study of patients with chronic inflammatory demyelinating polyneuropathy (CIDP): Identifying ultrasonographic features for diagnosis**

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Introduction: Diagnosis and treatment monitoring in CIDP is primarily based on clinical parameters. High-frequency ultrasound of peripheral nerves can reflect pathophysiology and changes with treatment in CIDP in a quick, non-invasive, and painless manner. This project furthered identification of potentially useful diagnostic, prognostic, and treatment-related biomarkers utilizing parameters found on neuromuscular ultrasound.

Methods: We conducted a standardized clinical and ultrasonographic assessment of 50 CIDP patients (25 at Wake Forest Baptist Medical Center, 25 at Austin Health), comparing to 25 healthy controls and 25 axonal neuropathy subjects. Our protocol included bilateral, whole length assessment of the median and ulnar nerves, with unilateral assessment of other nerves.

Results: 25 of 25 CIDP patients studied at WFBMC had an abnormality on ultrasound (as determined by focal nerve enlargement determined by increased cross-sectional area), with 23 of 25 subjects having > = 4 enlarged segments. 23 of 25 Austin CIDP patients had at least one enlarged segment, and 20 of 25 had > = 4 enlarged segments. Of the 48 patients with detectable nerve enlargement, 46 had at least one abnormality in either median or ulnar nerve. Mild nerve enlargements were infrequently seen in healthy and disease controls. However, CIDP patients had clear difference in the extent and pattern of enlargements found, particularly with proximal upper limb nerve enlargements. Specific markers that differentiate CIDP patients will be presented. We analyzed our data in line with previously published diagnostic scores and protocols. We will discuss these findings for typical vs atypical CIDP subtypes, and correlation with clinical findings.

Conclusions: This cross-sectional study of neuromuscular ultrasound in patients with CIDP suggests assessing bilateral median and ulnar nerves from wrist to axilla may be adequate in providing diagnostic information, as well as differentiating potentially treatment responsive immune-mediated neuropathies from axonal neuropathies and healthy controls.

Grant Support: Austin Medical Research Foundation Grant recipient 2018 and 2021 National Blood Authority, via an Immunoglobulin Scholarship Grant under the National Blood Sector Research and Development Program 2020.

Keywords: CIDP, chronic inflammatory demyelinating polyneuropathy, neuromuscular ultrasound, biomarkers, diagnosis.

Poster No: 95 | **AAV mediated gene therapy for CMT4C**

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Introduction: Charcot-Marie-Tooth type 4C (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 and progressive peripheral neuropathy with slowing of motor and sensory nerve conduction velocities and early onset hypomyelination and demyelination. The aim of this proposal is to develop a clinically translatable gene therapy to treat CMT4C.

Methods: A minimal version of the myelin protein zero (Mpz) promoter (miniMpz) was used to drive expression specifically in Schwann cells. We generate a novel AAV9-miniMpz.SH3TC2.myc vector for Schwann cell-targeted expression of human SH3TC2 in order to rescue the phenotype of the Sh3tc2−/− mouse model. We tested this gene therapy approach in the Sh3tc2−/− mouse model of CMT4C at early and late stages of the neuropathy. The vector was delivered into 8 weeks old Sh3tc2−/− mice by lumbar intrathecal injection and gene expression was assessed 4 weeks after injection.

Results: Immunofluorescence analysis showed presence of myc-tagged hSH3TC2 in sciatic nerves and lumbar roots in the perinuclear cytoplasm in a subset of Schwann cells. A treatment trial was initiated in 1-month (early treatment) or 4-month old (late treatment) Sh3tc2−/− littermate mice randomized to receive either the full or mock (AAV9-miniMpz.EGFP) vector. Behavioral analysis 8 weeks and 16 weeks after injection showed improved motor performance in grip strength and rotarod tests in treated Sh3tc2−/− mice compared to mock-treated mice. In addition, motor nerve conduction velocities were increased in treated mice. The morphological analysis revealed significant improvement in g-ratios, myelin thickness and ratios of demyelinated fibers in lumbar roots and sciatic nerves of treated Sh3tc2−/− mice. Furthermore, treated mice also showed improved nodal molecular architecture.

Conclusions: This study provides the proof of principle for clinical translation of CMT4C gene therapy.

Grant Support: CMT ASSOSIATION.

Keywords: Sh3tc2, Charcot- Marie- Tooth, gene therapy, Schwann cells, neuropathy.

Poster No: 96 | Vaccinations and preceding infections: results from the IGOS-1000 cohort

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Introduction: During the previous PNS meeting we presented data of the occurrence of preceding infections in patients with Guillain-Barré syndrome (GBS) included in the International GBS Outcome Study (IGOS). Here, we looked at the occurrence of a recent vaccination in relation to preceding infections in this cohort.

Methods: The first 1000 patients included in IGOS with serum samples available from the first week from study entry were included. Sera were tested for recent infection with *Campylobacter jejuni*, *Mycoplasma pneumoniae*, and hepatitis E virus (HEV), based on IgM, IgA, and/or PCR. Recent cytomegalovirus (CMV) infection was defined as IgM with negative or low avidity IgG, and Epstein-Barr-virus (EBV) infection as VCA IgM and IgG with negative EBNA IgG. History of a recent vaccination was recorded by the treating physician.

Results: Of the 768 included patients serological evidence of a recent infection was found in 315 (41%): *C. jejuni* in 228 (30%), *M. pneumoniae* in 77 (10%), HEV in 22 (3%), CMV in 31 (4%) and EBV in 7 (1%). Two or more infections were found in 49 patients (6%). Antecedent events were reported in 587 (77%) patients. Of the 23 (3%) patients reporting a vaccination, four received combinations of vaccines, and in total 31 vaccines were given. The most common vaccine types included influenza ($n = 12$), tetanus ($n = 4$), and pertussis ($n = 3$). Serological evidence of a recent infection was found in 10 (43%) patients reporting a vaccination. Median time between vaccination and onset of GBS was 16 days (range 7-36 days).

Conclusions: Evidence of a recent infection was found in a high proportion of patients receiving a vaccination in the weeks before the onset of GBS. In light of the ongoing vaccine campaign for SARS-CoV-2 infection, these findings highlight the importance of thoroughly investigating other infectious causes in patients developing GBS in the weeks after receiving a vaccine.

Grant Support: IGOS was financially supported by the GBS-CIDP Foundation International, Gain, Erasmus MC University Medical Center Rotterdam, University of Glasgow, CSL Behring, Grifols, Annexon Biosciences and Hansa Biopharma.

Keywords: Guillain-Barré syndrome, Preceding infections, Vaccine, SARS-CoV-2, International GBS Outcome Study.

Poster No: 97 | IPSC-derived motor neurons recapitulate disease signatures of axonal CMT

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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 obtain and study common hallmarks of axonal degeneration among different CMT2 subtypes.

Methods: We differentiated motor neurons from five CMT2 patient iPSC lines with different causal mutations in the MFN2, NEFL, HSPB1 and HSPB8 genes, along with healthy control iPSC lines. An additional isogenic iPSC control was generated using CRISPR/Cas9 from the MFN2 patient line.

Results: We successfully generated motor neurons from hiPSCs and performed a transcriptome analysis to find common pathways in different CMT2 lines. An additional deep cellular phenotyping was performed, showing a decreased neurite density in all CMT2 patient lines. We demonstrated a progressive decrease in mitochondrial and lysosomal trafficking, along with an abnormal mitochondrial shape in all patient lines. Furthermore, we revealed electrophysiological abnormalities using MEA analysis, such as an altered burst rate in motor neurons derived from patients.

Conclusions: Our findings provide novel insights into the molecular and cellular phenotypes of CMT2 hiPSC-derived motor neurons.

Keywords: Axonal CMT, iPSC-derived motor neurons.

Poster No: 98 | RNAi-based gene therapy improves functional and histopathological outcomes in a CMT1A mouse model

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Introduction: CMT1A is the commonest inherited demyelinating peripheral neuropathy, mainly resulting after PMP22 gene duplication, creating a gene dosage effect that destabilizes myelin sheath structure leading to demyelination and ultimately to secondary axonal loss and disability. Despite the early characterization of CMT1A, none of the published therapeutic approaches has provided effective treatment to improve the disease phenotype.

Methods: Our goal is to develop a clinically translatable gene therapy approach to reduce PMP22 mRNA levels in order to treat CMT1A. Hence, we designed a cassette expressing a novel artificial microRNA designed to target mouse and human PMP22. We then packaged this construct into an AAV9 viral vector and intrathecally delivered it into C61-Het mice, a model of CMT1A overexpressing human PMP22.

Results: Immunohistochemistry, western blot and VGCN analysis showed that our AAV9-miR vector transduced on average 50% of all PNS cells. Protein and mRNA analysis on C61-Het PNS tissues confirmed that this miR decreased PMP22 levels specifically while increasing the expression of other myelin-related genes. We treated two cohorts of animals at early or late disease stages and observed significant improvements in several phenotypes. C61-Het mice treated at the early time point were indistinguishable from wild-type animals in behavioral assays, nerve conduction velocities and histopathology. Specifically for the latter, lumbar roots and femoral motor nerves showed significantly decreased numbers of thinly myelinated and demyelinated fibers and onion bulb formations. The late-treated group also reached the levels of wild-type controls in behavior assays, and showed significant, but not complete, improvement in nerve conduction velocities. The number of demyelinated fibers and onion bulb formations were significantly decreased while the number of thinly myelinated fibers remained unchanged.

Conclusions: Taken together, our AAV9-miR driven silencing of human PMP22 improves the phenotype of a CMT1A model providing a proof of principle for a promising and translatable approach to treat CMT1A.

Grant Support: CMT Research Foundation.

Keywords: Gene Therapy, Charcot Marie Tooth, AAV, microRNA, Schwann cell.

Poster No: 99 | EAN/PNS guideline on the diagnosis and treatment of Guillain-Barré syndrome (GBS)

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Introduction: Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy. Symptoms may vary greatly in presentation and severity, and the diagnosis may be difficult. Besides weakness and sensory disturbances, patients may have severe pain and fatigue. Intravenous immunoglobulin (IVIg) and plasma exchange (PE) are proven effective treatments. There is currently no systematic consensus guideline available for the diagnosis and treatment of GBS.

Methods: A Task Force of the European Academy of Neurology (EAN) and the Peripheral Nerve Society (PNS), consisting of a multinational group (12 countries) of 21 experts, including a patient representative and two methodologists, started in 2018 to develop this GBS Guideline. We defined 14 PICO questions (Patients, Intervention, Comparison, Outcomes). If appropriate, we used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method of assessing the certainty of evidence, and the strength of recommendations using the Evidence to Decision (EtD) framework. The Task Force received unrestricted grants from the EAN, PNS, GBS/CIDP Foundation International, and the UK GAIN Charity to develop and write the Guideline.

Results: We conducted a systematic search and reached consensus for the six diagnostic PICO's: antecedent events, prediction of acute onset CIDP, CSF examination, antibodies, electrodiagnosis, ultrasound and MRI; and for the PICO on prognosis. For the seven intervention PICO's: IVIg, plasma exchange, corticosteroids, other treatments, need for ICU admission, pain, and fatigue we used the GRADE methodology. To facilitate the use of the GBS Guideline, we constructed three flowcharts: for diagnosis, the treatment, and for assessing the need for ICU admission. The Task Force is currently writing the Guideline.

Conclusions: We expect that the EAN/PNS Guideline on the diagnosis and treatment of GBS will be completed and available at the PNS 2021 Meeting.

Keywords: GBS, Clinical Trials.

Poster No: 100 | Exploring the impact of balance impairments and falls in people with CMT

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Introduction: People with Charcot-Marie-Tooth disease (CMT) develop slow, progressive neuropathy manifesting with distal

weakness and sensory loss. Balance confidence in people with CMT1A is reduced, though more exploration is needed to understand how this influences everyday activities, physical and psychological well-being. This qualitative work aims to gain further insight into the experience of living with balance impairments in people with CMT1A, with the view to increasing understanding of how people manage instability and avoid falls.

Methods: Participants enrolled on to a balance training intervention (BALTiC) study were invited to attend semi-structured interviews. Interviews took place prior to randomization. Questions focussed on diagnosis, symptoms, the impact of balance impairments on daily life, wellbeing, experience of rehabilitation and expectations of study participation. Interviews were transcribed and coded using thematic analysis.

Results: 13 of 15 participants recruited for the BALTiC intervention study agreed to take part. Themes included (1) Living with CMT; (2) Emotional Issues related to balance; (3) Physical Issues; (4) Strategies used to avoid falls. The patient journey was explored including diagnosis, negative and positive experiences related to their CMT and previous experiences of rehabilitation. Although some participants felt they had no solutions to improve their balance, others had clear strategies which they used. The idea of balance rehabilitation was positively received. Participants had a wealth of experiences to explore in the interviews and welcomed the opportunity to express them in the interviews.

Conclusions: The ability to cope with the changing nature of the condition is important. People with CMT adapt and identify strategies which work for them, though some feel more able to do this than others. Clinicians can use this information when supporting patients to self-manage their condition and subsequently reduce the impact of balance impairments and falls in this population.

Grant Support: This work is part of a PhD funded by Kingston University and St Georges, University of London.

Keywords: Charcot-Marie-Tooth Disease, Balance, Rehabilitation, Physical Therapy, Self-management.

Poster No: 101 | Sensory neuronopathy associated anti-FGFR3 antibodies induce neuronal cell death through MAP kinase and autophagy pathways

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Introduction: Antibodies recognizing the intracellular domain (TRK) of FGFR3 identify a subgroup of patients with sensory neuronopathies.

Methods: To test the hypothesis that anti-FGFR3 antibodies have a pathogenic role we submitted mice cortical neurons to different concentrations of a rabbit polyclonal antibody recognizing the FGFR3 intracellular domain. The antibody induced a dose dependent cell death. The main downstream pathway associated with FGFR signaling is the RAS/MAP kinase pathway. In order to decipher the molecular mechanism involved in neuronal death induced by FGFR3 antibodies, cultures were submitted to the rabbit antibody with and without p38 MAPK or ERK1/2 MAPK inhibitors. The expression of FGFR3, NR1, NR2A, NR2B subunit of NMDA receptor and GLUR1, GLUR2 subunit of AMPAR was analyzed by RT-qPCR.

Results: The rabbit antibody increased FGFR3, and NMDAR and AMPAR subunits mRNA expression which was prevented by ERK1/2 or P38 MAPK inhibitors. Treatment of neurons culture with Dovinitib, a FGFR3 kinase inhibitor, showed the same expression profile. These results suggest that cytotoxicity induced by the rabbit antibody increases NMDAR and AMPAR expression through a blocking of FGFR3 tyrosine kinase site and RAS/MAP kinase pathway activation and was compensated by an over expression of FGFR3. Autophagy induced by antibody internalization may be an alternative way of antibody cytotoxicity. We found that the rabbit anti-FGFR3 antibody induced an over expression of optineurin and p62 mRNA which was prevented by ERK1/2 or P38 MAPK inhibitors suggesting that autophagy activation through anti-FGFR3 antibody fixation may also play a role in neuron degeneration. Finally we submitted neuron cell cultures to four sera of patients with anti-FGFR3 antibodies and four normal controls and found a similar expression profile of FGFR3, NMDAR subunits and autophagy markers mRNA.

Conclusions: These preliminary results suggest that anti-FGFR3 antibody by activating exito-cytotoxicity and autophagy may play a role in the patient's sensory neuronopathy.

References

1. Antoine JC, Boutahar N, Lassablière F, et al. Antifibroblast growth factor receptor 3 antibodies identify a subgroup of patients with sensory neuropathy. J Neurol Neurosurg Psychiatry. 2015.

Grant Support: SFNP 2019 Grant (by CSL BEHRING).

Keywords: Sensory Neuronopathies, Anti-FGFR3 antibody, MAP-Kinase pathway, Autophagy, Biomarker.

Poster No: 102 | Does baseline BMI influence disability changes in pediatric Charcot-Marie-Tooth disease?

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Introduction: Unhealthy BMI is associated with greater disability at baseline in children with CMT. The aim of this study was to evaluate if baseline BMI influences disability progression in pediatric CMT.

Methods: 242 participants aged 3-20 years enrolled in the Inherited Neuropathies Consortium (INC) were assessed at baseline and two-years with the 0-44 point CMT Pediatric Scale (CMTPedS)[1]. BMI was classified using the International Obesity Task Force(IOTF) criteria as: severely-underweight (BMI < 17 kg/m2), underweight

(BMI≥17 kg/m2 to <18.5 kg/m2), healthy-weight (BMI≥18.5 kg/m2 to <25 kg/m2), overweight (BMI≥25 kg/m2to <30 kg/m2); obese (BMI≥30 kg/m2).

Results: Participants were stratified into those whose BMI remained in the same IOTF grouping (BMI stable n = 168), and those whose BMI group changed (BMI change n = 74), over a two-year period. BMI stable participants, who were severely-underweight at baseline, had a mean CMTPedS change of 26.4% across two-years (24.2 (±6.1) to 30.6 (±6.5) ($P < 0.05$) compared to a 13.7% change in those healthy-weight at baseline (14.9 (±9.1) to 17.0 (±9.5) ($P < 0.001$)). All other weight categories CMTPedS scores progressed between 7.2-13.8%. At two year follow up, both severely-underweight ($P < 0.05$) and obese ($P < 0.05$) participants were significantly more disabled than healthy-weight. ANCOVA showed a significant effect overall of BMI groups on CMTPedS scores at two years after controlling for baseline CMTPedS scores ($P < 0.05$). Post-hoc analysis showed a significant difference for progression between severely-underweight and underweight participants. In BMI change participants, those who moved from healthy-weight at baseline toward overweight/obese at 2 years had 22% increase ($P < 0.05$) on CMTPedS compared with a 13.7% change in those who remained in the healthy-weight group.

Conclusions: Disability in severely-underweight children progress faster than in healthy or overweight children. Independent of baseline disease severity BMI (severely-underweight or obese) is associated with greater disability at two-years. Maintaining BMI in the healthy range may decrease disability progression, and BMI should be considered an independent variable in pediatric CMT clinical trials.

References

Burns J, Ouvrier R, Estilow T, et al. Validation of the Charcot-Marie-Tooth disease pediatric scale as an outcome measure of disability. Ann Neurol. 2012;71(5):642-652.

Keywords: Neuropathy, Pediatrics, Outcome Measures, CMT, BMI.

Poster No: 103 | Mortality following Guillain-Barré syndrome: A 30-year nationwide cohort study

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Introduction: Intermediate and long-term mortality following Guillain-Barré syndrome (GBS) has been sparsely studied. We hypothesized that there is an increased mortality for up to 4 years after hospital discharge with GBS. We aimed to determine the association between GBS and short-term, intermediate and long-term all-cause mortality.

Methods: Individual-level data from nationwide medical registries were linked in this nationwide population-based matched cohort study comparing patients with first-time hospitalization for GBS from 1987 to 2016 and a 1:10 age, sex and date of GBS hospital admission matched reference population from the general population. Within three time periods; short-term (0-6 months), intermediate (7 months - 4 years) and long-term (> 4 years), we estimated cumulative mortality. Cox regression analysis was used to compute adjusted hazard ratios (HRs).

Results: We identified 2414 patients with GBS (median age 52) and 23 909 age-matched individuals from the general population. The 6 months short-term mortality was 4.8% (95% CI, 4.0-5.8) for GBS patients and 0.78% (95% CI, 0.7-0.9) for the reference population. The corresponding adjusted HR was 6.2 (95% CI, 4.8-8.1), with the strongest association observed for females (HR, 11.1; 95% CI, 7.2-17.2). Intermediate mortality up to 4 years after GBS was 7.6% (95% CI, 6.5-8.9) compared with 5.8% (95% CI, 5.5-6.1) for the reference population, corresponding to adjusted HR of 1.3 (95% CI, 1.1-1.6). Long-term mortality (maximum follow-up: 30 years) showed similar mortality rates for GBS patients and the reference population (51.8%; 95% CI, 45.1-59.5 and 57.2%; 95% CI, 52.0-62.8, respectively), adjusted HR = 1.0 (95% CI, 0.9-1.1).

Conclusions: GBS hospital admission was associated with a highly increased all-cause mortality during the first 6 months after the GBS admission date, and a 30% increased all-cause mortality for up to 4 years after, compared to the general population.

Grant Support: This work received funding from Bevica Foundation, teacher Svend Aage Nielsen Wacherhausens Foundation, Aase and Ejnar Danielsen Foundation and A.P. Møller Foundation.

Keywords: Guillain-Barré syndrome, Inflammatory neuropathy, Epidemiology.

Poster No: 104 | Neurofascin-155 CIDP patients: Clinical, immunological and biomarker features

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Introduction: Our objective is to study the clinical and biomarker features of anti-neurofascin-155 (NF155) positive chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Methods: Patients with anti-NF155 antibodies detected on routine immunological testing were included. Clinical characteristics, treatment response and functional scales (mRS and I-RODS) were retrospectively collected at baseline and at follow-up. Autoantibody and neurofilament light (NfL) chain levels were analyzed at baseline and at follow-up.

Results: Forty NF155+ CIDP patients were included. Mean onset age was 42.4 years. Patients presented with a progressive (75%), sensorimotor (87.5%), and symmetric distal-predominant weakness in upper (97.2%) and lower extremities (94.5%), with tremor and ataxia (75%). HLA-DRB1*15 was detected in 91.3% of patients. Patients received 3 [2-4] different treatments in 46 months of median follow-up. Response to IV immunoglobulin (86.8%) or steroids (72.2%) was poor in most patients, while 77.3% responded to rituximab. IgG4 antibodies were predominant in all patients and anti-NF155 titers correlated with mRS within the same patient ($r = 0.48$, $P = 0.007$). sNfL levels were higher in anti-NF155+ CIDP than in healthy controls (36.47 pg/mL vs 7.56 pg/mL, $P < 0.001$) and correlated with anti-NF155 titers ($r = 0.43$, $P = 0.001$), with I-RODS at baseline ($r = -0.88$, $P < 0.001$) and with maximum I-RODS achieved ($r = -0.58$, $P = 0.01$). Anti-NF155 titers and sNfL levels decreased in all rituximab-treated patients.

Conclusions: Anti-NF155 CIDP presents a distinct clinical and treatment-response profile. Rituximab is effective in treatment-resistant anti-NF155+ CIDP. Autoantibody titers and sNfL are useful to monitor disease status in these patients.

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Keywords: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), neurofascin-155 (NF155), neurofilament light chain (NfL), NF155 antibody titers.

Poster No: 105 | Cancer and the risk of Guillain-Barré syndrome: A 30-year nationwide population-based case-control study

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Introduction: Cancer may increase risk of developing Guillain-Barré syndrome (GBS) due to mechanisms resembling molecular mimicry or by immunosuppression, but the exact relationship is unclear. We aimed to determine the association between incident cancer and the following risk of GBS development.

Methods: We conducted a nationwide population-based case-control study of all patients with first-time hospital-diagnosed GBS in Denmark between 1987 and 2016 and 10 age-, sex- and index date-matched population controls per case. We identified diagnoses of incident cancers by discharge codes within the period from six months prior to - until two months after the GBS index date. To assess the burden of the preceding ten years of comorbidity the Charlson Comorbidity Index (CCI) score was determined. CCI-adjusted analyses were performed to assess potentially increased comorbidity in cancer patients as a potential confounder.

Results: Of the 2414 GBS cases and 23 909 controls included, 49 cases (2.0%) and 138 controls (0.6%) had a cancer diagnosis, respectively, with a matched odds ratio (mOR) of 3.6; 95% confidence interval (CI), 2.6-5.1. Subanalyses showed highest mOR for cancers of the respiratory tract (mOR, 5.6; 95% CI, 2.7-11.9), breast (mOR, 5.0; 95% CI, 1.7-14.5), lymphatic and hematopoietic tissue (mOR, 7.2; 95% CI, 2.9-18.0), and prostate and other male genital organ cancers (mOR, 5.6; 95% CI, 2.7-11.9). Following adjustment for CCI-score the overall association remained unchanged (mOR, 3.6; 95% CI, 2.6-5.0).

Conclusions: In this large nationwide epidemiologic study, incident cancer was associated with a markedly increased risk of GBS occurrence. Several organ-specific cancers contributed to this association, suggesting shared triggering mechanisms.

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Keywords: Guillain-Barré syndrome, Inflammatory neuropathy, Epidemiology.

Poster No: 106 | An ambispective cohort study of chronic inflammatory demyelinating neuropathy, and its variants

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Introduction: The clinical presentation, findings, and outcome may vary between typical chronic inflammatory demyelinating polyradiculopathy (CIDP) and its variants.

Methods: Objective: To compare clinical profile and outcome of typical CIDP and its variants. Setting: Tertiary care referral hospital. Materials and Methods: The CIDP patients diagnosed as per EFNS/PNS criteria were included. Hospital records were assessed to note retrospective data of patients included. Prospective patients were subjected to detailed history and examinations. The clinical disability was assessed using ODSS, NIS, IRODS, SCOPA AUT scales. Based on presentation and investigations for underlying diseases, the patients were categorized into typical CIDP and its variants. Treatment prescribed was noted and outcome was assessed at 3 months. The study is ongoing and intends to recruit 100 patients.

Results: A total of 34 patients have been included till now, ranging from age 20 to 76. 10 (29.4%) had atypical CIDP and its variants, POEMS being the commonest variant (7), followed by MADSAM (2) and diabetic amyotrophy (1). Age and sex distribution was similar in both groups, however atypical CIDP and its variants had worse scores on ODSS, NIS, IRODS and SCOPA scales, had more relapses (30% vs 0%) and required polytherapy (90% vs 62.5%) compared to typical CIDP. The study intends to assess treatment response in both groups after 3 months.

Conclusions: Of the total patients with CIDP, 29.4% of patients had atypical CIDP and its variants, which was associated with more severe presentation, more relapses and less response to treatment, requiring the use of polytherapy.

Keywords: CIDP, atypical, secondary, treatment.

Poster No: 107 | Hereditary transthyretin amyloidosis: Description of a Swiss cohort

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Introduction: Hereditary transthyretin amyloidosis (hATTR) is a rare, autosomal dominant genetic disease with tissular aggregation of amyloid deposits. hATTR patients develop neuropathic, cardiac and dysautonomic symptoms. No epidemiological data are available for this population in Switzerland. Our objective was to describe the clinical phenotype of hATTR patients followed by our nerve-muscle unit, and to create a database for further studies.

Methods: We included all hATTR patients and asymptomatic carriers followed since 2012. We retrospectively analyzed demographic, clinical (including functional and walking disability scores) and nerve conduction studies data from the first neurological manifestation (or positive genetic testing date) and during follow-up. We performed a descriptive statistical analysis using simple linear regression with mixed effects. The local ethic committee approved the study protocol.

Results: We analyzed data from 127 follow-up visits of 28 patients, belonging to 22 families. Most patients (21/28, 75%) were symptomatic and 7 (25%) were asymptomatic carriers. Patients were mainly of Portuguese ancestry with pVal50Met mutation being the most frequent (86%). The majority of patients presented with a classic, small fiber length-dependent early-onset neuropathy; 3 (11%) had a late onset, with the first manifestation after 50 years of age. The majority (75%) of our patients was at an early stage of the disease (PND I = 46%). Repeated clinical scores confirmed progressive worsening of the disease. Surprisingly, patients receiving any anti-amyloid treatment (n = 7 Tafamidis, 3 patisiran, 8 liver transplant) had a faster disease progression. Cardiac, ophthalmic and renal complications occurred respectively in 43%, 14% and 11% of symptomatic patients.

Conclusions: This study is the first describing hATTR patients in Switzerland. All analyzed parameters worsened progressively during follow-up which is consistent with the descriptions available in literature. The systematic recording of multiple variables in an organized database will allow us to optimize our clinical practice and research. Furthermore, our database could be proposed as a model for a national hATTR registry.

Grant Support:

Keywords: Hereditary transthyretin amyloidosis, pVal50Met mutation, Amyloid neuropathy.

Poster No: 108 | Myelinated, human stem cell-derived sensory neurons for screening for the presence of peripheral nerve-reactive autoantibodies in patient sera

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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. Current methods for high-throughput testing, such as ELISA and a cell-based assays (CBA), assess reactivity to pre-specified targets. 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 1 were seeded onto 96 well microplates, and myelinated using rat Schwann cells. Specific labeling of serum IgG in co-cultures was validated in a cohort of suspected immune-mediated neuropathy patients previously confirmed as nodal/paranodal antibody positive or negative by targeted ELISA or CBA. Autoantibody reactivity was assessed by an observer blinded to the clinical phenotype and previous serological results.

Results: Co-cultures contained unmyelinated axons, myelinated internodes, and nodes of Ranvier. Overall, 62% (41/66) of nodal/paranodal seropositive samples demonstrated IgG reactivity. Specific patterns of labeling for axons, nodes of Ranvier or Schwann cell abaxonal

membranes were typical of samples seropositive for CNTN1/Caspr1, pan-neurofascin and NF155, respectively. 15% (9/60) of nodal/paranodal seronegative samples from neuropathy patients were also scored positive in the co-cultures, suggesting the presence of autoantibodies against unknown targets.

Conclusions: The use of live cell cultures that mimic the native molecular composition of peripheral nerves permits the detection of peripheral nerve reactive antibodies in neuropathy patients who are seronegative on routine diagnostic tests. This method has the potential to underpin novel autoantibody discovery. The clinical implications of these antibodies will be explored in future work.

References

1. Chambers SM, Qi Y, Mica Y, et al. Combined small-molecule inhibition accelerates developmental timing and converts human pluripotent stem cells into nociceptors. Nat Biotechnol. 2012;30:715-20.

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Keywords: Nodal/Paranodal, Inflammatory neuropathy, Autoantibodies, Stem cell-derived neurons.

Poster No: 109 | Neonatal FcReceptor therapy is not an effective target in an animal model of CIDP

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Introduction: Neonatal Fc Receptors (FcRn) are part of a recycling system increasing the turnover of IgG antibodies and extending IgG half-life in the circulation. In autoimmune disorders FcRn may represent a potential target to reduce the amount of disease-causing IgG autoantibodies. We investigated the therapeutic potential of an antibody targeting FcRn in the ICAM1-deficient NOD mouse, a model of chronic inflammatory neuropathy recapitulating the heterogenous treatment respond to IVIg as observed in patients.

Methods: ICAM1-deficient NOD mice were treated after onset of clinical signs of neuropathy twice a week with anti-FcRn antibody. Disease progression was compared to neuropathy mice treated with control IgG as negative control and with IVIg as positive control. Disease severity was monitored over a treatment period of 9 weeks and included grip strength measurements, a neuropathy specific disease score and assessment of ataxia and paresis score.

Results: In anti-FcRn antibody treated mice significantly lower IgG levels were detectable compared to controls. However, in contrast to IVIg receiving animals the treatment with anti-FcRn antibody did not reduce disease progression measured by clinical score and grip strength analysis. In line with that, infiltrating immune cell composition was not altered in the peripheral nerve of anti-FcRn antibody treated mice compared to controls.

Conclusions: These findings suggest that reduction of IgG levels by targeting the FcRn recycling system does not mitigate peripheral nerve inflammation in the chronic inflammatory neuropathies model of ICAM1-deficient NOD mice. These finding are contradicting convincing human clinical results and further ongoing studies will elucidate, if the IgG levels reduction is not strong enough to deplete detrimental autoantibodies or discrepancy is caused by the differing role of IgG levels and B cells in mouse and human chronic inflammatory neuropathy.

Grant Support:

Keywords: CIDP, IVIg, immune mediated neuropathy, neonatal Fc Receptor, ICAM-deficient NOD mouse.

Poster No: 110 | Late-onset peripheral neuropathy in the Labrador Retriever is a life-limiting disease that negatively impacts quality of life

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Introduction: Late-onset peripheral neuropathy (LPN) is an idiopathic disease of older dogs that has a genetic basis in the Labrador Retriever. LPN is a promising spontaneous large animal model for human peripheral neuropathy. Clinical signs of LPN include upper respiratory obstruction due to laryngeal paralysis and hindlimb weakness. LPN often leads to aspiration pneumonia, decrease in quality of life (QoL), asphyxiation, and death or euthanasia. Surgical intervention to increase glottic area is the only established treatment for LPN.

Methods: The negative effect of LPN on QoL in Labradors has never been quantified. It is unclear how patient specific factors and surgical intervention influence QoL or risk of death. The objectives of this study were to determine: 1) owner's perception of LPN's effects on their dog's QoL and cause of death; 2) whether glottic surgery influenced QoL, age of death or perceived cause of death; 3) whether sex, weight or coat color correlated with QoL, age of death or disease progression. Seventy-six owners of Labradors affected by LPN completed a validated QoL questionnaire. For each dog, sex, weight, coat color, whether surgery was performed, age of death and cause of death were recorded.

Results: Ninety-four percent of owners felt their dog's LPN affected QoL, and 47% of owners felt LPN was a primary cause of their dog's death. Dogs that underwent surgery to open the glottis were reported to have a better QoL, and the contribution of LPN toward death was less than dogs that did not have surgery. Increased weight negatively correlated with age of death, while sex and coat color were not influential factors.

Conclusions: LPN is a life-limiting disease that negatively impacts dog's QoL. Glottic surgery has a positive impact on QoL. Weight loss should be recommended for management of affected dogs.

Grant Support: NIH K01 OD019743/OD/NIH NIH T32 OD10999/NH/NIH.

Keywords: Quality of Life, Canine Model, Inherited Peripheral Neuropathy.

Poster No: 111 | **Phase 2 Proof-of-concept trial design for BIVV020, a monoclonal antibody targeting complement C1s, in CIDP**

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Introduction: Autoreactive antibodies and complement activation may play a key role in demyelination and axonal damage in chronic inflammatory demyelinating polyneuropathy (CIDP). BIVV020 is a humanized mAb that targets active C1s within the classical complement pathway, leaving the alternative and lectin pathways functionally intact for host defense.

Methods: This global multicenter, Phase 2, open-label study will evaluate the efficacy, safety, and tolerability of BIVV020 in 90 participants with CIDP across three subpopulations: (1) successfully treated with the standard of care therapies (SOC), immunoglobulin or corticosteroids; (2) refractory to SOC; and (3) naïve to SOC. Study participants will undergo an initial 24-week treatment period (Part A), followed by an optional extension period providing up to 52 additional weeks of treatment (Part B).

Results: In Part A, the primary endpoint for the SOC-Treated group is % participants with a relapse, defined as ≥1-point increase in adjusted INCAT score from Day 1 up to Week 24, after switching from SOC to BIVV020. The primary endpoint for the SOC-Refractory and SOC-Naïve groups is % participants with a response, defined as ≥1-point reduction in adjusted INCAT score from Day 1 up to Week 24, during the BIVV020 treatment period. Secondary endpoints include safety and efficacy during the period of overlap between SOC and BIVV020. Exploratory endpoints include additional efficacy assessments (I-RODS, MRC sum score, grip strength) and PK/PD. Part B will examine long-term safety and efficacy. Data analysis will use Bayesian statistics with predefined efficacy criteria and placebo assumptions based on historical data. Each subpopulation will be assessed separately. Results from this study will establish proof-of-concept and inform future Phase 3 trial design.

Conclusions: This innovative trial design based on subgroups and Bayesian statistics provides an efficient option to evaluate new candidate treatments across the CIDP spectrum and can help accelerate the development of new therapies for this condition. ClinicalTrials.gov Identifier: NCT04658472.

Keywords: CIDP, BIVV020, Clinical trial design, Complement system.

Poster No: 112 | **Risk of relapse after COVID-19 vaccination in patients with chronic inflammatory neuropathies and safety and tolerability of the COVID-19 vaccines**

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Introduction: An important concern in the relationship between vaccines and inflammatory neuropathies is the putative risk of relapse following vaccination in patients with a chronic active immune disease. Only two retrospective studies including a small number of patients have investigated this issue in CIDP, while no studies focused on MMN. Information is also missing on the safety of vaccines in patients with inflammatory neuropathies under treatment with immune modulating or immune suppressive agents. The lack of evidence on the safety of vaccination in patients with inflammatory neuropathies might explain why vaccination coverage is slow in these patients.

Methods: Since December 2019 a pandemic illness (Coronavirus disease 2019, COVID-19) has spread to millions of persons worldwide. In response, a vaccination campaign is underway. We are performing a prospective, observational study, to evaluate the risk of relapse after COVID-19 vaccination in patients with CIDP and MMN. We will compare the frequency of relapse in patients undergoing vaccination to that observed in patients not receiving the vaccine. We will also evaluate the safety and tolerability of COVID-19 vaccination in CIDP and MMN patients with or without immune modulating or immune suppressive therapy. Participation in the study will be proposed to all the patients in disease remission included in the Italian CIDP database and the Italian MMN database and will be extended to CIDP and MMN patients not included in the databases.

Results: The study period will last 15 months and we expect to include at least 300 patients. Objective assessments will be performed before vaccination and after three months using the INCAT disability scale, the Medical Research Council (MRC) sum score, the Rasch-Overall Disability Scale, and a fatigue scale. Safety and tolerability of vaccination will be evaluated using a specific questionnaire.

Conclusions: This study will clarify safety of COVID-19 vaccination in chronic inflammatory neuropathies.

Keywords: CIDP, MMN, COVID-19, vaccine, Inflammatory neuropathies.

Poster No: 113 | Plasma MicroRNAs as candidate biomarkers for CMT1A

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Introduction: The goal of this study was to determine if microRNA's (miR) are elevated in the plasma of individuals affected by the inherited peripheral neuropathy Charcot-Marie-Tooth Disease, type 1A (CMT1A).

Methods: We undertook a screen of CMT1A and control plasma samples to identify microRNAs that are elevated in CMT1A using a pilot screen of plasma miR by next generation sequencing, followed by validation of selected miRs by quantitative PCR, and correlation with clinical data and protein biomarkers. After an initial pilot screen, a broader screen confirmed elevated levels of several muscle-associated miRNAs (known as myomiRs) along with a set of microRNAs (miRs) that are highly expressed in Schwann cells of peripheral nerve.

Results: Comparison to other candidate biomarkers for CMT1A (eg, Neurofilament L, NfL) measured on the same sample set shows a comparable elevation of several microRNAs, which have the ability to discriminate cases from controls. In addition, the putative Schwann cell miRs correlate with a recently described TMPRSS5 biomarker that is also elevated in CMT1A plasma, and this protein is most highly expressed in Schwann cells.

Conclusions: These studies identify a set of miRs that are candidate biomarkers for clinical trials in CMT1A. 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.

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Keywords: microRNA, biomarkers, Schwann, muscle, CMT.

Poster No: 114 | European academy of neurology (EAN)/ peripheral nerve society (PNS) guideline on diagnosis and treatment of CIDP

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Introduction: The objective is to revise the 2010 guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Methods: A Task Force (TF) of 20 experts from 11 countries worldwide, including a patient representative and two methodologists constructed 12 PICO (Population/Intervention/Comparison/Outcome) questions. Data were summarized in GRADE (Grading of Recommendations Assessment, Development and Evaluation) evidence profiles (treatment) or evidence tables (diagnosis). Statements were prepared according to Evidence-to-Decision (EtD) frameworks. The TF received unrestricted grants from the EAN, PNS, GBS/CIDP Foundation International, and the UK GAIN Charity.

Results: The TF distinguished typical CIDP and CIDP variants. The previously used term "atypical CIDP" was replaced by 'CIDP variants'. These variants, multifocal, focal, distal, motor, or sensory CIDP, are well characterized entities with specific clinical and electrodiagnostic phenotypes. Because there is insufficient distinction between criteria

for probable and definite CIDP without a gold standard for CIDP diagnosis, the TF reduced the levels of diagnostic certainty from three (definite, probable, possible CIDP) to only two: CIDP and possible CIDP. The TF agreed on Good Practice Points (GPP) to define clinical, electrodiagnostic, and supportive criteria and investigations to diagnose CIDP. The principal treatment recommendations are: (a) either IVIg or corticosteroids are strongly recommended in typical CIDP and CIDP variants; (b) if IVIg and corticosteroids are ineffective, plasma exchange is strongly recommended; (c) IVIg should be considered as the first-line treatment in motor CIDP (GPP); (d) no preference for either IVIg or SCIg for maintenance treatment is recommended; (e) if the response is inadequate or the maintenance dose of these treatments is high, consider either combination treatments or adding an immunosuppressant or immunomodulatory drug (GPP).

Conclusions: The second revision of the EAN/PNS Guideline on the diagnosis and treatment of CIDP has been completed and will be available at the PNS 2021 meeting.

Grant Support: unrestricted grants from the EAN, the PNS, GBS/CIDP Foundation International, UK GAIN Charity.

Keywords: chronic inflammatory polyradiculoneuropathy, diagnosis, treatment, guidelines, GRADE.

Poster No: 115 | Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome

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Introduction: Reports of Guillain-Barré syndrome (GBS) have emerged during the Coronavirus disease 2019 (COVID-19) pandemic. This epidemiological and cohort study sought to investigate any causative association between COVID-19 infection and GBS.

Methods: The epidemiology of GBS cases reported to the UK National Immunoglobulin Database was studied from 2016 to 2019 and compared to cases reported during the pandemic. Data were stratified by hospital trust and region, with numbers of reported cases per month. UK population data for COVID-19 infection were collated from UK public health bodies. In parallel, but separately, members of the British Peripheral Nerve Society prospectively reported incident cases of GBS during the pandemic at their hospitals to a central register. The clinical features, investigation findings and outcomes of COVID-19 (definite or probable) and non-COVID-19 associated GBS cases in his cohort were compared.

Results: The incidence of GBS treated from 2016 to 2019 was 1.65-1.88 per 100 000 individuals per year. In 2020, GBS and COVID-19 incidences varied between regions and did not correlate ($r = 0.06$, 95% confidence interval: -0.56 to 0.63, $P = 0.86$). GBS incidence fell between months of the two pandemic waves compared to the same months of 2016-19. In an independent cohort study, 47 GBS cases were reported (COVID-19 status: 13 definite, 12 probable, 22 non-COVID-19). There were no differences in the pattern of weakness, time to nadir, neurophysiology, CSF findings or outcome between these groups. Intubation was more frequent in the COVID-19 cohort (7/13, 54% vs 5/22, 23% in COVID-19-negative) likely related to COVID-19 pulmonary involvement.

Conclusions: Although not possible to entirely rule out the possibility of a link, this study finds no epidemiological or phenotypic clues of SARS-CoV-2 being causative of GBS. GBS incidence has fallen during the pandemic, which may be the influence of lockdown measures reducing transmission of GBS inducing pathogens such as *Campylobacter jejuni* and respiratory viruses.

Keywords: GBS, COVID-19, Epidemiology.

Poster No: 116 | Loss of function MPZ mutations in American and Italian families with CMT1B

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Introduction: Mutations in Myelin Protein Zero (MPZ) cause CMT1B, the second leading cause of CMT1. Many of the >200 mutations cause neuropathy through a toxic gain of function by the mutant protein such as ER retention, activation of the Unfolded Protein Response (UPR) or disruption of myelin compaction. While there is extensive literature on the loss of function consequences of MPZ in heterozygous MPZ $+/-$ null mice there is little known of the consequences of MPZ haploinsufficiency in humans.

Methods: We identified six patients with heterozygous c.306 deletions of MPZ that are predicted to cause a frameshift, premature termination and nonsense mediated decay of the mutant allele. Five patients were evaluated in Milan and one in Iowa City; all should be haploinsufficient for MPZ. Patients were evaluated clinically and by electrophysiology.

Results: Sensory ataxia dominated the clinical presentation with only mild weakness present in 5 of the 6 patients. Symptoms presented in adulthood in all patients and only one individual had a CMTNSv2 > 5. Deep tendon reflexes were absent in all patients.

Conclusions: Patients with likely MPZ loss of function due to a heterozygous c.306del mutation have a mild predominantly large fiber sensory neuropathy that serves as a human equivalent to the

neuropathy observed in heterozygous MPZ null mice. Successful therapeutic approaches in treating MPZ deficient mice may be candidates for trials in these and similar patients.

Grant Support: This consortium Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01).

Keywords: CMT1B, Genetics, MPZ, CMT.

Poster No: 117 | Peripheral neuropathy with intermediate velocities presenting complaint of RASopathy

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Introduction: RASopathies such as Noonan Syndrome and Cranio-Facial-Cutaneous (CFC) syndrome, are developmental genetic conditions caused by mutations in genes in the RAS/mitogen-activated protein kinase pathway. The phenotypic spectrum includes typical dysmorphic features, cardiac defects, short stature, ectodermal anomalies, and intellectual disability. Neuropathy has not been established as part of the spectrum in RASopathies, although, Stark et al. describes a mother and son with a pathogenic KRAS variant (c.211 T > C p.Y71H) and nerve conduction studies with "mixed axonal and demyelinating features" in a boy and "mild slowing" of conduction velocity in his mother.

Methods: We present a 38-year-old woman with mild upper and lower extremity distal muscle weakness, length-dependent sensation loss, and hyporeflexia with onset of symptoms in her 20s. NCS/EMG revealed a sensory motor polyneuropathy with intermediate conduction velocities. History was notable for an atrial septal defect in infancy and jenu valgus in childhood, requiring surgery. There was no known family history of neuropathy, and no known consanguinity. Extensive lab work for reversible causes of neuropathy was unrevealing. CSF examination was normal aside from a mildly elevated protein (55 mg/dL). Brain MRI revealed a meningioma over the left calvarium, and spine MRI showed symmetric enlargement of the cervical and lumbosacral nerve roots. Genetic testing for hereditary neuropathy was initiated.

Results: Genetic testing revealed a heterozygous pathogenic mutation in FIG4 (c.1373dup), however FIG4 protein level in fibroblasts from skin biopsy was normal. The patient received three cycles of IVIG without improvement. Clinical whole exome sequencing (WES) revealed a heterozygous likely pathogenic mutation in KRAS (c.214A > T; p.M72L), consistent with the diagnosis of autosomal dominant RASopathy spectrum disorder.

Conclusions: The unexpected diagnosis of a RASopathy for an individual presenting with a sensorimotor neuropathy with intermediate conduction velocities presents a diagnostic challenge. The individual will remain a subject in the Inherited Neuropathy gene discovery research.

References

1. Stark Z, Gillessen-Kaesbach G, Ryan MM, et al. Two novel germline KRAS mutations: expanding the molecular and clinical phenotype. Clin Genet. 2012:81: 590-594.

Keywords: CMT, intermediate, genetic, KRAS, Noonan.

Poster No: 118 | Role of pyruvate in maintaining Schwann cell viability and energy production under high glucose conditions

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Introduction: Pyruvate functions as a glycolysis accelerator and an antioxidant. The efficacy of pyruvate supplementation in diabetic complications has been shown in animal models; however, its significance in the functional maintenance of neurons and Schwann cells under diabetic conditions remains unknown.

Methods: Primary cultured adult rat dorsal root ganglion (DRG) neurons and immortalized adult mouse Schwann (IMS32) cells 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 hours. Cell viability was evaluated using Trypan blue exclusion and MTS cell proliferation assays. Glucose uptake and metabolism of IMS32 cells under each culture condition were evaluated using liquid chromatography coupled with tandem mass spectrometry, metabolome and the Extracellular Flux Analyzer.

Results: Rapid and extensive cell death of DRG neurons and IMS32 Schwann cells under high glucose and pyruvate-starved conditions was observed. Exposure of IMS32 cells to these conditions led to a significant decrease in glycolytic flux, mitochondrial respiration and ATP production, accompanied by enhanced polyol pathway and other collateral glycolysis pathways. Cell death could be prevented by supplementation with 2-oxoglutarate (a TCA cycle intermediate), benfotiamine (the vitamin B1 derivative that suppresses the collateral pathways), or the poly (ADP-ribose) polymerase (PARP) inhibitor, rucaparib.

Conclusions: Pyruvate starvation enhances the glucose flux into the polyol and other collateral pathways of glycolysis, and reduces the flux into the glycolysis-TCA cycle under high glucose conditions. These metabolic alterations may result in the deficient ATP production in mitochondria, thereby being a cause of rapid neuronal and Schwann cell death. Exogenous pyruvate plays a pivotal role in maintaining glycolysis-TCA cycle flux and ATP production under high glucose conditions by suppressing PARP activity.

Keywords: pyruvate, Schwann cells, energy production, metabolomics, diabetic neuropathy.

Poster No: 119 | **Plasma and skin biomarkers for CMT**

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Introduction: Building upon previous studies of CMT1A, we have initiated biomarker studies to identify biomarkers in other common forms of Charcot Marie Tooth (CMT) disease, including CMT1B, CMT1X, and CMT2A. Although Neurofilament L has emerged as a common indicator of axon degeneration, additional biomarkers that are treatment responsive will help improve clinical trial design.

Methods: We have collected plasma and skin samples from >100 individuals with genetically confirmed cases of CMT1B, CMT1X, and CMT2A, and are evaluating plasma samples using the Olink Target Neurology 384 immunoassay platform and microRNA profiling. We also have screened for plasma nerve-enriched transcripts using Nanostring analysis of skin biopsies with a custom gene Codeset based on bioinformatic analysis of peripheral nerve data sets from CMT models. Biomarker levels are correlated with other patient data to test if biomarkers levels correlate with disease severity.

Results: Screening plasma proteins using the new Olink platform confirmed that NfL plasma levels are elevated in CMT1B, 1X, and 2A compared to controls. In contrast, the previously described TMPRSS5 elevation is specific to CMT1A. We also found elevation of additional candidate microRNAs and proteins (eg, NID2 and NDRG1) that are being validated in larger sample cohorts. Ongoing analysis is testing if previously observed increases in myomiRs and Schwann cell microRNA's in CMT1A are also observed in other CMT subtypes.

Conclusions: In the last several years, there have been several candidate biomarkers that have been developed to assess not only CMT disease status, which may provide useful treatment biomarkers for clinical trials. Some biomarkers identified so far appear to be elevated in several major forms of CMT, whereas others are more specific to a given subtype.

References

1. Svaren J, Moran JJ, Wu X, et al. Schwann cell transcript biomarkers for hereditary neuropathy skin biopsies. Ann Neurol. 2019;85(6):887-898.

2. Wang H, Davison M, Wang K, et al. transmembrane protease serine 5: a novel schwann cell plasma biomarker for CMT1A. 2020.

Grant Support: Funding was provided by the Charcot-Marie-Tooth Association, and by NIH: R21 TR003034, U54 NS065712 provided by NINDS/NCATS-ORD, and a core grant to the Waisman Center from NICHD (U54 HD090256).

Keywords: CMT, biomarker, microRNA, Schwann.

Poster No: 120 | **An allosteric specific activator of sirtuin 1 induces growth of axons and prevents experimental diabetic neuropathy**

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Introduction: Sirtuin1 (SIRT1) is an NAD + -dependent deacetylase enzyme. Overexpression of SIRT1 protein in neurons, including dorsal root ganglion (DRG) neurons, prevented and reversed high fat diet (HFD)-induced peripheral neuropathy (Brain. 2019;142(12):3737-3752). To translate these findings, we tested whether an allosteric activator of SIRT1, SRT2104, would prevent peripheral neuropathy induced by a HFD?

Methods: C57BL6 mice (n = 8) were fed either with Control Diet (CD) or HFD or HFD plus added SRT2104 at a dose of 1.33 g/kg diet for 2 months. Neuropathy endpoints (Sciatic Motor Nerve Conduction Velocity (SMNCV), Tail Sensory Conduction Velocity (TSNCV), Tail Motor Latency (TML), and Mechanical Allodynia (MA-Von Frey) were measured at 1 month and 2 months after feeding. Intraepidermal nerve fiber density (IENFD) was measured in the hind-paw.

Results: MA, NCV, and IENFD were decreased in HFD-fed mice compared to CD-fed mice at 2 months. Two months of feeding HFD + SRT2104, we observed prevention of MA, NCV, and IENFD. Western blot of protein extracts from DRG neurons showed that HFD increased acetylation of proteins, and administration of SRT2104 abolished the HFD-induced acetylation of proteins. Measurement of Mt respiration in cultured dorsal root ganglion (DRG) neurons using the Seahorse XF24 analyzer showed that SRT2104 treatment increased mitochondrial maximal reserve capacity in a SIRT1 activity-dependent manner. Treatment of cultured DRG neurons with SRT2104 increased axonal growth via deacetylation (activation) of a critical E3 Ubiquitin Ligase protein, NEDD4-1.

Conclusions: Dietary addition of SRT2104, an allosteric activator of SIRT1 protein, prevents experimental diabetic neuropathy associated with altered acetylation of proteins through pathways that promote mitochondrial metabolism and induce axonal growth.

Grant Support: National Institutes of Health 1R01DK107007-01A1.

Keywords: Diabetic Neuropathy, Mitochondrial Metabolism, SIRT1, Dorsal Root Ganglion, NEDD4.

Poster No: 121 | **Interleukin-10 promoter polymorphisms in patients with Guillain-Barré syndrome in Bangladesh**

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Introduction: Interleukin-10 (IL-10) is a multifunctional cytokine with both pro- and anti-inflammatory effects on immune system as well as 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 influence the susceptibility and severity of GBS in Bangladesh.

Methods: Genotyping of the IL-10 gene promoter polymorphism was performed by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) and allele specific oligonucleotide-polymerase chain reaction (ASO-PCR) in 152 patients with GBS and 152 ethnically matched healthy controls in Bangladesh. Verification of Hardy-Weinberg equilibrium and comparison of genotype and allele frequencies were performed using Pearson's chi-square test or Fisher's exact test (two-sided) when appropriate. P values <0.05 were considered to be statistically significant.

Results: The homozygous -819TT genotype was the most 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). Moreover, the -819TT genotype tended to be associated with disease susceptibility when patients were compared with healthy controls as P value lost its significance after Bonferroni correction for multiple comparisons ($P = 0.029$, OR = 2.73, 95% CI = 1.15-6.45; Pc = 0.08). No other genotypes or haplotypes of IL-10, −1082G/A, -819C/T and -592C/A polymorphisms showed significant association with disease susceptibility. The high IL-10 expression haplotype combinations (GCC/GTA, GCC/ATA and GCC/GCA) may influence severity of the disease ($P = 0.008$, OR = 3.22, 95% CI = 1.4-7.43; Pc = 0.024).

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

References

1. Myhr KM, Vågnes KS, Marøy TH, Aarseth JH, Nyland HI, Vedeler CA. Interleukin-10 promoter polymorphisms in patients with Guillain-Barré syndrome. J Neuroimmunol. 2003;139(1-2):81-3.

2. Press R, Deretzi G, Zou LP, et al. IL-10 and IFN-γ in Guillain-Barré syndrome. J Neuroimmunol. 2001;112(1-2):129-38.

Geleijns K, Emonts M, Laman JD, et al. Genetic polymorphisms of macrophage-mediators in Guillain-Barré syndrome. J Neuroimmunol. 2007;190(1-2):127-30.

Grant Support: icddrb, Dhaka, Bangladesh.

Keywords: Interleukin-10, Polymorphism, Genotype, Variant, Haplotype.

Poster No: 122 | **Multifaceted approach to profiling vincristine-induced peripheral neuropathy**

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Introduction: Vincristine is a chemotherapy agent widely used to treat hematological malignancies. Vincristine-induced peripheral neuropathy (VIPN) is a pervasive, dose-limiting side effect resulting in sensory and motor nerve disturbances. Unfortunately, understanding of VIPN development, recovery and functional impairment profiles remain limited. This study aimed to investigate the characteristics of VIPN using a comprehensive battery of assessments.

Methods: Forty-one patients (mean age = 60.2 ± 14.7 years, 65.9% male) who had completed vincristine treatment within 5 years were recruited to the study (mean time since treatment = 19.2 months, range = 3-56 months). Patients completed the validated EORTC-CIPN20, Rasch-Overall Disability Score (R-ODS), a neurological grading scale (Total Neuropathy Score, clinical version [TNSc]) and sural and tibial nerve conduction studies (NCS) measuring sensory nerve and compound muscle action potentials respectively (SNAP, CMAP).

Results: Among vincristine-treated cancer survivors, 78.1% (n = 32) reported persisting VIPN. Symptom phenotyping revealed 62.5% of patients with VIPN reported both sensory (numbness and/or tingling) and motor (cramps and/or weakness) disturbances, and 37.5% reporting shooting/burning pain. 53.1% of patients with VIPN reported symptoms in both upper and lower limbs and 50.0% reported functional difficulty resulting from their VIPN. Furthermore, patients with significant VIPN ("quite a bit"/'very much') symptoms on the CIPN20 demonstrated increased overall disability than patients with none-mild symptoms ('none'/"a little bit") (R-ODS diff = 10.0, $P < 0.01$). On neurological assessment in patients with VIPN, 43.8% had reduced pin-prick, 53.1% had reduced vibration sensation and 51.6% had reduced reflexes. NCS demonstrated 46.4% of patients with VIPN had a reduced sural SNAP and 7.1% had a reduced tibial CMAP.

Conclusions: VIPN remains a long-term disability for cancer survivors, significantly impacting overall disability. Persistent VIPN has been identified by patient report at a higher frequency than neurological and neurophysiological assessments. Further research in prospectively phenotyping the development and recovery of VIPN is critical to better our understanding of mechanisms and profiles of VIPN.

Keywords: Chemotherapy-induced peripheral neuropathy, Vincristine, Phenotyping, Neurophysiology, Outcome measures.

Poster No: 123 | **The impact of obesity on neuropathy outcomes for paclitaxel and oxaliplatin-treated cancer survivors**

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Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) is a major side effect of neurotoxic cancer treatment, often impacting treatment tolerability and patient functioning. Factors predicting an individual's vulnerability for developing CIPN remain ill-defined. However patient characteristics may contribute to CIPN risk, with obesity being a prevalent patient comorbidity. This study aimed to evaluate if being overweight (BMI≥25 kg/m2) was associated with worse symptomatic, clinical, and functional CIPN following neurotoxic cancer treatment.

Methods: 379 cancer survivors were assessed 5 (IQR:3-5) months post oxaliplatin or paclitaxel treatment via comprehensive patient reported (FACT-GOG-Ntx), clinical (Total Neuropathy Score, clinical version [TNSc]) and functional (grooved pegboard; standing balance via postural sway) CIPN measures. Patients classified as overweight (BMI≥25 kg/m2) were compared to those within the normal BMI range (< 25 kg/m2). Multilinear regression was conducted to evaluate the association between patient clinical factors and CIPN severity.

Results: Most patients reported CIPN symptoms (78%), with deficits evident on clinical examination consistent with a sensory predominant neuropathy. Compared to those with a normal BMI, overweight patients (n = 242, 63.8%) had significantly worse ($P < .05$) CIPN across symptomatic (FACT-GOG-Ntx; normal:43.80 ± 8.35, overweight 40.20 ± 8.93), objective clinical (TNSc; normal:3.71 ± 2.85, overweight:4.85 ± 2.86) and functional outcomes (peg board; normal:72.75 ± 24.43 seconds, overweight: 80.93 ± 25.72 seconds.; postural sway; normal:723.48 ± 235.79 mm, overweight:824.26 ± 281.88 mm). In multivariate linear regression, older age (B = .088, 95%CI = .053-.122, $P < .001$), larger waist circumference (B = .030, 95%CI = .001-.059, $P < .05$), and larger BSA (B = 2.41, 95% CI = .340-4.48, $P < .05$) were associated with CIPN. Diabetes and BMI were significant on univariate analysis but not in the final models.

Conclusions: Overweight patients represent a large proportion of cancer survivors who may be particularly impacted by CIPN, requiring closer monitoring and referral to supportive services. Accessible data such as a patient's general and abdominal obesity status may aid in formulating informing treatment decisions. Identifying routinely measured patient characteristics which may contribute to an individual's CIPN risk profile could assist with personalized medicine.

Keywords: Chemotherapy, Neuropathy, Risk Factors, Obesity, Body Mass Index.

Poster No: 124 | Translating CMT clinical outcome measures into practice using a co-designed digital platform

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Introduction: The Inherited Neuropathy Consortium has developed reliable, sensitive and responsive clinical outcome measures for children and adults with Charcot-Marie-Tooth disease and related neuropathies (CMT). The CMTInfs,(1) CMTPedS,(2) CMT-FOM (3) and CMTNS (4) are used for research and clinical care to inform disease progression and intervention efficacy. We aimed to re-develop the existing CMTPedS online calculator to include all measures and enable real-time scoring and reporting based on normative reference data informed by the 1000 Norms Project.(5).

Methods: A process of consultation including user interviews and co-design with the development team informed the new scoring website. The project implementation included a process evaluation of current users, establishment of design elements including user experience, technical requirements and embedded google analytics.

Results: We successfully delivered the first stage of this project (December 2019-July 2020) and developed the website (www.clinicaloutcomemeasures.org). This platform optimized the CMTPedS calculator website which was widely used both clinically and for research. The website is freely available. Registered users can calculate individual patient results and a large data upload function is available for research datasets of clinical outcomes. An easily downloadable patient report is available for users to enable clinical reporting. The website currently has 205 registered users from 25 countries, with an average of 50 calculations per month.

Conclusions: The clinical outcomes available on this website can be more broadly translated into clinical practice, research studies and clinical trials. With normative reference data collected from the 1000 Norms Project, scores for these clinical outcomes can be calculated to measure disease progression in natural history studies and determine treatment efficacy. The next phase of implementation will be to design and embed an online clinical evaluator training and quality assurance program to ensure fidelity.

References

1. Mandarakas MR, Menezes MP, Rose KJ, et al. Development and validation of the Charcot-Marie-Tooth disease infant scale. Brain. 2018;141:3319-3330.

2. Burns J, Ouvrier R, Estilow T, et al. Validation of the Charcot-Marie-Tooth disease pediatric scale as an outcome measure of disability. Ann Neurol. 2012;71:642-652.

3. Eichinger K, Burns J, Cornett K, et al. The Charcot-Marie-Tooth functional outcome measure (CMT-FOM). Neurology. 2018;91:e1381-e1384.

4. Shy M, Blake J, Krajewski K, et al. Reliability and validity of the CMT neuropathy score as a measure of disability. Neurology 2005;64:1209-1214.

5.McKay MJ, Baldwin JN, Ferreira P, et al. Normative reference values for strength and flexibility of 1,000 children and adults

Keywords: Implementation, Clinical outcome measures, Measurement, CMT.

Poster No: 125 | Severe back pain and burning pain all over can be seen in atypical presentations of hereditary neuropathy with liability to pressure palsy

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Introduction: Hereditary neuropathy with liability to pressure palsy (HNPP) is an autosomal dominant genetic disorder characterized by multiple episodes of focal weakness and sensory loss caused by compression or trauma. It commonly involves a deletion of chromosome 17p11.2 of the peripheral myelin protein 22 (PMP22) gene. Given its variable presentation, it is possible that HNPP can be under-recognized. This abstract describes two cases of an atypical presentation of HNPP.

Methods: We report two unrelated individuals with HNPP who were evaluated with clinical, laboratory, electrophysiological, and genetic testing.

Results: Case 1 is a 32-year-old gentleman with occasional numbness in his hands, an episode of transient biceps weakness after rotating his arm while stretching, and unbearable radiating back pain with stiffness and worse with certain positions since he was a child. The back pain was so severe that he could not move his back many times over the years. He had no other episodes of compressive neuropathies. Case 2 is a 46-year-old woman with congestive heart failure and Takayasu's arteritis who presented with many years of burning sensations in her head, feet, hands, knees, and groin area. She reported tingling in her fingers, which was positional and sporadic when laying down. She had severe back pain that worsened with certain positions. Family history was positive in case 1 but not in case 2. There were no clinical features of pes cavus, sensory loss, or weakness on exam. Electrodiagnostic testing in both cases showed evidence of a sensorimotor polyneuropathy with slowing at common compression sites.

Conclusions: Although HNPP typically presents with transient compressive mononeuropathies, this study suggests that HNPP can present with various broad clinical presentations, including severe back pain and painful burning sensations. Neurologists need to broaden their spectrum of clinical presentations to help diagnose these rare conditions.

Keywords: HNPP, Back pain, Burning pain, Atypical Presentation.

Poster No: 126 | Serum neurofilament light chain as a blood biomarker of severity in paclitaxel-induced peripheral neurotoxicity

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Introduction: There is compelling experimental evidence that neurofilament light chain (NfL) could sensitively be detected in serum as a biomarker of neuro-axonal damage induced by chemotherapy. We sought to assess the significance of measuring serum NF-L (sNfL) levels in the clinical setting of paclitaxel-induced peripheral neurotoxicity (PIPN).

Methods: We longitudinally measured sNfL levels in breast cancer patients, scheduled to receive the 12-weekly paclitaxel-based regimen. Patients were clinically examined by means of the Total Neuropathy Score-clinical version (TNSc), while sNfL levels were quantified, using the highly-sensitive Simoa technique, before the onset of chemotherapy (T0), after commencing 2 courses (T1); 3 courses (T2); at the end of chemotherapy (T3) and 3 months post-treatment (T4).

Results: A total of 24 female patients, having a mean age of 56.6 ± 12.6 (33-78) years, were included. Among them, 10 (41.7%) developed grade 0-1 and 14 (58.3%) grade 2-3 PIPN at T3. ANOVA of repeated measures disclosed a significant longitudinal increase in sNfL levels (pg/mL) from T0 to T3 (15.3 ± 11.9-T0; 30.1 ± 38.5-T1; 51.5 ± 82.1-T2; 134.9 ± 118.6-T3, $P < 0.001$) and a drop from T3 to T4 (4 ± 11.3). Patients with grade 2-3 PIPN had significantly increased sNfL levels at T3, compared to those with grade 0-1 ($P < 0.001$). Mean levels of sNfL significantly correlated with TNSc scoring. Logistic binary regression analysis revealed that the difference of sNfL levels between T1 vs T0 independently predicted the manifestation of severe grade 3 PIPN at T3. ROC analysis defined that a discriminative increase of >21.5 in sNfL levels at T1 vs T0, predicted with sensitivity 71% and specificity 100% the development of grade 3 PIPN at T3.

Conclusions: sNfL seems to be a strong biomarker of neuro-axonal injury, while its early increase after 2 chemotherapy courses (T1) possess a predictive value of final PIPN severity. Our findings could be relevant for future neuroprotection trials.

Grant Support: None.

Keywords: toxic neuropathies, paclitaxel induced neurotoxicity, serum neurofilaments, biomarker, severity.

Poster No: 127 | Development and validation of the small fiber neuropathy patient satisfaction questionnaire in a tertiary referral center

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Introduction: Small fiber neuropathy is a disorder of thinly myelinated Aδ and unmyelinated C fibers, leading to neuropathic pain and autonomic dysfunction. International referral SFN centers worked on improving patient-centered care by implementing a standardized diagnostic approach, but never reflected this against patients' input. Patient satisfaction is a major indicator in the improvement of quality

in health care. Patient experience and satisfaction results can inform hospitals requiring improvement from patients' perspective. Current patient satisfaction questionnaires are limited in use because of varied patient care processes. We developed an SFN-patient satisfaction questionnaire, tested its content validity and evaluated the SFN diagnostic service.

Methods: An SFN patient satisfaction questionnaire (SFN-PSQ) was developed through a multiphase development process. First, appropriate items of existing instruments were adopted and adjusted to develop the SFN-PSQ of the SFN diagnostic service. Second, content validity of the SFN-PSQ was conducted by the collaborative input of ten associated SFN caregivers and, after that, with nine patients by using the three-step test method with individual cognitive interviews. Third, a single-center, retrospective, survey-based cohort study the final version of the SFN-PSQ was completed by 100 patients who had had completed the small fiber neuropathy diagnostic workup in the past year (regardless of the diagnosis of SFN). The SFN-PSQ consisted of 56 questions, related to 6 domains: Prior to the visit, reception and stay, diagnostic tests, patient consultation, follow-up services and a general part, scored on a 5-point Likert scale. From November 2020 data collection was started with a hyperlink to the online SFN-patient satisfaction questionnaire by email and responses were collected.

Results: The (preliminary) results of this study will be presented.

Conclusions: A patient satisfaction questionnaire is developed to collect patients experiences and satisfaction on all aspects of our the standardized, integrated diagnostic SFN service for improving the quality in SFN health care.

Keywords: small fiber neuropathy, standardized diagnostic approach, patient satisfaction, patient satisfaction questionnaire, quality of care.

Poster No: 128 | **Pain in Guillain-Barre' syndrome: A prospective observational study from Bangladesh**

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Introduction: Pain is a common and one of the severe symptoms in Guillain-Barré syndrome (GBS) that is often paid less attention. We evaluated the frequency, character, and intensity of pain among GBS patients in Bangladesh using one of the largest GBS cohorts from developing countries.

Methods: We conducted a prospective hospital-based study at Dhaka, Bangladesh from 2010-2016. Detailed clinical, electrophysiological and serological data were collected at enrollment and predefined time points of follow up. Differences in proportion between groups were tested by chi square (χ^2) test or Fisher exact test as appropriate. Longitudinal analysis of pain intensity scores and its correlation with disease severity was performed using repeated-measurement ANOVA and Spearman rank correlation test respectively.

Results: A total of 513 patients with GBS were included in the analysis. Median age of patients was 27 years (IQR 17, 41) with male predominance (67%). In the acute phase of GBS, 69% of patients had reported pain which persist in 14-15% patients after 6-12 months of disease onset. Pain in the acute stage of the disease was significantly associated with disease severity measured by GBS disability score ($P = 0.003$); axonal variant of GBS ($P < 0.001$); cranial nerve involvement including facial nerve involvement ($P = 0.021$) and bulbar dysfunction ($P = 0.038$); recent *Campylobacter jejuni* infection (0.014); and presence of anti GM1 IgG antibody ($P = 0.020$). Mean pain intensity was significantly higher among females compared to males in all time points of follow up. Disease severity and muscle weakness were significantly correlated with pain intensity in the acute stage but not after 6 months.

Conclusions: Pain is a distinctive clinical feature among GBS patients in Bangladesh, and significantly correlates with disease severity in acute stage. Systematic evaluation of pain is crucial for integrative management of GBS patients.

Keywords: Guillain-Barré Syndrome, Pain, Bangladesh.

Poster No: 129 | **Squalenoyl siRNA PMP22 nanoparticles, a potent therapy for Charcot-Marie-Tooth disease type 1A**

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Introduction: Charcot-Marie-Tooth disease type 1A (CMT1A), caused by a duplication in chromosome 17, results in peripheral myelin protein 22 (Pmp22) over-expression and axon demyelination. The diagnosis of CMT1A is based on decreased nerve conduction velocity (NCV) and compound muscle action potential (CMAP), with progressive muscle weakness and impaired sensations. To date there is no effective therapy for CMT1A except surgical corrections and relief of pain. Our study provides a new therapy for CMT1A, based on the normalization of PMP22 expression by specific siRNA conjugated to squalene nanoparticles (siRNA PMP22-SQ NPs).

Methods: siRNA was conjugated to squalene using click chemistry method. Nanoparticles size was analyzed by DLS and TEM microscopy. CMT1A mouse models were used to test the efficiency of siRNA PMP22-SQ NPs. Behavioral tests, were performed to study the locomotion and muscular strength of the mice. Electrophysiological, molecular and histological studies were performed.

Results: Conjugation of siRNA PMP22 to squalene resulted in the formation of active, stable and hydrophobic nanoparticles. Intravenous administration of siRNA PMP22-SQ NPs to transgenic mouse models of CMT1A resulted in the normalization of Pmp22 protein levels and restored their locomotor and muscular activity. Moreover, electrophysiological parameters, NCV and CMAP, were significantly improved. Pathological studies demonstrated the regeneration of myelinated axons and myelin compaction as observed by sciatic nerve electron microscopy. The levels of sciatic nerve transcriptional factors

Krox20, and Sox10 as well as neurofilament protein levels were normalized that reflected the regeneration of both myelin and axons. Importantly, the positive effects of siRNA PMP22-SQ NPs lasted for as long as three weeks, and their renewed administration resulted in full functional recovery.

Conclusions: Beyond CMT1A, our findings can be considered as a potent therapeutic strategy for dominantly inherited peripheral neuropathies. They provide the proof of concept for a new precision therapy based on the normalization of disease gene expression by siRNA.

Grant Support: This work was supported by a public grant overseen by the French National Research Agency (ANR) as part of the "Investissements d'Avenir" program (Labex NanoSaclay, reference: ANR-10-LABX-0035).

Keywords: CMT1A, siRNA, PMP22.

Poster No: 131 | Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (Canvas) is an important cause of late-onset ataxia

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Introduction: Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) is a late-onset, disorder characterized by the combination of slowly progressive cerebellar ataxia, sensory neuropathy and bilateral vestibulopathy. Recently, a biallelic intronic AAGGG repeat expansion, (AAGGG)exp, in the Replication Factor C1 (RFC1) gene was identified as the cause of this disorder.

Methods: In this study, we describe the phenotypic features of five patients from five different families diagnosed as CANVAS.

Results: The mean age at onset was 49.00 ± 9.05 years (between 34 and 56 years). The most frequent presenting symptom in CANVAS was gait ataxia, followed by sensory disturbances. Persistent coughing was noted in three patients, and it preceded core clinical symptoms in two patients. Parental consanguinity was present in three patients. Two patients demonstrated symptoms or signs suggesting autonomic involvement. Sural nerve biopsy disclosed axonal neuropathy in two patients. Neuro-otological examination was performed in four patients, and video-nistagmography was performed in two of them, which was consistent with vestibular impairment.

Conclusions: Our study highlights the clinical findings and diagnostic clues of CANVAS from Turkey that has a high consanguineous marriage rate. We concluded that repeat expansion in the RFC1 gene should be considered in all cases with late-onset ataxia, especially when sensory disturbances, vestibular involvement and persistent coughing coexist.

Grant Support: None.

Keywords: genetic, neuropathy, coughing, polyneuropathy, RFC1.

Poster No: 133 | High content screening using patient-derived primary cells and *C. elegans* models identifies therapeutic candidates for CMTX6

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Introduction: X-linked Charcot-Marie-Tooth disease 6 (CMTX6) is caused by a missense mutation (p.R158H) in the PDK3 gene. The PDK3 missense mutation leads to hyperphosphorylation of the pyruvate dehydrogenase complex (PDC), a key regulator of the energy-producing Krebs Cycle in the mitochondria, and downstream disruption of cellular energy metabolism and mitochondrial dysfunction (Neurobiology of Disease, Perez-Siles G, 2016). In this project we have developed and performed in-house high-content drug screening (HCS) to accelerate the discovery of therapeutic candidates for the treatment of CMTX6.

Methods: We have screened 1840 FDA-approved bioactive compounds on a 3-phase approach that includes the use of CMTX6 derived skin fibroblasts, patient-derived iPSC motor neurons (iPSC-MN_CMTX6) and an in vivo *C. elegans* model overexpressing the human PDK3_R158H mutation.

Results: Our HCS identified 20 molecules that efficiently reverted PDC hyperphosphorylation in the CMTX6 skin fibroblasts toward physiologically normal levels. Following the exclusion of neurotoxic molecules from the initial HCS, the hits identified have been interrogated in iPSC-MN_CMTX6 for their capacity to revert the metabolic dysfunction recently reported in these cells when compared with an isogenic control (Scientific Reports, Perez-Siles G, 2020). These experiments have led to the identification of 3 candidate molecules that will be evaluated in our CMTX6 *C. elegans* model for their capacity to ameliorate axonal damage in GABAergic neurons, revert synaptic defects and locomotor dysfunction observed in this model (Human Molecular Genetics, Narayanan R, under review).

Conclusions: The compounds identified through this HCS using in vitro and patient-derived in vivo models represents a primary step toward discovery of the first effective CMTX6 pharmacological therapy.

References

1. Pathogenic mechanisms underlying X-linked Charcot-Marie-Tooth neuropathy (CMTX6) in patients with a pyruvate dehydrogenase kinase 3 mutation. Neurobiol Dis. 94:237-244.

2. Energy metabolism and mitochondrial defects in X-linked Charcot-Marie-Tooth (CMTX6) iPSC-derived motor neurons with the p.R158H PDK3 mutation. Sci Rep. 2020;10(1):9262.
3. A new locus for X-linked dominant Charcot-Marie-Tooth disease (CMTX6) is caused by mutations in the pyruvate dehydrogenase kinase isoenzyme 3 (PDK3) gene. Hum Mol Genet. 2013;22 (7):1404-16.

Grant Support:

Keywords: High Content Screening, iPSC motor neurons, *C. elegans*, Fibroblasts.

Poster No: 134 | Acute flaccid paralysis: Consider thick-borne encephalitis virus, even In non-endemic regions

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Introduction: Tick-born encephalitis virus (TBEV) is an important cause of viral encephalitis and meningitis in Central and Eastern Europe. It is transmitted mainly by tick bites. Here, we present the first case of a TBEV indigenous infection with an anterior poly-radiculitis presentation in Belgium. Herein our goal is 2fold. First to warrant the clinician to consider TBEV as a potential cause of radiculitis even in the absence of encephalitis. Second to shed light on the emergence and spread of this tick-borne virus in regions, considered non-endemic.

Methods: Patient description.

Results: A 59-year old male worker at a farm developed lower-back pain radiating to the left leg after a tick bite. A few weeks later, headache and fever developed together with progressive painful weakness leading to wheelchair dependence. On admission, two months after the thick bite, clinical evaluation showed a severe asymmetrical flaccid paralysis, atrophy and fasciculations involving appendicular and axial muscles. No signs of pyramidal tract involvement. Nerve conduction studies showed normal sensory conductions and reduced amplitude of the compound motor action potentials in lower limbs. Striking signs of acute axonal loss were shown by needle EMG. Cerebrospinal fluid (CSF) analysis first showed a predominantly neutrophilic pleiocytosis, high protein (88 mg/L) with absence of oligoclonal bands. Repeated lumbar puncture showed a predominantly lymphocytic pleiocytosis. Spine Magnetic Resonance Imaging showed contrast enhancement of the ventral surface of the conus and the anterior nerve roots at cervical and lumbar levels. TBEV IgG and IgM were positive both in serum and CSF. A serum virus neutralization (SVN) assay showed a positive result (1/149), confirming the diagnosis of a TBEV infection. The patient reported no recent travels abroad.

Conclusions: Neurologists should be aware that TBEV may be a rare cause of acute flaccid paralysis even in areas considered non-endemic.

Keywords: Thick-borne encephalitis virus, anterior radiculitis, non-endemic.

Poster No: 135 | Circulating biomarkers may serve as sensitive outcome measures in CMT1A patients

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Introduction: Charcot-Marie-Tooth disease 1A (CMT1A) is caused by a duplication of the gene encoding PMP22 and is the most common inherited neuropathy with no approved therapy available. Patients present with a slow disease progression and high variability with unknown cause. Biomarkers may be able to serve as surrogate measures for disease severity and progression.

Methods: In this translational study, we set out to identify circulating markers of disease severity on the transcriptional level. Patients were clinically examined applying a battery of 13 standardized clinical scales over two years within the Charcot-Marie-Tooth Disease Network (CMT-NET) at four university hospitals in Germany. Applying RNA sequencing in five mildly and five severely affected CMT rats and CMT1A patients, we screened for candidates of circulating biomarkers. Overlapping differentially expressed genes in the animal model and patients were then validated via RT-PCR in a cohort of 139 CMT1A patients and reexamined after two years.

Results: We found 249 regulated genes derived from blood between mildly and severely affected rats and 876 genes when comparing mildly and severly affected age matched CMT1A patients. 49 genes

overlapped and first candidates were validated via RT-PCR. When correlating expression profiles to the 13 clinical outcome measures, we identified candidates that showed significant correlations to clinical parameters and were sensitive to change over 2 years.

Conclusions: Differentially regulated gene expression derived from blood in a CMT1A animal model and patients may yield novel circulating biomarkers for disease progression.

Grant Support: This study was part of the German network on Charcot-Marie-Tooth Disease (CMT-NET, 01GM1511) funded by the German Federal Ministry of Education and Research (BMBF, Bonn, Germany) from 2016-2019.

Keywords: Peripheral Neuropathy, Charcot-Marie-Tooth Disease, Biomarker, Outcome Measure, Clinical Study.

Poster No: 136 | Alpha-adrenoreceptor-blocker phentolamine mesylate inhibits human sodium channel Nav1.7

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Introduction: Phentolamine mesylate is an α-adrenoreceptor antagonist, inducing vasodilatation at its injection site, thus leading to faster systemic clearance of locally injected drugs. It is for example, injected as a reversal agent after treatment with soft-tissue local anesthesia and vasoconstrictors to avoid unwanted numbness. Previous studies suggested that phentolamine mesylate may also interact with voltage-gated sodium channels (VGSC), like local anesthetics do, and thus may lead to additional side effects like cardiac arrhythmia. Here we investigate whether phentolamine mesylate affects the human VGSC Nav1.7, which is primarily expressed in peripheral nociceptors and is one of the direct targets of local anesthetics.

Methods: Heterologously expressed human Nav1.7 in HEK293 cells were investigated with whole cell patch-clamp electrophysiology. Phentolamine mesylate in concentrations of 16, 32, 64, 128, 256 and 512 μM or vehicle control were applied with a gravity-driven perfusion system during the recordings. The concentration-response relationship was obtained using 100 ms pulses from −120 mV to +10 mV every 10 seconds. The mean reduction of peak currents after 50 to 55 pulses after the start of perfusion was measured and normalized to the mean of the last five peak currents before the phentolamine mesylate application for comparison.

Results: Phentolamine mesylate inhibited Nav1.7 channels with an IC50 of 73.5 ± 14.27 μM.

Conclusions: The effect of phentolamine mesylate on VGSC can conflict with its current indication as an antidote for local anesthetics. Lidocaine for example, blocks VGSC in a low micromolar range. Thus, interactions by phentolamine mesylate may reinforce the effect of local anesthetics as well as competing for the same binding site on the channel protein. Effects of phentolamine mesylate on different channel gating modalities and in combination with local anesthetics will be investigated in future studies.

Keywords: Phentolamine mesylate, Voltage-gated sodium channels, Nav1.7, local anesthetics.

Poster No: 137 | Pain, fatigue and depressive symptoms in a cohort of 84 patients with chronic immune-mediated polyneuropathies

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Introduction: Pain is a significant symptom of chronic inflammatory demyelinating polyneuropathies (CIDP). Neuropathic pain (NP) is caused by inflammatory infiltration of the somatosensory nervous system in CIN. However, there is little data on the incidence of pain in CIDP and what impact pain has on patients' daily lives.

Methods: 84 patients with CIDP were evlaluated for pain, depressive symptoms and fatigue using the painDETECT questionnaire (PDQ), the Beck Depression Inventory-II (BDI-II) and the Krupp's Fatigue Severity Scale (FSS) and relationships were statistically evaluated. Sensory deficits were quantified using the INCAT Sensory Score (ISS).

Results: 84 CIDP patients (female: 24.0%, median age at disease onset: 55.0, mean disease duration: 37.9 ± 45.0 months) were included. Pain was reported by PDQ in 52 (61.9%) CIDP patients. 46.2% (24/52) of patients showed characteristics of NP, 26.9% (14/52) were uncertain, and 26.9% (14/52) had no NP. The proportion of patients with depressive symptoms was significantly higher in the group of pain compared to the pain-free patients (60.5% vs 33.4%, $P = 0.02$). Depressive symptoms were significantly more frequent in patients with NP than in patients with no NP (81.8% vs 41.7%, $P = 0.0028$). Depressive symptoms were minimal in 18.8%, mild in 27.1%, moderate in 10.4% and severe in 4.2% of patients with pain. The FSS revealed no evidence of fatigue symptoms in 83.3% of 32 pain-free patients, while 38.0% of 52 patients with pain reported fatigue ($P = 0.044$). CIDP patients with pain had a significantly worse ISS than patients without pain ($P = 0.002$), There was no significant difference in disease duration between the group of patients with and without pain.

Conclusions: Pain in CIDP is complained by 2/3 of patients and seems to be an underestimated symptom. As it is associated with more

depressive symptoms and fatigue, its recording and consideration seems to have a prognostic and therapeutic consequence.

Keywords: neuropathic pain, depression, fatigue, Immune-mediated polyneuropathies, chronic inflammatory demyelinating polyneuropathy.

Poster No: 138 | **Familial Guillain-Barré syndrome in Bangladesh: A retrospective cohort analysis**

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Introduction: Guillain-Barré syndrome (GBS) usually occurs sporadically and familial occurrence is rare. Several studies reported familial GBS which postulated genetic susceptibility making such cases worth reporting. Therefore, we aimed to identify familial GBS cases in GBS cohorts of Bangladesh and investigated the clinical, serological, electrophysiological features and outcome of familial GBS.

Methods: We retrospectively screened a cohort of 693 GBS patients in Bangladesh between 2010 and 2018. Severity of disease was measured by the GBS disability score (GBS-DS). We analyzed serum IgG, IgM and IgA antibodies against *Campylobacter jejuni* by an indirect enzyme-linked immunosorbent assay (ELISA) and IgG antibodies against GM1 ganglioside.

Results: We identified a case of familial GBS in Bangladesh which affected two siblings at the same time point in 2017. The two siblings developed quadriparesis at an interval of 4 days and were diagnosed as GBS according to National Institute of Neurological Disorders and Stroke (NINDS) criteria. During hospital admission, GBS-DS of elder and younger sibling were 3 and 4 respectively. The electrophysiological findings were consistent with axonal subtype of GBS in both siblings. *Campylobacter jejuni* serology, *C. jejuni* lipooligosaccharide (LOS) and anti-GM1 IgG antibody were tested and found positive in both patients. The elder brother with less severe disease did not receive any specific treatment such as Intravenous Immunoglobulin (IVIg) of plasmapheresis, whereas, the younger brother with severe disease received 5 dosages (2 g/Kg in 5 days) of IVIg therapy. At two-year of inclusion, the elder sibling was in healthy-state, whereas the younger sibling still had residual neurological deficit.

Conclusions: Familial history of GBS should be inquired when patient presents with GBS. Residual neurological deficit may persist longer even after treatment with IVIg. Further studies are warranted to explore the factors associated with non-response to IVIg. Furthermore, genetic predisposition, gut microbiome, nutritional status and other host factors should be investigated.

Grant Support: The study was funded by GBS|CIDP Foundation International, USA.

Keywords: Guillain-Barré syndrome, Familial GBS, Outcome, Bangladesh.

Poster No: 139 | **Serum albumin and inflammatory markers: The determinants of disease prognosis in Guillain-Barré syndrome**

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Introduction: Intravenous Immunoglobulin (IVIg) is the proven effective therapy for Guillain-Barré syndrome (GBS) although one-third patients with GBS remain unresponsive to IVIg. Serological biomarkers can predict the treatment response and outcome of GBS. We investigated whether serological biomarkers including serum albumin, IgG and inflammatory markers can anticipate the disease prognosis and outcome of GBS in Bangladesh.

Methods: We included 43 patients with GBS in a prospective study. Blood samples and clinical data were obtained from all patients at different time points. Serum albumin, IgG and inflammatory markers including C-reactive protein (CRP), absolute neutrophil count and neutrophil-lymphocyte ratio (NLR) were measured using routine automated analyzer. Statistical analyses were performed using logistic regression, ANOVA and survival analysis was performed by Kaplan-Meier method.

Results: Out of 43 patients, the median age was 31 years (IQR: 21-40) with male predominance (69.8%); 20 patients received IVIg. Among IVIg treated patients, mean serum albumin increased by 1.41 g/L and mean serum IgG decreased by 650.31 mg/dL after 4 weeks of treatment. Reduction of serum albumin was found significantly associated with disease severity ($P = 0.025$) and poor outcome ($P = 0.011$) at 26 weeks. Requirement of mechanical ventilation was significantly associated with elevated serum IgG ($P = 0.036$), CRP ($P = 0.007$), absolute neutrophil count ($P = 0.003$) and NLR ($P = 0.005$) and lower serum albumin levels ($P = 0.013$). Kaplan-Meier survival analysis revealed that hypoalbuminemia (<34 g/dL) and high CRP level (>1 mg/L) comparatively increased the duration of mechanical ventilation.

Conclusions: Readily available serological markers related to clinical course of GBS are yet to be established. Our study revealed that decreased albumin, elevated IgG and inflammatory markers may be considered as biomarkers to predict the disease prognosis and treatment related outcome in GBS. Large sample size is required to validate the clinical relevance of these biomarkers.

References

1. Fokkink WJ, Walgaard C, Kuitwaard K, Tio-Gillen AP, van Doorn PA, Jacobs BC. Association of albumin levels with outcome in intravenous immunoglobulin-treated guillain-barré syndrome. JAMA Neurol. 2017;74(2):189-96.

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Keywords: Serum albumin, inflammatory markers, Guillain-Barré syndrome, disease prognosis, clinical outcome.

Poster No: 140 | **Blockade of cholecystokinin type 2 receptor prevents vincristine-induced sensory neuropathy in mice**

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Introduction: Vincristine (VCR), which is largely used for lymphoma treatment, is one of the most neurotoxic chemotherapeutic agent of the vinca-alcaloids family. Our previous transcriptomic analysis performed on dorsal root ganglia (DRG) 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). CCK system acts as a neuromodulator, in sensitive and pain tract, where CCK2R exhibits pronociceptive properties. We investigated preventive effects of CCK2R antagonist on VIPN, using proglumide (PRGL) and Ly225910 (LY).

Methods: VIPN was induced by intraperitoneal (i.p.) injections of VCR at 100 μg/kg/d during 7 days (D0 to D7). PRGL (30 mg/kg/d, i.p.), a CCK1R and CCK2R antagonist, and LY (1 mg/kg/d, i.p.), a selective CCK2R antagonist, were administered one day before VCR treatment until D7. Development of tactile allodynia induced by VCR was assessed by von Frey testing. Immunohistochemistry and morphological analyses were performed on DRG, skin and sciatic nerve.

Results: VCR induced a high tactile allodynia from D1 to D7. VIPN was characterized by DRG neuron loss, enlargement and loss of myelinated axon in sciatic nerve and intraepidermal nerve fiber (IENF) loss. PRGL accelerated recovery of normal tactile sensitivity and LY completely prevented the occurrence of allodynia. Decrease of IENF and swelling of myelinated axon are prevented by both PRGL and LY. Only LY prevent DRG neuron loss and myelinated nerve fiber loss in sciatic nerve.

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

Keywords: vincristine-induced peripheral neuropathy, allodynia, Cholecystokinin receptor type 2, Ly225910, proglumide.

Poster No: 141 | **7T MRI first exploitation in a chemotherapy induced peripheral neurotoxicity in vivo model**

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Introduction: Chemotherapy induced peripheral neurotoxicity (CIPN) is a common, long lasting (or even permanent) adverse event of anti-cancer drugs. No disease-modifying treatments are available due to incomplete pathogenetic knowledge. Moreover, detection/grading of CIPN in clinical setting still represents a major challenge. High resolution diffusion MRI could be a surrogate, translational, marker to characterize early morphological changes as neuropathy ensues, creating a virtuous link between bench and bed side.

Methods: We aimed at characterizing MRI changes in a consistent model of CIPN. We selected paclitaxel (PTX) as neurotoxic agent, given expected axonal damage is quite relevant. We compared 2 groups (n = 12 each) of female Wistar rats: control (CTRL, vehicle treated, iv) and PTX (10 mg/kg, 1qwx4, iv). At the end of treatment, neuropathy development was verified via Dynamic test and nerve conduction studies (NCS) of caudal and digital nerves. 7 T MRI was performed on rat tails (paraffin fixed after sacrifice) to study caudal nerves and their anatomical relationship with adjacent structures. High resolution anatomical images were acquired by means of a T1w sequence with a voxel size of 50x50x50 μm3. Diffusion weighted images were acquired in five b-shells: b of 500, 2000, 4500, 6000, 8000 seconds*mm-2 with 15, 24, 33, 42, 51 isotropically distributed gradient directions and a voxel size of 125x125x125 μm3. Diffusion data were then fitted with Diffusion Tensor Imaging (DTI) standard model and with Neurite Orientation Dispersion and Density Imaging (NODDI) and Spherical Mean Technique (SMT) microstructural models.

Results: Dynamic test confirmed mechanical allodynia development ($P < 0.0001$) in PTX group, and NCS showed a moderate-severe axonal polyneuropathy. Therefore, we confirmed PTX group had a relevant neuropathy burden to be used as a test bench for 7 T MRI acquisitions.

Conclusions: Microstructural metrics allowed to decouple the intra/extracellular water component and evaluate their diffusivity to characterize axonal damage and to draw a parallel with NCS changes.

Keywords: 7 T MRI, CIPN, in vivo model, axonal damage, biomarker.

Poster No: 142 | **Ramipril prevents paclitaxel-induced peripheral neuropathy through AT2R involvement**

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Introduction: Paclitaxel (PTX)-induced peripheral neuropathy (PIPN), associated with neuropathic pain, could lead to decreased patient quality of life, decreased chemotherapy doses and cycles, or even therapy cessation. We evaluate the effect of a safe and cheap drug, the ramipril, an angiotensin-converting enzyme (ACE) inhibitor, in the prevention of PIPN. Previous studies reported the beneficial role of ramipril in attenuating neuropathic pain in several rodent models. Since years, a link between the angiotensin II type 2 receptor (AT2R) and neuropathic pain was revealed. Thus, we used AT2R-KO mice to further investigate the potential involvement of AT2R in the effect of ramipril.

Methods: PTX was administered by intraperitoneal (i.p.) injections in Swiss mice every other day during 8 days at an 8 mg/kg cumulative dose (2 mg/kg each injection). Ramipril was administered everyday by i.p. injections, beginning 24 hours before the first PTX injection, until 14 days following the last PTX injection. Development of PIPN was assessed by functional tests investigating motor performance, tactile and thermal sensitivity. Tissues (palm skin, sciatic nerve, dorsal root ganglia) were collected for morphological analyses.

Results: PTX mice developed tactile allodynia, without significant alteration of motor coordination or thermal sensitivity. A loss of myelinated fiber in sciatic nerves, a degeneration of dorsal root ganglion neurons but no significant loss of intraepidermal nerve fiber density characterized PIPN. Ramipril totally prevented functional and morphological alterations in PTX mice. The preventive effect of ramipril against tactile allodynia was completely lost in AT2R KO mice.

Conclusions: Our work highlights ramipril as a new potential preventive treatment of PIPN, and points out the role of AT2R in the neuroprotective role of ramipril of PIPN.

Keywords: Chemotherapy-induced peripheral neuropathy, paclitaxel, Ramipril, allodynia, angiotensin II type 2 receptor.

Poster No: 143 | Insights from proteomics: Characterization of the sciatic nerve of CMT1A rat

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Introduction: Charcot-Marie-Tooth-1A (CMT1A) is the commonest inherited disorder of peripheral nerves. It is caused by duplication of the PMP22 gene that plays an important role in myelin sheath physiology. CMT1A has a significant impact on the quality of life of patients. Treatments are limited by patient heterogeneity and incomplete understanding of the pathological mechanisms. The CMT1A rat is a valuable model to study CMT1A disease. It harbors three additional murine copies of Pmp22 gene, and faithfully reproduces the sensori-motor symptoms observed in patients. The present proteomic study aims to characterize the protein profile of the sciatic nerve of CMT1A rat model.

Methods: It was performed using distal sciatic nerve samples extracted from 3-months-old male CMT1A rats (n = 5) and WT (n = 5) rats. By SWATH liquid chromatography mass-spectrometry (LC-MS/MS) approach, 445 proteins mapped to Swissprot or trEMBL Uniprot databases were identified and quantified.

Results: Following statistical analysis, 153 proteins were significantly different ($P \leq 0.05$) between CMT1A vs WT groups. The majority of these proteins were overexpressed in CMT1A in comparison to the WT group. Ninety-nine proteins were upregulated in CMT1A (fold change [FC] > 2), whereas 7 proteins were downregulated in CMT1A (FC <0.5) group. Functional enrichment, using Gene Ontology, served to group the proteins based on their biological effects. Distinguished proteins were selected and their variation was analyzed in the scope of the CMT1A pathophysiology. Our results showed that young adult CMT1A rats develop compensatory mechanisms at the level of redox balance, protein folding, myelination, and axonogenesis. Notably, response to oxidative stress appears to be a significant feature of CMT1A, potentially playing a role in the pathological process.

Conclusions: Finally, this proteomic analysis of CMT1A sciatic nerve would improve the characterization of the CMT1A rat model, thus helping to reveal new molecular biomarkers/targets for diagnosis/therapy.

Keywords: Charcot-Marie-Tooth-1A, Sciatic nerve, PMP22, Oxidative stress, Proteomics.

Poster No: 144 | NT-3 gene transfer therapy attenuates muscle pathology in the GarsP278KY/+ mice model of CMT2D

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Introduction: The GarsP278KY/+ model is known best for its early onset neuropathic phenotype (1). Muscle involvement remains largely unexamined. NT-3 improves radial growth of muscle fibers through activation of Akt/mTOR pathway and stimulates the mitochondrial biogenesis regulator, PGC1α in neurogenic muscle. We further characterized muscle involvement for assessment of the efficacy of AAV1.tMCK.NT-3 gene therapy in this model.

Methods: Twelve GarsP278KY/+ mice at 4-6 weeks of age received AAV1.tMCK.NT-3 (1x1011 vg, IM); eight untreated GarsP278KY/+ mice served as control. At 12-weeks post gene delivery, oxidative

enzyme histochemical stains (SDH and COX) and molecular analyses for expression levels of PGC1α and oxidative phosphorylation-markers (COX1, COX3 and ATP5D) were performed on skeletal muscles.

Results: Enzyme histochemistry in the GarsP278KY/+ muscle revealed reduced SDH and COX activities, most prominent at the superficial zones of gastrocnemius which was reversed with AAV1.NT-3 gene therapy. Compared to age-matched wild-type muscle, PGC1α relative expression levels in the GarsP278KY/+ mutant were 5.7-fold higher with no sex difference ($P = 0.0289$) and COX1, COX3 and ATP5D transcripts were approximately half, 1/third and 1/sixth of the wild-type controls, respectively. Improvement in COX staining was reflected in COX1, COX3 and ATP5d expression levels following NT-3 gene transfer showing over 70, 40 and 50-fold increases in these transcripts ($P < 0.0001$) respectively, without sex difference. We found no significant change in PGC1α relative expression levels in GarsP278KY/+ muscles with treatment although a higher trend was seen in females compared to untreated cohort. Mitochondria copy number was higher in the untreated muscle from females, which was reversed with NT-3, representing a pattern seen in the wild type, favoring males.

Conclusions: These findings show that the muscle pathology developed later in life in GarsP278KY/+ mice are compatible with an ongoing myopathic process, associated with mitochondria dysfunction. AAV1.NT-3 gene therapy attenuates these abnormalities in muscle, which we report here as a novel finding.

References

1. Seburn KL, Nangle LA, Cox GA, Schimmel P, Burgess RW. An active dominant mutation of glycyl-tRNA synthetase causes neuropathy in a Charcot-Marie-Tooth 2D mouse model. Neuron. 2006;51:715-726.

Grant Support: Sarepta Therapeutics, Inc.

Keywords: CMT, Neuromyopathy, NT-3, Gene therapy, Gars.

Poster No: 145 | Novel DNAJB2 mutation in a CMT2 family with hearing loss and parkinsonism

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Introduction: Mutations in heat shock protein J1 gene (HSJ1), also called DNAJB2, were reported in families with autosomal recessive HMN/CMT2. We describe the clinical features of the first Italian family with CMT2 due to HSJ1 mutation.

Methods: Genetic screening of CMT2 patients was performed by using a probe-based customized NGS panel including 94 CMT disease genes. Mutation was validated by Sanger sequencing and segregation analysis. HSJ1-mutated patients were characterized clinically, electrophysiologically and by means of skin biopsies.

Results: Three affected sibs (a 58 year-old female and two males, aged 60 and 51 years, respectively) were found to carry a homozygous HSJ1 null mutation (c.144delG, p.Val49TrpfsTer25). The mutation segregated with the disease and was absent in a healthy sister. The unaffected parents were not consanguineous but were from a small village in Northern Italy. The disease manifested in the second decade of life and ran a slowly progressive course. Clinical examination showed mild-to-moderate distal paresis at upper limbs, a severe weakness of the thigh muscles and complete loss of movements in the foot and leg muscles. Joint position and vibration sense was reduced at lower limbs up to the ankle or knee. Deep tendon reflexes were absent. Interestingly, all patients had hearing loss and the proband also Parkinson disease (PD). Nerve conduction study was consistent with an axonal motor and sensory length-dependent polyneuropathy. Skin biopsy results were consistent with an absent protein expression at both western blot and immunohistochemistry analysis. Interestingly, in the proband's skin nerves we detected alpha-synuclein deposits as already seen in PD patients.

Conclusions: Our results broaden the clinical spectrum of the disease and provide evidence that HSJ1 mutations should be taken into account as another causative gene of CMT2 with hearing loss and parkinsonism. The mutation likely acts through a loss of function mechanism.

Keywords: CMT, HSJ1, skin nerves, parkinsonism.

Poster No: 146 | Do ankle kinematics predict CMTPedS outcomes in children with Charcot-Marie-Tooth disease type 1?

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Introduction: The Charcot-Marie-Tooth (CMT) Pediatric Scale (CMTPedS) measures impairment over multiple domains in children with CMT. It has been shown that a patient's ability to toe and heel walk relates to CMTPedS total score[1] but it remains unknown whether gait patterns can predict CMTPedS domain or total scores. The goal of this study was to examine the relationship between an important characteristic of CMT gait, ankle dorsiflexion (DF) in terminal stance (TST)[2], and CMTPedS outcomes in children with CMT Type 1 (CMT1).

Methods: A consecutive sample of 25 patients (20 male; mean age 14.0 years, SD 2.8, range 7-19) with CMT1 from a larger prospective study underwent comprehensive gait analysis and CMTPedS assessment by a trained clinician following standard procedures. Participants' limbs were grouped by their peak DF in TST (45-55% gait cycle) as having increased (>1SD above mean), typical (within +/-1SD of mean), or decreased (>1SD below mean) DF based on typically developing controls[3]. CMTPedS scores were compared among groups using chi-square tests.

Results: Ankle DF in TST was significantly related to long jump ($P = 0.001$), 6-minute walk test ($P = 0.008$), and total ($P = 0.02$) CMTPedS scores. It was not related to plantar flexion or dorsiflexion strength, balance, gait, hand dexterity, or vibration scores ($P > 0.10$).

Conclusions: Performance of the 6-minute walk test and long jump is generally lower for children with CMT1 who have greater DF than typical during the TST. This is consistent with our understanding that increased plantar flexor weakness leads to greater peak DF in TST and reduced step length, walking velocity and push-off power. Plantar flexor strength tended to be lower in the increased DF group (56% with CMTPedS score ≥ 3 vs 28% in the other groups). Since patients with increased DF in TST tend to have poorer function as reflected by CMTPedS, they may have different bracing and treatment needs.

References

1. Wojciechowski SA, Cornett K, Raymond J, et al. Gait patterns of children and adolescents with Charcot-Marie-Tooth disease. Gait Posture. 2017;56:89-94.

2. Õunpuu S, Garibay E, Solomito M, et al. A comprehensive evaluation of the variation in ankle function during gait in children and youth with Charcot-Marie-Tooth disease. Gait Posture. 2013;38:900-6.

3. Ounpuu S, Gage JR, Davis RB. Three dimensional lower extremity joint kinetics in normal pediatric gait, J Pediatric Orthop. 1991; 11:341-349.

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Keywords: CMT Type 1, CMTPedS, Gait Function, Peak dorsiflexion stance, Plantar flexor strength.

Poster No: 147 | A novel mouse model for the MPZ-D61N mutation identifies hyperglycosylation as a new pathogenetic mechanism in CMT1B

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Introduction: Mutations in the Myelin Protein Zero gene (MPZ), encoding P0, the major structural glycoprotein of peripheral myelin, are the cause of Charcot-Marie-Tooth (CMT) type 1B. CMT1B phenotype can vary considerably, from early onset and severe forms to late onset and milder forms. Despite these differences most mutations are dominantly inherited, suggesting diverse gain of function mechanisms. In recent years, misglycosylation (either gain- or loss-of-glycosylation) emerged as a novel pathomechanism encompassing several genetic disorders. The MPZ-D61N mutation, which causes a severe early form of CMT1B, determines the generation of a new N-glycosylation site, suggesting that hyperglycosylation may interfere with myelin formation.

Methods: To investigate how gain-of-glycosylation in P0 can cause neuropathy we established, using the CRISPR/Cas9 system, a new mouse model carrying the MPZ-D61N mutation. The phenotype was characterized via behavioral tests (rotarod, grip strength), electrophysiological analysis and neuropathology. Biochemical analysis, RNaseq and immunofluorescence on sciatic nerve were then used to dissect the underlying molecular mechanisms. Finally, myelinating dorsal root ganglia (DRG) explants cultures from WT and Mpz-D61N/+ embryos were also established.

Results: D61N/+ mice developed a tremor as early as P15 which worsened with age and correlated with a significant motor impairment on the accelerating Rotarod and a reduction in grip strength. All electrophysiological parameters were also significantly altered. The pathological analysis confirmed a severe dysmyelinating phenotype characterized by diffuse hypomyelination and focal hypermyelination. P0-D61N protein is properly trafficked to myelin where it is likely to cause myelin uncompaction. Myelinating DRG cultures replicate some of the abnormalities seen in vivo, suggesting that they may represent a valuable tool to investigate potential therapeutic approaches.

Conclusions: Collectively our data indicate that the MPZ-D61N mouse represents an authentic model of severe CMT1B affirming gain-of-glycosylation in P0 as a novel pathomechanism of disease.

Keywords: Schwann cell, CMT, myelin, gain-of-glycosylation, mouse model.

Poster No: 148 | Curcumin delivered by cyclodextrine-cellulose nanocrystals reduces oxidative stress and ameliorates the symptoms of CMT1A rat

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Introduction: Although Charcot-Marie-Tooth disease type 1A (CMT1A) is the commonest hereditary peripheral neuropathy, treatments are still lacking. It is caused by PMP22 gene duplication leading to sensori-motor impairments. Recently, oxidative stress was described as a feature of CMT1A disease. Moreover, as CMT1A has a genetic origin causing perturbations in protein expression, endoplasmic reticulum (ER) stress appears to be also an important feature of this disease. Curcumin has caught attention due to its neuroprotective properties, specifically against oxidative and ER stress. However, its use is limited by its unfavorable pharmacokinetics. Consequently,

curcumin-cyclodextrin/cellulose nanocrystals (Nano-Cur) were developed.

Methods: Curcumin bioavailability was tested after an intraperitoneal (i.p.) injection of Nano-Cur in WT rats. Moreover, Nano-Cur treatment was tested in vitro, in Schwann cells (SC) and SC/neuron cultures, as well as in vivo in CMT1A rats. Daily Nano-Cur treatment (0.2 mg/kg/day, i.p.) was administered for 8 weeks in 1-month-old male CMT1A and WT rats. The effects of Nano-Cur on CMT1A rats functional recovery, myelination, and oxidative stress were tested.

Results: In SC, reactive oxygen species were decreased and myelin basic protein expression was increased after Nano-Cur treatment. In vivo, Nano-Cur strongly enhanced the bioavailability of curcumin. Nano-Cur significantly improved sensorimotor functions (grip strength, balance performance, mechanical and thermal sensitivities) in CMT1A rats. We proved that markers of oxidative stress were increased in CMT1A vs WT rats, supporting its role in the pathological process. Interestingly, Nano-Cur displayed anti-oxidant activity through the activation of Nrf2, elimination of ROS, and increased expression of antioxidant enzymes (ex: peroxiredoxins-1, −5 and thioredoxin-1). Data extracted from our proteomic study revealed that Nano-Cur could alleviate ER stress by stimulating chaperon expression.

Conclusions: Taken together, Nano-Cur showed anti-oxidant and pro-myelinating activities, consequently improving the symptoms of CMT1A rats. Further studies are crucial to elucidate the effect of Nano-Cur on ER adaptive mechanisms in CMT1A disease.

Keywords: Charcot-Marie-Tooth-1A, Schwann cells, PMP22, Oxidative stress, ER stress.

Poster No: 149 | Update on the International Guillain-Barré syndrome Outcome Study (IGOS)

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Introduction: Guillain-Barré syndrome (GBS) is a rare immune-mediated polyradiculoneuropathy with a highly variable clinical course and outcome. A better understanding of the pathophysiology and predictors of disease course are necessary to develop better treatments and improve long-term outcome.

Methods: 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. 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 standardized 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: Since the start of IGOS in April 2012, the consortium has included 1981 patients, of whom 120 since February 2020. Of these patients, 146 (7%) were excluded because of alternative diagnoses (n = 103, of whom 61 have CIDP), insufficient data (n = 8) or protocol violations (n = 35). For the first 1000 patients, a biobank and electrophysiological database have been completed. For these patients, the available blood samples from entry or week 1 (n = 768) have been tested for five infections previously associated with GBS (*Campylobacter jejuni*, *Mycoplasma pneumoniae*, hepatitis E virus, Cytomegalovirus and Epstein-Barr virus), and are currently tested for anti-ganglioside antibodies. The electrophysiology data are available from 790 patients which have been classified according to the criteria of Hadden et al.

Conclusions: In IGOS clinical, electrophysiological and serological findings are combined in the largest database on GBS to date. At the PNS meeting we expect to have reached our final aim of 2000 inclusions and will present on the further planning.

Keywords: Guillain-Barré syndrome, IGOS, Disease course.

Poster No: 150 | Guillain-Barré syndrome following SARS-CoV-2 infection in the international GBS outcome study

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Introduction: The Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) pandemic has affected the entire world population. Several neurological disorders linked to this infection have been reported, including the Guillain-Barré syndrome (GBS). In this study, we investigated the occurrence of clinical and laboratory signs of SARS-CoV-2 infection in GBS patients included in the International GBS Outcome Study (IGOS) during the first months of the pandemic and described in detail their clinical phenotype and disease course.

Methods: Patients were included from January 30th, 2020 until May 30th, 2020 and were classified according to the SARS-CoV-2 case definitions of the European Center for Disease Prevention and Control and laboratory recommendations of the World Health Organization. All data were collected prospectively in accordance with the IGOS study protocol.

Results: Forty-nine GBS patients were included, of whom eight (16%) had a confirmed and three (6%) a probable SARS-CoV-2 infection. These patients frequently had a sensorimotor GBS variant (8/11, 73%) often with facial palsy (7/11, 64%), and all had a demyelinating electrophysiological subtype, which was significantly more often compared to the other patients included in the same time period: 8/8 (100%) vs 14/30 (47%), $P = 0.012$. Nine of the 11 confirmed/probable SARS-CoV-2 patients did not have serological evidence for other recent preceding infections associated with GBS.

Conclusions: We identified a confirmed/probable SARS-CoV-2 infection in 22% of the GBS patients during the first months of the pandemic in the context of a large international prospective cohort study. These patients shared similar features that were previously described in relation to other viral triggers for GBS. However, the number of patients with GBS after SARS-CoV-2 infection is very small in comparison to the infected population and this study was not designed to determine a causative relationship between GBS and SARS-CoV-2.

Keywords: Guillain-Barré syndrome, COVID-19, SARS-CoV-2, preceding infections, clinical phenotype.

Poster No: 151 | Treatment and clinical course of peripheral neuropathy associated with anti-MAG antibodies

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Introduction: Neuropathy associated with anti-MAG antibodies is typically associated with IgM monoclonal gammopathy and often follows slowly progressive course with worsening of sensory loss, ataxia, and mostly distal weakness. Aggressive immunosuppressive treatment may lead to more significant complication and morbidity than neuropathy itself.

Methods: Study included adult patients with peripheral neuropathy associated with high titers of anti-MAG antibodies who were followed at University of Pittsburgh Medical Center neuromuscular clinic between 2016 and 2020.

Results: There were 8 patients who were 75% men with mean age at onset at 59 (range 46 to 78), and mean follow-up of 10 years (range 3 to 22). All patients had IgM monoclonal gammopathy of uncertain significance, and none developed Waldenstrom's macroglobulnemia or other hematologic malignancies during follow-up. Three patients improved with immunomodulatory treatment, and one remained clinically stable after treatment was stopped. Symptoms stabilized without subsequent progression with immunosuppressive treatment in two patients, and two patients did not respond to immunomodulatory or immunosuppressive therapies and continued to slowly progress. Symptoms remained mild in two patients over 4 and 5 years of follow-up and did not require any treatment. Patients were treated with IVIG (n = 5, 3 improved, 1 stabilized), rituximab (n = 4, 1 stabilized), corticosteroids (n = 2), and plasmapheresis (n = 2, 1 improved). One patient who responded to IVIG did not tolerate IVIG taper and subsequently required walker for safe ambulation until IVIG was resumed when he was able to go back to work full time and remained stable during subsequent 7 years.

Conclusions: Clinical course in patients with anti-MAG neuropathy varies, and the pace of progression may be very slow. Selected patients with neuropathy associated with anti-MAG antibodies may benefit from immunomodulatory treatments with IVIG and additional studies are needed to identify patients who may respond to immunomodulatory therapies.

References

1. Nobile-Orazio E, et al. Brain. 2000;123 (Pt 4):710-7. doi: 10.1093/brain/123.4.710

2. Svahn J, et al. J Neurol Neurosurg Psychiatry. 2018;89(5):499-505. doi: 10.1136/jnnp-2017-316715

3. Ellie E, et al. J Neurol. 1996;243(1):34-43. doi: 10.1007/BF00878529

Grant Support: N/A.

Keywords: CIDP, Paraproteinemic neuropathy, Anti-MAG antibody.

Poster No: 152 | Long-term follow-up in anti-caspr1-associated paranodopathy: A monophasic disease?

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Introduction: Anti-Caspr1 (contactin-associated protein 1) antibodies of different IgG subclasses occur in Guillain-Barré syndrome (GBS)

and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), but because of a low prevalence, the clinical phenotype is not as clearly defined as in anti-contactin-1 and anti-neurofascin-associated nodo-paranodopathy. We therefore aimed to facilitate antibody screening and provide data on clinical features including long-term follow-up.

Methods: We used a self-established ELISA to screen for anti-Caspr1 antibodies including subclasses in a cohort of 60 patients with GBS, 30 patients with acute-onset CIDP, 115 patients with CIDP and 75 controls. Results were confirmed by cell-based assay and compared to previously assessed teased-fiber screening data. Follow-up sera were available in all seropositive patients. Clinical data were assessed retrospectively.

Results: We identified four anti-Caspr1 seropositive patients using ELISA and cell-based assay, of whom two showed clear paranodal binding to teased fibers and had been reported in a previous study. Clinical presentation was GBS in a patient with IgG3 subclass and acute-onset CIDP in three patients with predominant IgG4 subclass, with antecedent respiratory infection in all patients. Sera with a mean follow-up interval of 56 (18-79) months revealed a total decrease of the antibodies both in the GBS and acute-onset CIDP patients. Two of the latter (both young, male patients) had received rituximab, but remained seronegative despite an extended treatment interval of 14 and 26 months. All patients showed either clinical and electrophysiological amelioration or stabilization without further immunomodulatory treatment.

Conclusions: ELISA is a novel quick and sensitive tool in the diagnostic workup of anti-Caspr1-associated neuropathy. Here, anti-Caspr1-related disease was possibly triggered by antecedent infection and showed monophasic course even after prolonged disease in IgG4-seropositive patients. Early antibody detection and therapeutic depletion is crucial to prevent irreversible axonal damage resulting in disabling clinical residues. After stabilization, intra-individual serological follow-up could facilitate treatment reevaluation and reduction.

Keywords: paranodopathy, inflammatory neuropathies, Caspr, antibodies, ELISA.

Poster No: 153 | **Disease progression in Charcot-Marie-Tooth disease related to MPZ mutations: A longitudinal study using rasch analysis-based weighted CMT examination**

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Introduction: Mutations in the MPZ gene result in varied clinical phenotypes, ranging from severe, infant-onset demyelinating neuropathies to milder, adult-onset, axonal forms. Recent biological insights have led to a number of potential therapies for MPZ-related neuropathy; however, the paucity of longitudinal natural history studies has been a barrier to effective clinical trials. We have previously shown that Rasch analysis-based weighted CMT Examination Scores (CMTES-R) are sensitive in detecting clinical progression in CMT1A.

Methods: We report a 5-year longitudinal study evaluating change in the CMTES-R in patients with MPZ-related CMT.

Results: Baseline scores, and one, two, three, four and five-year CMTES-R scores were available for 141, 70, 45, 39, 34 and 32 patients, respectively. There was a steady increase in the CMTES-R, with mean CMTES-R scores (+/− SD) as follows: 14.89 +/− 7.41 at baseline, 14.92 +/− 7.38 at one year, 15.79 +/− 7.18 at two years, 15.64 +/− 7.59 at three years, 17.28 +/− 7.15 at four years, and 16.88 +/− 7.82 at five years. A mixed regression model showed significant change in CMTES-R at years two, four and five [mean change from baseline of 0.91 points at two years ($P = 0.036$), 2.4 points at four years (p = <0.0001) and 1.99 points at five years ($P = 0.0002$)]. Subgroup analysis revealed greater change in CMTES-R at two years in subjects with axonal as compared to demyelinating neuropathy [mean change of 1.81 points, ($P = 0.03$) vs 0.64 points, ($P = 0.36$)]. Patients with axonal neuropathy were older ($P < 0.0001$) and reported gait difficulty at a later age ($P < 0.0001$). Patients with a moderate baseline neuropathy severity also showed more notable change than those with mild neuropathy [mean 2 year change of 1.87 for baseline CMTES-R 10-20 ($P = 0.007$), vs 0.32 for baseline CMTES-R < 10 ($P = 0.66$)].

Conclusions: We conclude CMTES-R scores are sensitive to change over time in axonal forms of MPZ-related CMT.

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Keywords: CMTES-R, CMT1B, MPZ, Hereditary neuropathy, CMT.

Poster No: 154 | **Biallelic RFC1 repeat expansions in a WES-negative cohort of HSAN with cough**

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Introduction: Hereditary Sensory and Autonomic Neuropathies (HSAN) are a group of rare peripheral nerve disorders, resulting in length-dependent sensory loss, sometimes accompanied by neuropathic pain and autonomic dysfunction. Using high-throughput methods like whole-exome-sequencing (WES), the underlying genetic mutation can still not be identified in approximately 80-90% of HSAN patients. For the specific phenotype of HSAN with chronic cough genetic linkage was established with a locus on chromosome 3 but a causative gene or gene mutation were not identified.

Methods: In 2019, a new RFC1 intronic repeat expansion was linked to CANVAS (Cortese et al., 2019), and since then also with ataxia with persistent cough and sensory neuropathy, mimicking Sjögren's syndrome. Due to the presence of chronic cough we decided to investigate possible RFC1 repeat expansions in a cohort of WES-negative HSAN cough families.

Results: We identified biallelic RFC1 expansions of the AAGGG conformation in five out of eight investigated families, showing that RFC1 repeat expansions may play a significant role in HSAN with cough without primary ataxia. We are currently investigating nine additional families that will be presented in detail. Intriguingly, in several families with presumed dominant inheritance, we found a pseudo-dominant inheritance pattern, likely due to the relatively high carrier rate of RFC1 repeat expansions in the general population.

Conclusions: We conclude that biallelic RFC1 pentanucleotide expansions might be a relatively common cause of HSAN with cough and that a unique and clinically recognizable phenotype should prompt RFC1 genetic testing by routine diagnostic procedures.

Keywords: HSAN+cough, RFC1, genetic diagnosis.

Poster No: 155 | **Characterization of late onset CMT1B-P0P70S mouse model**

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Introduction: Charcot-Marie-Tooth disease type 1B (CMT1B), the second most common CMT1, is caused by mutations in the Myelin Protein Zero (MPZ) gene. MPZ mutations are usually associated with primary demyelinating CMT with early onset. But the substitution of proline by a serine in position 70 of MPZ gene (P70S) causes a later onset CMT1B neuropathy (also known as CMT2I), with extensive axonal loss but only marginal compact myelin involvement. Because axonal degeneration is uncoupled from myelin defect in CMT2I, analysis of the P70S mouse model could help us to understand how a mutation in myelin gene causes axonal neuropathy.

Methods: To study the mechanisms at the base of axonal degeneration in late onset CMT1B, we generated, using CRISPR/Cas9 technology, MPZ-P70S mutant mice. We characterized this model via behavioral tests, electrophysiological measurements (EMG) and electron microscopy. To investigate signaling pathways involved in P70S axonopathy, we also performed RNAseq analysis at 2-month-old.

Results: Up to 12 months, we could not observe an obvious phenotype. However, starting at 18-month-old, consistent with late-onset disease, we noticed clear signs of axonal degeneration. Indeed, morphological analysis of P70S sciatic nerve reveals a reduction of myelinated fibers. However, we did not notice compact myelin modification. Consistent with these observations, EMG measurement shows a reduction of compound motor action potential amplitudes but normal nerve conduction velocities. Despite these alterations, P70S mutants do not manifest any locomotor defects. Finally, RNAseq analysis indicates a possible alteration of the glycolytic pathway. This defect in metabolic support could be involved in CMT2I axonopathy.

Conclusions: The P70S mouse model appears to reproduce human neuropathy and could be useful to investigate the glial mechanism contributing to axon protection and/or degeneration.

Grant Support: Telethon.

Keywords: Charcot Marie Tooth, Schwann cells, axons, neuropathy, metabolic support.

Poster No: 156 | **Progressive brachial plexus enlargement as longitudinal biomarker in familiar amyloidotic polyneuropathy**

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Introduction: The most common manifestation of hereditary transthyretin amyloidosis (ATTRv, v for variant) in non-endemic regions is a length-dependent axonal sensorimotor polyneuropathy (PN). Recently, an enlargement of brachial plexus was demonstrated at nerve ultrasound (US) in patients with familial amyloid polyneuropathy (ATTRv-PN) but not in pre-symptomatic carriers pointing to brachial plexus enlargement as a possible morphological biomarker of disease progression. We now report on nerve US follow-up study in the same cohort of patients, in order to assess possible morphological changes during disease progression.

Methods: Follow-up US evaluation along the main nerve trunks was performed in both ATTRv patients and pre-symptomatic carriers with mutated TTR gene. Nerve cross-sectional area (CSA) was measured and compared to the baseline evaluation.

Results: Thirty-eight subjects (22 men and 16 women; mean age 59.2 years) were evaluated at follow-up. Among them 21 (55%) ATTRv subjects were diagnosed with axonal polyneuropathy, 17 subjects (45%) were pre-symptomatic carriers. Mean follow-up was 17.1 months. The brachial plexus CSA (measured in 18 subjects) significantly increased (23.8%) when considering the whole cohort ($P < 0.0001$) of patients, but also when considering only the ATTR-PN patients ($P = 0.008$) and the pre-symptomatic carriers group independently ($P = 0.012$). Notably, CSA at brachial plexus showed the same increasing rate between ATTR-PN patients and pre-symptomatic carriers. Changes in nerve CSA at other nerve sites did not survive at multiple comparison correction.

Conclusions: Brachial plexus enlargement in ATTRv patients and carriers is progressive and may be considered as a potential longitudinal morphological biomarker of both disease progression and, more importantly, of disease occurrence in pre-symptomatic carriers.

References

1. Salvalaggio A, Coraci D, Cacciavillani M, et al.

Keywords: Amyloidosis, Transthyretin, Brachial Plexus, Ultrasound.

Poster No: 157 | Stance and swing phase ankle phenotypes in children with Charcot-Marie-Tooth disease type 1

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Introduction: Charcot-Marie-Tooth disease (CMT) causes muscle weakness and associated gait deviations at the ankle. Understanding the variation in ankle function in both the stance and swing phase and how they combine has relevance for treatment decision-making. The purpose of this study was to evaluate the stance/swing phase ankle kinematics in children with CMT Type 1 (CMT1).

Methods: A consecutive sample of 25 patients (20 male; mean age 14.0 years, SD 2.8, range 7-19) with CMT1 were selected from a larger prospective study. All patients underwent gait analysis following standard procedures[1]. Each limb was classified into stance and swing phase ankle phenotypes based on peak dorsiflexion (DF) in terminal stance (TST) (45-55% gait cycle, GC) and peak sagittal ankle angle in mid-swing (70-90% GC) compared with mean values (+/− 1SD) from typically developing controls[2]. Groups were compared using ANOVA with Bonferroni-adjusted post-hoc tests and Fisher's exact tests.

Results: All combinations of stance/swing phenotypes were observed. Many patients had their right and left limbs classified into different stance (44%) or swing (36%) phase groups. The limbs with increased DF in TST had weaker PF strength ($P < 0.0001$), delayed peak DF ($P < 0.0001$) and greater knee flexion ($P < 0.001$) in stance. The limbs with increased PF in swing had reduced passive DF ROM ($P < 0.02$) and strength ($P < 0.03$). Walking performance was primarily related to stance phase ankle phenotype ($P = 0.0001$).

Conclusions: Patients with CMT1 may have ankle function deviations in stance and/or swing. Increased PF in swing can be due to dorsiflexor weakness and/or plantar flexor tightness, while increased DF during TST typically signifies plantar flexor weakness. Stance phase ankle phenotypes may help identify specific bracing needs for patients with similar drop foot presentation in swing and prevent "over" bracing in some and underbracing in others. Understanding associated

secondary gait deviations, such as increased knee flexion, provides further justification for treatments.

References

1. Davis RB, Ounpuu S, DeLuca PA. Analysis of Gait. In: Peterson DR, Bronzino JD, editors. Biomechanics: Principles and Practices. 2nd ed. Boca Raton: CRC Press;2014:1-13.

2. Ounpuu S. Gage JR, Davis RB. Three Dimensional Lower Extremity Joint Kinetics in Normal Pediatric Gait, J Pediatric Orthop 1991;11:341-349.

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Keywords: CMT Type 1, Ankle Phenotypes, Stance phase, Swing phase, Gait analysis.

Poster No: 158 | Distribution of sensory impairment in chronic inflammatory demyelinating polyneuropathy compared with axonal polyneuropathy and healthy subjects

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Introduction: Patients with typical chronic inflammatory demyelinating polyneuropathy (CIDP) show proximal as well as distal muscle weakness, whereas most of polyneuropathies have distal dominant symptoms. We studied distribution of sensory disturbance in typical CIDP and axonal polyneuropathies by measuring sensory threshold. We also examined age-dependent effects on sensory threshold in healthy subjects.

Methods: A total of 105 subjects (21 typical CIDP patients, 23 axonal polyneuropathy patients and 61 healthy controls) were included into this study. Control subjects were divided into young (< 50 years old) and elderly groups. Seven-parts of the body, including the forehead, limbs and trunk, were assessed, using von Frey Filaments (vFF), which detect twenty-levels of threshold (0.008-300 g).

Results: In normal controls, sensory thresholds became higher with aging at the index finger (young; 0.054 g, elderly; 0.21 g, $P < 0.001$) and first toe (young; 0.30 g, elderly; 0.78 g, $P < 0.05$). In CIDP and axonal polyneuropathy, vFF disclosed higher thresholds at the abdomen (CIDP; 1.4 g [$P < 0.01$], axonal polyneuropathy; 1.0 g [$P < 0.0001$], control; 0.36 g), index finger (CIDP; 0.41 g [$P < 0.05$], axonal polyneuropathy; 0.34 g [$P < 0.001$], control; 0.14 g) and first toe (CIDP; 27.8 g, axonal polyneuropathy; 9.7 g, control; 0.57 g, both $P < 0.0001$), compared with controls. CIDP was characterized by higher thresholds were disclosed at the forehead (CIDP; 0.10 g, control; 0.069 g, $P < 0.05$) and sternum (CIDP; 0.84 g, control; 0.26 g, $P < 0.01$), compared with controls.

Conclusions: Sensory thresholds physiologically increase with aging at the distal limbs. While both CIDP and axonal polyneuropathy have sensory deficits in the limbs, CIDP patients have prominent deficits at the trunk, suggesting non-length dependent sensory, as well as motor nerve involvement.

Keywords: chronic inflammatory demyelinating polyneuropathy, distribution, sensory test, von Frey Filament.

Poster No: 159 | Neurofilament light plasma concentration associates with age, weight and height in labrador retrievers

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Introduction: Plasma neurofilament light chain (pNfL) concentration is a biomarker for neuroaxonal injury and degeneration. Spontaneous canine neurodegenerative diseases are a valuable comparative resource for understanding similar human conditions and as large animal treatment models. Despite the pervasive use of dog models, the features of pNfL concentration in healthy dogs is not well established, limiting the utility of pNfL concentration in canine treatment models. Late-onset peripheral neuropathy (LPN) is a common genetic degenerative condition that is prevalent in the aged Labrador population (≥ 11 years old) and may serve as a spontaneous large animal model for inherited peripheral neuropathies in humans.

Methods: In this study, we present data reporting pNfL concentration trends in healthy purebred Labrador Retrievers, and preliminary data evaluating pNfL concentration in Labradors affected with LPN. Ninety-five Labrador Retrievers were enrolled. Of these, 55 were systemically healthy with no evidence of neuropathy, 18 were deemed stringent controls, based on age (≥ 11 years old), for analysis comparing pNfL concentration with 40 LPN affected Labradors.

Results: For the healthy dog population ($n = 55$), pNfL concentration was correlated to age, sex, neuter status, height, weight, body mass index, and coat color. We found that pNfL concentration increases with age ($P < 0.0001$), decreasing height ($P = 0.009$) and body weight ($P < 0.001$). These are similar to findings reported in humans. We did not find a difference in pNfL concentration between LPN affected Labradors ($n = 40$) and aged controls ($n = 18$) ($P = 0.30$).

Conclusions: The lack of a difference between these two study groups may be reflective of insufficient power; future work will focus on increasing these sample sizes. Overall, these data provide insight into variables that can affect pNfL concentration, and should be accounted for, in the canine model.

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Keywords: Neurofilament, Canine model, Inherited Peripheral Neuropathy.

Poster No: 160 | A novel PMP22 3'UTR deletion suggests a role of the 3'UTR in post-transcriptional gene regulation

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Introduction: Charcot-Marie-Tooth disease type 1A (CMT1A) accounts for 60% of all genetically confirmed CMT cases and it is caused by a 1.4 Mb duplication at the 17p locus which includes the PMP22 gene. Deletion of the same region causes another form of CMT (hereditary neuropathy with pressure palsies) and this copy number variation illustrates the importance of the correct PMP22 protein dosage in peripheral nerve function. Patients with CMT1A show phenotypic heterogeneity and genetic modifiers may account for this variable expressivity. Furthermore, evidence from rat Schwann cell studies suggests a role of the 3'UTR in the post-transcriptional regulation of PMP22 expression.

Methods: We present phenotypic and transcriptomic data from a two-generation family with a novel heterozygous 650 bp deletion in the PMP22 3'UTR. The 3'UTR deletion was identified through whole genome sequencing and the variant was confirmed with long range PCR and amplicon sequencing. PMP22 transcript analysis was done with Nanostring technology on punch skin biopsies containing epidermal myelinated nerve fibers, which were obtained from the proband using standard techniques.

Results: The proband and her daughter, both presented in early childhood with walking difficulties as toddlers and neurophysiological studies confirmed CMT1. The proband progressed significantly, such that she required a wheelchair by her 40s. The PMP22 3'UTR deletion, which encompasses the miR29a binding site, was a de novo occurrence in the proband and subsequently inherited in the affected daughter. PMP22 transcript levels were significantly elevated comparative to CMT1A disease controls even after standardizing for gliomedin. Transfection studies with a luciferase reporter assay showed an increased reporter activity in the presence of the deletion that was resistant to repression by a miR29-mimic.

Conclusions: In our study, we observed a severe CMT1 phenotype with significantly elevated PMP22 transcript levels, confirming the role of the PMP22 3'UTR in post-transcriptional regulation of gene expression.

References

1. Svaren J, Moran JJ, Wu X, et al. Schwann Cell Transcript Biomarkers for Hereditary Neuropathy Skin Biopsies. Ann Neurol. 2019;85(6):887-898.

2. Verrier JD, Lau P, Hudson L, Murashov AK, Renne R, Notterpek L. Peripheral myelin protein 22 is regulated post-transcriptionally by miRNA-29a. Glia. 2009;57(12):1265-1279.

Grant Support: This research was made possible through access to the data and findings generated by the 100 000 Genomes Project.

Keywords: Charcot-Marie-Tooth disease type 1A, Schwann cell, Whole genome sequencing, PMP22 transcript, miR29a.

Poster No: 161 | Management of ATTRv amyloidosis in Spanish Hospitals. Results of EMPATia study

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Introduction: Hereditary transthyretin amyloidosis (ATTRv) is a rare multisystemic disorder caused by mutations in the transthyretin (TTR) gene. Multidisciplinary follow-up of carriers and patients is crucial to enable early diagnosis and optimal outcomes. Limited data have been reported about the clinical management of ATTRv population in Spain, main related to endemic area.

Methods: EMPATia is a multicenter, cross-sectional, non-interventional, descriptive epidemiological study aimed to unfold clinical management of Spanish carriers and patients with stage I ATTRv amyloidosis diagnosed in the past year.

Results: A total of 7 hospitals (including 1 from each one of the endemic areas) across the country participated and collected information on their management of carriers and patients with ATTRv amyloidosis. Mean number of carriers in follow-up is 34.5 (min 15 - max 84); 46.1% are males, the age of carriers being followed-up ranges 19-81 years old. Maximum recorded follow-up for a carrier is 15 years. Mean age of carrier at diagnosis is 42.9 years old. Each site has a mean of 3 different mutations among their carriers. The most frequent mutations were V50M (100% sites), S97Y (75% sites) V142I (50% sites). Follow-up frequency is 12 months for stable carriers, 3-6 months for "unstable" carriers, 6 months for stable patients and 3-6 months for 'unstable' patients. Carriers are initially assessed by neurophysiology (Np), cardiology (C) neurology (N), Internal medicine (IM) and Genetic in most sites; the routinely follow-up includes N, NP, IM, C. During the last 12 months mean delay to diagnosis was 1.8 years, even though 63.2% of the patients had family history of ATTRv amyloidosis.

Conclusions: These results show that hospitals with experience in the disease that manage high number of subjects are organized for the assessment of this multisystemic disease, following recent international recommendations and providing better experience for patients and carriers.

Grant Support: Study funded and promoted by Pfizer Spain.

Keywords: ATTRv amyloidodis, Multidisciplinary, Follow-up, Management.

Poster No: 162 | **The evaluation of small fibers in asymptomatic carriers of Val30Met mutation: Results of three years follow-up**

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Introduction: Therapeutic advances in transthyretin familial amyloid polyneuropathy (TTR-FAP) extended life expectancy and delayed symptom progression. However, there is no consensus on carrier detection and follow-up. In this study, we followed asymptomatic carriers by different diagnostic tests.
Methods: The members of a family with Val30Met mutation were evaluated annually during three years by neurological examination, DN4 questionnaire, plasma creatine, brain natriuretic peptide, urine protein, electrocardiography, transthoracic echocardiogram and nerve conduction studies. The small fibers were assessed by sympathetic skin response test (SSR), heart rate variability (HRV), quantitative sensory testing (QST), in vivo corneal confocal microscopy (CCM) and skin punch biopsy.
Results: Five asymptomatic carriers were included to the study. The mean age at first evaluation was 39.6 (18-60) years and four of five were female. None of the carriers experienced nephropathy or cachexia. Nerve conduction studies, SSR and HRV were normal in all carriers during three years. Although echocardiography depicted mild insufficiency in mitral and tricuspid valves, there was no evidence supporting cardiac involvement of amyloidosis. Baseline DN4 scores were normal in all but baseline intraepidermal nerve fiber density (IENFD) and small fiber density assessed by CCM was low in two and in five carriers respectively compared to age-sex matched controls. Besides, IENFD decreased during the follow-up in all carriers. Although, baseline QST was normal in all, 40 year-old male carrier developed neuropathic pain symptoms and had an abnormal QST in the third-year follow-up when tafamidis initiated.
Conclusions: We showed that small fiber loss can be detected by CCM and skin biopsy long before symptom onset and was not correlated with the age of the carriers supporting the clinical heterogeneity in non-endemic regions. We also concluded that CCM, skin biopsy and QST are superior to HRV and SSR in the diagnosis of small fiber neuropathy during annual follow-up of carriers.
Grant Support: None.
Keywords: Familial amyloid polyneuropathy, Small fiber neuropathy, Skin biopsy, Quantitative sensory testing, Corneal confocal microscopy.

Poster No: 163 | **Sensory and innervation deficits reversed by a ketogenic diet in mice with type 1 diabetes**

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Introduction: Peripheral diabetic neuropathy (PDN) is a common complication of diabetes and etiology of small-fiber neuropathies. Hyperglycemia, advanced glycation end-product accumulation, and glucotoxicity all exacerbate PDN, resulting in aberrant sensation, numbness, chronic pain, and reductions in intraepidermal nerve fiber density (IENFD). A very-low carbohydrate, ketogenic diet (KD) has recently gained traction as a potential therapeutic intervention for various neurologic conditions. Here, we report that consumption of a KD can reverse sensory abnormalities and loss of IENFD in a C57Bl/6 mouse model of type 1 diabetes.
Methods: Diabetes was induced via intraperitoneal injections of streptozotocin (180 mg/kg) and mices were randomized based on mechanical paw sensitivity. Three weeks after diabetes induction, groups were fed either a KD or standard chow diet (n = 8-12). In a rescue paradigm, groups of mice were maintained as nondiabetic or rendered diabetic for 9 weeks. Groups were then either sacrificed for tissue harvest, or diabetic mice were fed a chow or KD for 4 additional weeks (n = 7-8).
Results: Diabetic mice developed severe mechanical allodynia within 2 weeks of streptozotocin-injection. Mice fed a KD had their mechanical allodynia reversed within one week after beginning the KD ($P < 0.001$). KD-fed mice also exhibited improvements in fasting blood glucose (FBG) and hemoglobin-A1C (FBG, $P < 0.05$; Hb-A1C, $P < 0.001$). Diabetic chow-fed mice had reduced IENFD compared to nondiabetic chow-fed mice ($P < 0.01$), and KD-fed diabetic mice were not significantly different from nondiabetic chow-fed mice. Diabetic mice fed a KD in our rescue paradigm developed immediate improvement in mechanical allodynia ($P < 0.001$), thermal sensation ($P < 0.001$), bodyweight ($P < 0.001$), and FBG ($P < 0.001$). Additionally, chow-fed diabetic mice displayed reduced IENFD as both 9 and 13 weeks, which was reversed by consumption of a ketogenic diet ($P < 0.001$).
Conclusions: These studies illustrate powerful benefits of a KD on improving blood markers of type 1 diabetes along with improvements in neuropathy-related sensation and epidermal innervation in mice.
Grant Support: 5R01NS043314-15.
Keywords: Diabetes, Neuropathy, Ketogenic Diet, Regeneration, Pain.

Poster No: 164 | **Role of Stress Exposure In Itch And Pain: Protocol For a Study in Atopic Dermatitis**

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Introduction: Growing evidence shows that symptomatology of atopic dermatitis (AD), such as itch and pain, can be exacerbated by acute stress. However, the influence of longer stress exposures over the symptomatology, sensory profile and skin innervation is not clear. This study aims to determine the effect of stress exposure over itch

and pain and whether long-lasting stress is related to the induction of a small fiber neuropathy (SFN) in patients with AD.

Methods: We have designed a study in adult patients with AD (N = 56) and healthy controls (N = 28), matched by age and sex. First, detailed information about psychological traits, including stress perception, will be obtained by online questionnaires in all participants. One week after, each subject will attend the study visit to evaluate their physiological skin characteristics, itch, pain and stress levels. Then, a first quantitative sensory testing (QST) will be performed, and after it, moderate acute psychosocial stress will be induced by the Montreal Imaging Stress Task (MIST). The MIST is a validated protocol consisting of a series of computerized arithmetic problems with social evaluative elements. Heart rate will be monitored, and several saliva samples will be obtained for measuring free cortisol levels. Immediately after, a second QST will be performed, and previous measurements will be repeated. Finally, blood samples and skin biopsies will be obtained for -omics and IENFD analyses. Machine learning methods will be applied for sub-grouping subjects according to stress exposure using several psychological and biological variables.

Results: Recruitment will begin as soon as possible according to COVID-19 outbreak in Chile. Results of questionnaires, QST, skin evaluation, and IENFD will be analyzed in parallel with the recruitment. Cortisol levels and -omics results are expected for 2022.

Conclusions: The in-depth study of this protocol shall provide crucial information to understand the potential neurobiological basis of dermatological diseases that may end in a SFN modulated by stress.

References

1. Mochizuki H, Lavery M, Nattkemper L, et al. Impact of acute stress on itch sensation and scratching behavior in patients with atopic. 2019.

2. Schneider G, Stumpf A, Burgmer M, Volmering L, Broecker P, Ständer S. Relations between a standardized experimental stressor and cutaneous sensory function in patients with chronic pruritus and healthy controls: an experimental case-c. 2018.

3. Dedovic K, Renwick R, Mahani NK, Engert V, Lupien SJ, Pruessner JC. The montreal imaging stress task: using functional imaging to investigate the effects of perceiving and processing psychosocial stress in the human brain. Journal. 2005.

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Keywords: Itch, Pain, Stress, Small fiber neuropathy, Atopic dermatitis.

Poster No: 165 | Scavenging methylglyoxal and preventing methylglyoxal-evoked nociception with a ketogenic diet

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Introduction: Methylglyoxal (MGO) is a reactive dicarbonyl produced as a byproduct from dihydroxyacetone phosphate during glycolysis that is strongly associated with chronic pain conditions including diabetic neuropathy, certain chemotherapy-induced neuropathies, and lumbar disc herniation. Subcutaneous methylglyoxal injection in humans elicits a robust pain response, which is recapitulated in rodent models of nociception. While a reaction between acetoacetate, a major circulating ketone, and MGO has been proposed since the 1930's, this reaction has only recently been characterized in vivo. Here, we investigated whether elevation of acetoacetate via consumption of a ketogenic diet (KD) scavenges MGO and prevents MGO-evoked nociceptive behavior in mice.

Methods: We fed male and female C57/Bl6 mice a KD prior to intraperitoneal (720 ng) or intraplantar (30 μg) MGO injection. We assessed pain behavior, blood-metabolite levels, and early activation in these animals.

Results: Intraperitoneal MGO injection elicited mechanical allodynia within 24 hours that persisted for at least 13 days. Mice fed a KD prior to MGO injection never developed mechanical allodynia ($n = 8$, $P < 0.001$). Chow-fed, MGO-injected mice exhibited significantly elevated circulating MGO levels 48 hours post-injection ($P < 0.0001$), which was not detected in KD-fed, MGO-injected mice. Additionally, there was a negative correlation between circulating MGO and β-hydroxybutyrate (Spearman's Method, $\rho = -0.86$, $P < 0.0001$). KD-fed mice exhibited reduced nocifensive behavior (ie, licking, lifting, biting) following intraplantar MGO injection compared to chow-fed, MGO-injected mice ($P < 0.0001$). While females exhibited marginally increased sensitivity to MGO ($P < 0.01$), consumption of a KD reduced MGO-evoked nocifensive behaviors in both sexes. Analysis of phospho-ERK (p-ERK) expression as a marker of spinal neuron activation revealed increased numbers of p-ERK+ neurons in the dorsal horn 10 minutes following MGO injection. This increase in p-ERK+ neurons was completely ameliorated in KD-fed mice.

Conclusions: We report consumption of a KD decreases circulating MGO levels perhaps through MGO-scavenging, reduces noxious-stimulus evoked activation of spinal neurons, and reduces MGO-evoked nocifensive behaviors.

Grant Support: 5R01NS043314-15.

Keywords: Pain, Methylglyoxal, Ketogenic Diet, Neuropathy.

Poster No: 166 | A description of Spanish ATTRv amyloidosis carriers. Results of EMPATia study

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Introduction: Hereditary transthyretin (ATTRv) amyloidosis is a rare multisystemic fatal disease with a heterogeneous clinical presentation caused by mutations in transthyretin (TTR) gene. Incomplete penetrance and unspecific initial symptoms convert the prompt diagnosis into a challenge. Red-flags recognition and detection of earliest symptoms of the disease in carriers are the key. EMPATia study aim to describe clinical characteristics of Spanish ATTRv carriers.

Methods: A multicentre, cross-sectional, non-interventional, descriptive epidemiological study in 7 hospital across Span, including sites in both endemic areas. Carriers of pathogenic mutations were included.
Results: 86 carriers were included, mean age was 45.5 years old (min 18 - max 81), 56.5% males, mean BMI 26.5 Kg/m2. 3 carriers (3.5%) were homozygotes and 1 (1.2%) was compound heterozygote. Frequency of included mutations among carriers was: V50M (77.9%), S97Y (10.5%), V142I (7.0%), others (4.7%). Most frequent carrier relationship to index patient was: son/daughter (36%), parent (14%), nephew/niece (12.8%) Carriers were from: Balearic Islands (32.6%), Huelva (16.3%), Barcelona (11.6%), Valencia (9.3%), Madrid (8.1%), Castellon (5.8%), Gerona (2.3%) and Alicante, Burgos, Ceuta, Cuenca, Toledo, Valladolid, Vizcaya (1.2% each) (Figure 1). When reviewing ATTRv amyloidosis red-flags, carriers presented most frequently: autonomic neuropathy (16.3%), digestive symptoms (15.1%), cardiac symptoms (11.6%), CTS (11.6%). Mean intraventricular septum was 12.2 mm; EF was 64.7%. Small fiber assessment with Sudoscan was: mean ESC Feet (77.1 μS) and mean ESC Hands (72.4 μS). Regarding Scales, mean NIS was 0.8 (min 0 - max 13), mean CCI was 0.4 (min 0 - max 3.0), mean Norfolk QoL-DN was 6.9 (min −2 - 46).
Conclusions: This is the first description of the Spanish ATTR-PN carrier population. While subjects are not considered patients, the presence of red-flags, calls for a closer further review of health records and multidisciplinary assessment of the carriers.
Grant Support: Study funded and promoted by Pfizer Spain.
Keywords: ATTRv amyloidosis, Carriers, Mutations, Red-flags.

Poster No: 167 | **Sensory neuronopathies: A case series**

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Introduction: Sensory neuronopathies are heterogeneous disorders of dorsal root ganglia. We describe clinical and laboratory features in a single-center series, including response to treatment and outcome.
Methods: We retrospectively included 54 patients meeting Camdessanché et al 2009 criteria for sensory neuronopathy. We classified patients according to their likely etiology and analyzed their demographic, clinical, neurophysiological, histological and spinal MRI features. We evaluated outcome with the modified Rankin Scale (mRS), and assessed the response to treatment.
Results: 54 patients were included (18 male; median age 54.5 years). The most common initial symptoms were hypoaesthesia, paraesthesia, ataxia and pain. Half of patients had a slow onset, >12 months before seeing a neurologist. We classified the etiology as possibly inflammatory (meaning nonspecific laboratory evidence of immune abnormality) in 18 patients (33%), paraneoplastic 8 (15%), autoimmune 7 (13%) and idiopathic 6 (11%). 31 patients received immune therapy of which 11 (35%) improved or stabilized. Corticosteroids were the most used treatment (24 patients) and cyclophosphamide had the highest response rate (3/6, 50%). At the final follow up (median 24 months) 67% had mRS ≥3 and 46% mRS ≥4, including 15% who died. Worse outcome was associated with generalized areflexia and pseudoathetosis by logistic regression, and with motor involvement and raised CSF protein by univariate analysis.
Conclusions: Sensory neuronopathies caused severe disability, especially in patients with generalized areflexia and pseudoathetosis. Of those without an obvious cause, most had some evidence of dysimmunity. Some patients had a positive response to immunotherapy, but rarely enough to improve disability much.
Keywords: Sensory neuronopathy, ganglionopathy, Sensory neuron disease, inflammation, immunotherapy.

Poster No: 168 | **A description of Spanish ATTR-PN amyloidosis patients. Results of EMPATia study**

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Introduction: Hereditary transthyretin amyloidosis (ATTRv amyloidosis) is a rare, fatal, multisystemic disease caused by mutations in the transthyretin (TTR) gene. The EMPATia study is the first epidemiological study aimed to describe stage I ATTRv patient population in Spain.
Methods: A multicentre, cross-sectional, non-interventional, descriptive epidemiological study, including endemic and non-endemic regions; to describe and assess stage I ATTRv amyloidosis patients diagnosed in the past year. Neurological and autonomic impairment, cardiological status and QoL where assessed.
Results: 19 stage I ATTR-PN patients diagnosed during the previous 12 months were included, mean age was 59.7 years old (min 37 - max 77), 57.9% males, mean BMI 25.4 Kg/m2. 1 patient (5.4%) was homozygote. Frequency of included mutations among patients was: V50M (84.2%), S97Y (5.3%), E109K (5.3%), others (5.3%). Mean age at onset of symptoms was 56.8 years old and mean age at diagnose was 58.9 years old. Patients were from: Balearic Islands (36.8%), Huelva, Madrid, Valencia (10.5% each), Caceres, Castellon, Lleida, Lugo y Vizcaya (5.3% each). When reviewing ATTRv amyloidosis red-flags, patients presented most frequently: sensorimotor PN (84.2%) autonomic neuropathy (73.7%), cardiac dysfunction (63.2%) and digestive symptoms (47.4%). Mean intraventricular septum was 15.2 mm; EF was 60.8%. Small fiber assessment with Sudoscan was: mean ESC Feet (54.7 μS) and mean ESC Hands (68.3 μS). Regarding Scales, mean NIS was 17.7 (min 0 - max 64.5), mean CCI was 2.7 (min 0 - max 9.0), mean Norfolk QoL-DN was 46.6 (min −0.5 - 123).
Conclusions: EMPATIa study represent the first description of stage I ATTRv patients diagnosed in the last year in Spain. The analysis assessed that time to diagnosis in this cohort is 1.8 years, revealing a high level of disease awareness. In addition, the results indicate that, as well as neurological impairment, cardiac dysfunction and digestive symptoms are the most frequent symptomatology.

Grant Support: Study funded and promoted by Pfizer Spain.
Keywords: ATTR amyloidosis, Patients, Stage I, Red-flags, Mutations.

Poster No: 169 | **ActiGraph monitors provide insight into daily activity of patients with CMT**

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Introduction: Charcot Marie Tooth disease (CMT) impairs balance and gait. Current CMT research lacks insight into the daily activity levels of individuals with CMT. Although the CMT Exam Score (CMTES) and CMT Functional Outcome Measure (CMT-FOM) have the ability to describe severity of the disease,1,2 they do not capture information about how disease affects an individual's daily activity. ActiGraph monitors can continuously record daily activity including steps taken, intensity of physical activity, sedentary periods, and sleep information.
Methods: Ten individuals (18-70 years) with a genetic confirmation of CMT were provided an ActiGraph activity monitor (wGT3X-BT) to wear continuously for 7 days following an in-clinic assessment. Participants were evaluated in clinic with the CMTES and CMT-FOM. The ActiGraph device recorded the amount of time worn, daily step count, and daily activity levels (sedentary/light/moderate/high intensity).
Results: A significant relationship was found between CMTES and sedentary activity; a higher percentage of sedentary activity is correlated with a more severe CMTES. However, no significant correlation was found between sedentary activity and BMI or age in this preliminary study. CMT-FOM correlated with steps taken per day; the walking tests in the CMT-FOM correlated with steps per day and percentage of sedentary activity.
Conclusions: This initial data suggests that ActiGraph data can be utilized to evaluate the daily physical activity of patients with CMT, and that disease severity of CMT could affect daily physical activity. Future studies with more patients will be needed to confirm these results and investigate the usefulness of longitudinal ActiGraph data.

References

1. Sadjadi R, Reilly MM, Shy ME, et al. Psychometrics evaluation of Charcot-Marie-Tooth Neuropathy Score (CMTNSv2) second version, using Rasch analysis. J Peripheral Nervous Syst. 2014;19(3):192-6.
2. Eichinger K, Burns J, Cornett K, et al. The Charcot-Marie-Tooth functional outcome measure (CMT-FOM). Neurology 2018;91(15):e1381-e1384.

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Keywords: Charcot Marie Tooth (CMT), ActiGraph, Activity.

Poster No: 170 | **Deep phenotyping Of CMT1A patients in a longitudinal prospective multicenter study (German CMT-NET Natural History Study)**

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Introduction: CMT1A is the most common form of hereditary neuropathy. No treatment is available. Trials are hampered due to insenstitve outcome measures.
Methods: 164 CMT1A patients were recruited and clinically examined applying a battery of 13 standardized clinical scales over two years within the Charcot-Marie-Tooth Disease Network (CMT-NET) at four university hospitals in Germany.
Results: We observed the following change over two years: CMT Neuropathy Score Version 2 (CMTNSv2) (16.54 to 16.90; $P = 0.0077$; 2.2% change), CMT Examination Score (CMTES) (11.42 to 11.79; $P = 0.0226$; 3.1%) and the CMTNSv2-Rash (20.46 to 21.01; $P = 0.0033$; 2.7%) showed a significant increase. Interestingly, only the moderately affected patients revealed a significant change of the CMTNSv2 (from 14.49 to 15.35; $P = 0.0481$). The Overall Neuropathy Limitations Scale (ONLS) exhibited a highly significant increase ($P = 0.0086$), as well as the 9 Hole Peg Test (9-HPT) ($P = 0.0073$), the 10 Meter Walk Test (10-MWT) ($P = 0.0271$) and the recorded step number (from 15.40 to 15.49; $P = 0.0267$). The Fatigue Severity Scale (FSS) indicated a significant increase from 4.58 up to 5.10 ($P = 0.0006$). The compound muscle action potential (CMAP) decreased from 4.39 to 3.26 ($P < 0.0001$). The other scales (SF-36, PSQI, BDI-II, ESS, Dynometry, Walk12, 6 MWT) did not display significant changes. The CMTNSv2 showed a strong positive correlation with the ONLS ($r = 0.71$), the 9-HPT ($r = 0.5$), the 10-MWT ($r = 0.48$) and the FSS ($r = 0.49$).
Conclusions: In this longitudinal 2 year multicenter standardized national history study of CMT1A patients in Germany, the CMTNSv2, CMTNSv2-Rash, CMTES, ONLS, 10 MWT, ONLS, 9-HPT and FSS showed a significant deterioration. These parameters may be useful to measure disease progression in CMT1A patients.

Poster No: 171 | **Epidemiology of chronic inflammatory demyelinating polyradiculoneuropathy in The Netherlands**

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Introduction: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare but disabling disorder that often requires long-term immunomodulatory treatment. Background incidence and prevalence rates and risk factors for developing CIDP are still poorly defined. In the current study, we used a longitudinal population-based cohort study in The Netherlands to assess these rates and demographic factors and comorbidity associated with CIDP.
Methods: We determined the incidence rate (IR) and prevalence rate (PR) of CIDP between 2008-2017 and the occurrence of potential risk factors in a retrospective Dutch cohort study using the Integrated Primary Care Information (IPCI) database. Cases were defined as CIDP if the diagnosis of CIDP was described in the electronic medical file.
Results: In a source population of 928 030 persons with a contributing follow-up of 3 525 686 person-years, we identified 65 patients diagnosed with CIDP. The overall IR was 0.68 per 100 000 person-years (95% CI 0.45-0.99). The mean PR was 7.00 per 100 000 (95% CI 5.41-8.93). The overall IR was higher in men compared to woman (1.03 95% CI 0.63-1.59 vs 0.34 95% CI 0.14-0.71)($P = 0.01$), and higher in elderly of ≥50 years compared to people <50 years (1.50 95% CI 0.97-2.21 vs 0.09 95% CI 0.01-0.31)($P < 0.01$). Twenty percent of CIDP cases had DM and 9% a co-existing other autoimmune disease.
Conclusions: These background rates are important to monitor changes in the frequency of CIDP following infectious disease outbreaks, new vaccination programs or other potential risk factors, and to estimate the social and economic burden of CIDP.
Grant Support: This study is funded by the Dutch Prinses Beatrix Spierfonds (grant application number: W.OR16-18).
Keywords: CIDP, Chronic inflammatory demyelinating polyradiculoneuropathy, Epidemiology, Incidence, Prevalence.

Poster No: 172 | **Efgartigimod in chronic inflammatory demyelinating polyneuropathy (CIDP): Interim baseline characteristics of the phase 2 ADHERE trial**

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Introduction: Efgartigimod is a human IgG1 antibody Fc fragment that blocks neonatal Fc receptor (FcRn). This blockage decreases recycling of immunoglobulin G (IgG) and thereby reduces pathogenic IgG autoantibody levels that may play a role in the pathogenesis of CIDP. Currently, not all patients with CIDP achieve clinically meaningful benefits from available treatments, which can carry long-term safety risks, high costs, and burdensome administration. The ongoing global ADHERE trial (NCT04281472) investigates the efficacy and safety of subcutaneous (SC) efgartigimod co-formulated with recombinant human hyaluronidase PH20 (efgartigimod PH20 SC) as a weekly ~6-mL dose treatment.
Methods: ADHERE aims to enroll adult patients with CIDP who are treatment naive or who have active CIDP and are treated with standard of care. Patients receiving therapy (ie, corticosteroids, intravenous immunoglobulin [IVIg]) at study entry were withdrawn during a ≤ 12-week run-in period. Following a ≤ 12-week open-label phase of 1000 mg efgartigimod PH20 SC weekly (Stage A), responders enter a 48-week randomized phase of weekly treatment vs placebo (Stage B). Approximately 130 patients will be enrolled in Stage B and included in the primary analysis. Here, we describe baseline characteristics of the patients currently enrolled in Stage A. An interim futility analysis was planned after the first 30 patients who completed Stage A.
Results: As of January 11, 2021, 32 patients (8 from USA, 24 from Europe and Middle East) were enrolled and had received efgartigimod PH20 SC. Prior to enrollment, 40.6% (13/32) were treatment naive, 21.9% (7/32) had received IVIg, and 37.5% (12/32) had received corticosteroids. In an early efficacy review before 30 patients had completed Stage A, the number of responders exceeded the predefined futility boundary; therefore, the study will continue as planned.
Conclusions: A phase 3 trial will investigate the effect of efgartigimod in CIDP. This trial is expected to be completed in 2023.
Keywords: chronic inflammatory demyelinating polyneuropathy, efgartigimod, neonatal Fc receptor, immunoglobulin G autoantibody, human IgG1 antibody Fc-fragment.

Poster No: 173 | **Efficacy and safety with >3 years of inotersen treatment for hereditary transthyretin amyloid polyneuropathy**

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Introduction: Hereditary transthyretin amyloidosis is a progressive, debilitating, and ultimately fatal disease that causes multisystem dysfunction. Here we report long-term efficacy and safety of inotersen, an antisense oligonucleotide inhibitor of transthyretin protein production, in patients with the polyneuropathy of hereditary transthyretin amyloidosis.

Methods: Patients who completed NEURO-TTR (NCT01737398) enrolled in its open-label extension (OLE; NCT02175004). Assessments included modified Neuropathy Impairment Score + 7 (mNIS +7), Norfolk Quality of Life-Diabetic Neuropathy questionnaire (Norfolk QOL-DN), Short-Form 36 Health Survey Physical Component Summary score (SF-36 PCS), and safety monitoring. Utilizing a data cutoff of July 28, 2020, efficacy is reported for patients from Europe and North America and safety is reported for all patients.

Results: Patients who switched from placebo to inotersen in the OLE (n = 39) demonstrated slowing of disease progression compared with natural history (based on NEURO-TTR placebo projection); mean change from NEURO-TTR baseline to OLE baseline/1/2/3 years for mNIS+7, Norfolk QOL-DN, and SF-36 PCS was 25.3/30.5/33.4/40.6, 11.6/9.0/12.3/17.3, and − 3.9/−3.5/−4.8/−4.6, respectively. Patients who received inotersen for 51 months (15 months in NEURO-TTR + 36 months in OLE; n = 67) continued to show benefit, with mean change from NEURO-TTR baseline to OLE baseline/1/2/3 years in mNIS+7, Norfolk QOL-DN, and SF-36 PCS of 4.0/9.5/17.8/19.2, 1.9/5.1/4.7/9.8, and − 0.4/−0.1/−0.4/−0.9, respectively. Six of 135 patients (4.4%) had serious treatment-related adverse events, and there were no treatment-related deaths. Under enhanced monitoring, there have been no reports of grade 4 thrombocytopenia or acute glomerulonephritis despite increased duration of exposure. No new safety concerns were identified.

Conclusions: Extended treatment with inotersen for more than 3 years slowed progression of the polyneuropathy associated with hereditary transthyretin amyloidosis, with greater functional stability observed in patients who initiated inotersen earlier. Long-term results further highlight the benefits of early treatment. Grade 4 thrombocytopenia and acute glomerulonephritis did not occur with enhanced monitoring.

Grant Support: This study was sponsored by Ionis Pharmaceuticals, Inc.

Keywords: hATTR, ATTRv, amyloidosis, inotersen.

Poster No: 174 | Axonal polineuropathy and the EMG parameters

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Introduction: The etiology of axonal polyneuropathy includes metabolic, toxic and paraneoplastic causes and a careful clinical and EMG evaluation plays a very important role in the diagnosis.

Methods: This is a prospective study in which patients with axonal polyneuropathy were included. All the patients underwent EMG examination that consisted on the study of bilateral median, ulnar, peroneus, tibial and suralis nerves with late responses study and concentric needle examination of the tibialis anterior and first interosesus. Also a DN4 questionnaire and a Total Neuropathy Score were implemented.

Results: The total number of cases was 100, mean age was 63.94 years, male/female ratio was 0.85. The patients were selected in order of referral at our practice. 46% of patients associated also a compression of the median nerve in the carpal tunnel. DN4 questionnaire and total neuropathy score had a very good correlation ($P = 0.0001$). The patients with lower amplitudines of the sural nerve had higher total neuropathy score ($P = 0.0001$), and also higher DN4 score ($P = 0.001$). Most interestingly the higher the total neuropathy score or DN4, the higher the probability of associating a median nerve compression in the carpal tunnel and also neurogenic abnormalities in the tibialis anterior ($P = 0.02$). Not lastly, there was a very significant correlation between the peroneal amplitudine and duration and the latency of the H reflex ($P = 0.0001$).

Conclusions: Because of the strong correlation between the EMG and total neuropathy score or DN4 questionnaire, these should be an usual tool in the diagnosis of polyneuropathy. Also the EMG examination should include the analysis of the late responses because they predict earlier the presence of polyneuropathy. Not lastly the diagnosis of compression of the median nerve in the carpal tunnel at patients over 60 years should alert to the possibility of an associated polyneuropathy and the EMG examination should be extended also to the lower limbs.

Keywords: polineuropathy, EMG, total neuropathy score.

Poster No: 175 | Monitoring of in vivo inflammation reveals PNS caspase-1 mediated inflammatory response in western diet fed rodents

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Introduction: Recently, studies have emerged indicating that low-grade inflammation may play an important role in the onset and progression of peripheral neuropathy in obese individuals. Several groups have reported that plasma levels of pro- and anti-inflammatory cytokines are dysregulated in neuropathic patients with prediabetes, type 1 and type 2 diabetes when compared to healthy controls. Current data has also suggested a role for gut microbiome in the development of peripheral pain, including chemotherapy-induced pain and fibromyalgia.

Methods: Our group has showed that modulation of gut microbiome in obese mice alleviated neuropathic indices, concurrent with changes in immune cell profile within the peripheral nerve system. In this model, butyrate - a microbiome metabolite - also decreased inflammatory markers in the dorsal root ganglia (DRG) of obese mice. In the present study, we used a caspase-1 biosensor murine model to monitor inflammation in vivo in a spatiotemporal manner in mice fed a Western diet (WD) and subjected to butyrate treatment.

Results: Immune cells' transcripts and pathways were differentially regulated in DRGs and sciatic nerves between normal chow and WD-fed animals. We also observed higher levels of caspase-1 mediated inflammation in vivo in obese mice. Ex vivo, we detected caspase-1 activation in metabolic and neural tissues, including heart and spinal cord.

Conclusions: We corroborated our findings by performing cytokine assay and immune cell profiling and we verified that butyrate may rescue inflammatory markers dysregulated in WD settings.

References

1. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860-7. doi: 10.1038/nature05485

2. Pop-Busui R, Ang L, Holmes C, Gallagher K, Feldman EL. Inflammation as a therapeutic target for diabetic neuropathies. Curr Diab Rep. 2016;16(3):29. doi: 10.1007/s11892-016-0727-5

3. Duksal T, Tiftikcioglu BI, Bilgin S, Kose S, Zorlu Y. Role of inflammation in sensory neuropathy in prediabetes or diabetes. Acta Neurol Scand. 2016;133(5):384-90. doi: 10.1111/ane.12474

4. Bonomo RR, Cook TM, Gavini CK, et al. Fecal transplantation and butyrate improve neuropathic pain, modify immune cell profile, and gene ex.

Keywords: obesity, neuropathy, butyrate, inflammation, caspase-1.

Poster No: 176 | Insights into the pathogenesis of POEMS syndrome through multiplex cytokine analysis

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Introduction: POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin lesions) is a rare multi-system disorder typified by a length dependent sensorimotor neuropathy. Pathogenesis is thought to be cytokine mediated, but the full repertoire of mediators have not been identified.

Methods: Meso Scale Discovery (MSD) platform was utilized to create a multiplex ELISA for 36 common cytokines, chemokines and proinflammatory markers implicated in immune mediated inflammatory disease. Sera from patients with POEMS syndrome pre and post treatment were tested against patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multiple myeloma and healthy controls.

Results: Interleukin-6 (IL-6), interleukin-16 (IL-16), interleukin-7 (IL-7) and vascular endothelial growth factor (VEGF) were significantly raised in pre-treated POEMS cases compared to disease and healthy controls (P-values <0.0001), as were the chemokines MIP-1a, MIP-1b, Eotaxin-3 and MCP-1 to a lesser degree. When measured in combination, this cytokine panel was more accurate at predicting POEMS syndrome than VEGF alone. IP10 and MDC were suppressed in POEMS syndrome and normalized post treatment. All forms of POEMS directed treatment (radiotherapy, chemotherapy and ASCT) significantly reduced cytokine levels by a similar degree. Relapsed POEMS syndrome results in significant increases of IL-6, IL-16, IL-7 and VEGF again supporting their pathogenic role. Regression analysis demonstrated that pre-treatment cytokine levels were not accurate predictors of neurological disability, disease progression or death in POEMS syndrome.

Conclusions: Stimulation of pre-B cell and plasma cells via IL-6, IL-16, IL-7 and VEGF appear consistent with the hypothesized pathogenesis of POEMS syndrome and the interplay between the malignant plasma cells and resultant cytokine storm. Chemokines additionally appear intrinsic to the inflammatory response. More research is required to determine the effect of suppressing such factors on the activity of disease.

Grant Support: Dr Keddie received funding from the ABN and Guarantors of Brain for his research fellowship.

Keywords: POEMS, Cytokines, VEGF, Pathogenesis.

Poster No: 177 | Addressing diversity, equity and inclusion within the inherited neuropathy consortium

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Introduction: The Inherited Neuropathy Consortium (INC) Diversity Committee has been formed 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.

Methods: Our committee is comprised of nine members including five 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. Current committee initiatives include (1) creating updated and more descriptive race/ethnicity sub-categories that can be used in the United States, the United Kingdom, Italy and Australia; (2) addressing myths and providing education to primary care physicians and neurologists about the prevalence of CMT in various populations; (3) validating CMT-specific virtual assessments; and (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.

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 and students.

Grant Support: The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065 712-01).

Keywords: diversity.

Poster No: 178 | LONGITUDINAL ASSESSMENT OF IOWA COHORT OF PATIENTS WITH SORD MUTATIONS

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Introduction: Sorbitol dehydrogenase (SORD) was recently identified as the most frequent gene causing recessive hereditary neuropathy1. There is also a potential pathway for treatment of this form of neuropathy by using aldose reductase inhibitors to normalize intracellular sorbitol levels. Detailed phenotype and natural history studies of SORD neuropathy is required to prepare for these forthcoming clinical trials. We seek to examine longitudinal change over time in a small cohort of patients with SORD neuropathy.

Methods: We reviewed longitudinal data on patients diagnosed with SORD neuropathy who had been seen at multiple visits in our clinic. Neurological exams were performed including the CMTESv2 as the primary detector of disease progression.

Results: Out of nine individuals in our cohort with SORD neuropathy, six had had multiple visits and evaluations. For those six, the average age at first exam was 29 years (range 15-66 years) with an average CMTESv2 of 4.5 (range 2-7). At the last exam, the average age of the cohort was 34 years (range 17-71 years) with the CMTESv2 average stable at 4.5 (range 3-7). Symptoms were predominantly or purely motor findings based on exam. The CMTESv2 remained in the mild range for this cohort.

Conclusions: In this small cohort of patients with SORD neuropathy, the CMTESv2 remained stable over time indicating that there may be a point of stabilization for these patients. The average age of this cohort changed by 5 years during their evaluation but the CMTESv2 remained datable during that time at 4.5 out of 28 point which is in the mild range for the duration. Further studies are required to compare our results with other patients with SORD neuropathy and to determine whether other outcome measures and biomarkers also demonstrate limited progression in patients.

References

1.Cortese A, Zhu Y, Rebelo AP, et al. Inherited Neuropathy Consortium; Biallelic mutations in SORD cause a common and poten

Grant Support: This consortium Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01); also supported by supplement award for SORD natural history study.

Keywords: SORD Neuropathy, CMTR, Disease progression.

Poster No: 179 | Digital Biomarkers of physical activity, gait and balance in Charcot-Marie-Tooth disease

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Introduction: Reliably and sensitively capturing the impact of therapeutic intervention on daily activity could supplement clinical outcome measures(COMs) for children and adults with Charcot-Marie-Tooth disease(CMT).[1,2,3] Advances in technology, specifically, wearable inertial sensors, provide opportunities to continuously monitor the impact disease has on individuals in their natural environment. Wearable sensors may also assess gait and balance in more sensitive ways than traditional COMs, serving as digital biomarkers. There are 2 aims of this study. Aim 1 is to characterize habitual physical activity

of individuals with CMT and Aim 2 is to validate digital biomarkers of gait and balance in individuals with CMT.

Methods: For aim 1, 500 participants aged over 6 years with CMT1A, CMT1B, CMT2A and CMTX1 will be recruited from 7 international sites. To assess physical activity, individuals with CMT will be asked to wear a wireless activity monitor (ActiGraph) for 7 days following their yearly in-person visit for 3 years. For aim 2, 300 participants will be recruited for assessment of gait and balance using the OPAL sensors and the APDM Mobility Lab. Assessments will be performed every 6 months to evaluate the sensitivity of these novel digital biomarkers to detect early changes in function. Data derived from these sensors will be compared with validated COMs (CMTPedS, CMTES, CMT-FOM).

Results: Data collection for the study began in November 2020 at 3 sites with ethics approval. To date, 31 participants have been recruited for Aim 1 and 25 for Aim 2. Preliminary baseline results for daily activity levels and gait and balance temporal spatial measures from the wearable sensors will be presented.

Conclusions: Understanding the validity and sensitivity of measures of habitual physical activity, using wearable sensors, may provide opportunities for novel outcome measures of function for clinical trials in children and adults with CMT.

References

1. Burns J, Ouvrier R, Estilow T, et al. Validation of the Charcot-Marie-Tooth disease pediatric scale as an outcome measure of disability. Ann Neurol. 2012;71(5):642-52.

2. Eichinger K, Burns J, Cornett K, et al. The Charcot-Marie-Tooth functional outcome measure (CMT-FOM). Neurology. 2018;91(15): e1381-e1384.

3. Sadjadi R, Reilly MM, Shy ME, et al. Psychometrics evaluation of Charcot-Marie-Tooth neuropathy score (CMTNSv2) second version, using rasch analysis. J Peripheral Nervous Syst. 2014;19(3):192-6.

Keywords: Charcot-Marie-Tooth disease, Digital Biomarker, Physical activity.

Poster No: 180 | Vasculitic neuropathy, disability and pain: Survey of 278 patients

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Introduction: We performed an anonymous survey of patients with vasculitis to assess self-reported disability and symptoms of peripheral neuropathy. Our goal was to estimate the prevalence and magnitude of disability from neuropathy as a pilot study for future research.

Methods: Patients with vasculitis (with or without neuropathy) were contacted through "Vasculitis UK" patient charity and invited to respond to an anonymous online survey. The survey included questions on the type and distribution of vasculitis, symptoms of neuropathy and validated scales assessing disability and pain.

Results: We received 278 responses. The median age was 61-70 years. The median duration of vasculitis was 4 years. Types of vasculitis included GPA (35%), MPA (10%), EGPA (9%), unspecified AAV (12%), GCA (11%), NSVN (2%) and other (21%). 34% had another disabling medical condition unrelated to vasculitis. Many patients reported persistent symptoms in feet or hands suggestive of neuropathy, including numbness (63%), pain (53%) or weakness such as foot-drop (41%). 52% reported difficulty walking because of numbness, leg weakness or imbalance. 68% had symptoms suggesting autonomic dysfunction. However, only 49% had been told by their vasculitis team that they had neuropathy. 213 patients (77%) met our definition of probable neuropathy: diagnosis with neuropathy by their vasculitis team and/or persistent numbness or weakness in feet or hands. Compared with 65 patients without any of these, patients with neuropathy had greater disability on inflammatory-RODS (mean 34.7 (SD 9.4) vs 40.6 (6.8) $P < 0.0001$) and INCAT disability scale (median 2 (IQR 1-4) vs 0 (0-2)) and greater pain on an 11-point numeric rating scale (mean 4.6 (SD 2.6) vs 3.4 (2.9) $P = 0.002$).

Conclusions: Among 278 patients with vasculitis, neuropathy was common but not consistently recognized by the treating clinician. Patients with neuropathy had greater disability and pain. We plan to develop a specific patient-reported outcome for vasculitic neuropathy.

Keywords: vasculitis, neuropathy, disability, pain, survey.

Poster No: 181 | Recessive Hereditary Motor Neuropathy Caused by an Ancestral 10-bp Repeat Expansion in VWA1

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Introduction: VWA1 (von Willebrand factor A domain containing 1) plays an important role in stabilizing the extracellular matrix structures. Here we provide evidence for a pathogenic role of biallelic VWA1 variants in hereditary motor neuropathy.

Methods: By interrogating the genome sequences of 74 180 individuals from the 100 K Genomes Project in combination with international gene-matching efforts and targeted sequencing, we identified 17 individuals from 15 families with an autosomal-recessive hereditary motor neuropathy and rare biallelic variants in VWA1.

Results: A single disease-associated allele p.(G25Rfs*74), a 10-bp repeat expansion, was observed in 14/15 families of European origin and was homozygous in 10/15. Haplotype analysis identified a shared 220 kb region suggesting that this founder mutation arose >7000 years ago. The age range of the cohort was between 6-83 years. The commonest disease presentation was an early-onset (mean 2.0 ± 1.4 years) non-length-dependent axonal hereditary motor neuropathy, confirmed on electrophysiology, which will have to be differentiated from other predominantly or pure motor neuropathies and neuronopathies. Because of slow disease progression, ambulation was largely preserved. Neurophysiology, muscle histopathology, and muscle MRI findings typically revealed clear neurogenic changes with single isolated cases displaying additional myopathic process. We speculate that a few findings of myopathic changes might be secondary to chronic denervation rather than

indicating an additional myopathic disease process. Duplex reverse transcription polymerase chain reaction and immunoblotting using patient fibroblasts revealed that the founder allele results in partial nonsense mediated decay and an absence of detectable protein. CRISPR and morpholino vwa1 modeling in zebrafish demonstrated reductions in motor neuron axonal growth, synaptic formation in the skeletal muscles and locomotive behavior.

Conclusions: We estimate that biallelic variants in VWA1 may be responsible for up to 1% of unexplained hereditary motor neuropathy cases in Europeans. The detailed clinical characterization provided here will facilitate targeted testing on suitable patient cohorts.

Keywords: Hereditary motor and sensory neuropathies, Nerve conduction studies, Genetics, Neuropathy, Whole-genome sequencing.

Poster No: 182 | GBS with treatment related fluctuations and acute-onset CIDP in the SID-GBS trial cohort

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Introduction: Guillain-Barré syndrome patients with treatment related fluctuations (GBS-TRF) and patients with acute-onset chronic inflammatory demyelinating polyneuropathy (A-CIDP) often need additional treatment. Therefore early recognition is important. The purpose of this study was to describe and compare patients with either GBS-TRF or A-CIDP in the SID-GBS trial cohort.

Methods: The SID-GBS trial compared the effect of a second IVIg course in GBS patients with a poor prognosis. All 298 included patients were treated with IVIg, the 93 (31%) patients with the poorest prognosis (mEGOS prediction model) were randomized for a second IVIg course or placebo. TRF was defined as clinical deterioration after initial improvement or stabilization following IVIg within 8 weeks of disease onset. CIDP was diagnosed according to the EFNS/PNS 2010 criteria. Results are descriptive as numbers are too small for statistical testing.

Results: Of the total cohort, 20 (6.7%) had a TRF and 14 (4.7%) were diagnosed with A-CIDP. In the poor prognosis group, 8 (8.4%) patients (3 were randomized to IVIg) had a TRF and 4 (4.3%) patients (2 were randomized to IVIg) were diagnosed with A-CIDP. Deterioration in GBS-TRF patients occurred after a median of 26 (range 11-44) days and in A-CIDP patients after a median of 33 (range 11-88) days. MRC sum scores were comparable in TRF-GBS and A-CIDP patients at entry, 1, 2, 4 and 26 weeks after onset, but worse at week 8 and 12 in de A-CIDP group. In GBS-TRF patients 25% needed mechanical ventilation, 55% had facial weakness and 65% had demyelinating nerve conduction studies compared to respectively 21%, 36% and 79% in A-CIDP patients.

Conclusions: A-CIDP occurred equally often in the poor prognosis group as in the total GBS cohort. The timing of the first deterioration or the clinical severity did not differ between GBS-TRF and A-CIDP.

Keywords: GBS, CIDP.

Poster No: 183 | Minimal clinically important difference of the first 1000 children assessed with the CMTPedS

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Introduction: The Inherited Neuropathy Consortium has now assessed 1000 children aged 3-20 years with the well-validated CMTPedS at a baseline visit. We have previously established the natural history over 2 years in 200 children. This larger population was evaluated to determine the minimum clinically important difference (MCID) of the CMTPedS to aid design of clinical trials.

Methods: Genotype-phenotype correlation of the first 1000 children will be evaluated from baseline data. Natural history data will be evaluated using the follow-up data available (up to 9 years). The MCID of the CMTPedS will be determined using an anchor-based approach with a patient impression of change question as an anchor. A distribution-based method of calculating the MCID will then be utilized as supporting evidence. Further evidence will be provided with the Delphi method using an expert panel in the CMTPedS.

Results: 1000 children aged 3-20 years (50% female) have been enrolled in this study and assessed with the CMTPedS at baseline. 53% of the children have CMT1A. CMTPedS scores ranged from mildly affected to severely affected in all types of CMT (CMTPedS score: 0-43) and CMT1A (CMTPedS score: 1-41) at baseline. Data cleaning and analysis are underway. Genotype-phenotype correlations, natural history data, and results for the MCID will be presented.

Conclusions: Understanding the natural history and MCID of the CMTPedS will promote robust design of clinical trials involving a sample size appropriate to detect clinically meaningful changes in participants.

References

1. Cornett KMD, Menezes MP, Shy RR, et al. Natural history of Charcot-Marie.

Keywords: Charcot-Marie-Tooth disease, Minimal Clinically Important Difference, Natural History.

Poster No: 184 | Something new about Bortezomib neurotoxicity

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Introduction: Bortezomib (BTZ) and Carfilzomib (CFZ) are proteasome inhibitors that represent the gold standard in the treatment of multiple myeloma. While both are very effective, they have different side effect profiles. In particular, BTZ induces peripheral neuropathy as a major side effect in a high percentage of patients, while this is only rarely observed with CFZ1. In this study, we investigated possible BTZ and CFZ off-targets able to explain the difference in their neurotoxicity profiles.
Methods: Off-targets were identified using SPILLO-PBSS, a software that perform a 3D in silico screening on a proteome-wide-scale2,3. The hypothesis was biologically validated in vitro in adult mice dorsal root ganglia primary sensory neuron cultures and in a cell free model of tubulin polymerization and depolymerization. NMR binding studies were performed to demonstrate the interaction with the identified off-target.
Results: Using an innovative in silico approach, we demonstrated that tubulin is a potential off-target of BTZ. A direct BTZ-microtubules interaction could inhibit the GTPase activity of tubulin, thus reducing microtubule catastrophe and increasing tubulin polymerization. In neuron cultures, BTZ, but not CFZ, induced neurotoxicity and increased the percentage of polymerized tubulin. Moreover, in a cell-free model of tubulin polymerization and depolymerization only BTZ slowed down the depolymerization of microtubules and reduced the free phosphate concentration released during GTP hydrolysis. Lastly, NMR binding studies clearly demonstrated that only BTZ is able to directly interact with both tubulin dimers and polymerized form.
Conclusions: In conclusion, our data for the first time gives evidence for a differential molecular mechanism of action of BTZ and CFZ that would explain their different side effect profiles: BTZ neurotoxicity is not related to its well-known proteasome inhibition, but to its ability to directly bind to tubulin, reducing microtubule catastrophe and consequently increasing the rate of polymerized tubulin.

References

1.Velasco R, Alberti P, Bruna J, Psimaras D, Argyriou AA. Bortezomib and other proteosome inhibitors-induced peripheral neurotoxicity: from pathogenesis to treatment. J Peripher Nerv Syst. 2019;24(Suppl 2):S52-S62. doi: 10.1111/jns.12338
2.Di Domizio A, Vitriolo A, Vistoli G, Pedretti A. SPILLO-PBSS: detecting hidden binding sites within protein 3D-structures through a flexible structure-based approach. J Comput Chem. 2014;35 (27):2005-2017. doi:10.1002/jcc.23714
3.Malacrida A, Rivara M, Di Domizio A, et al. 3D proteome-wide scale screening and activity evaluation of a new ALKBH5 inhibitor in U87 glioblastoma cell line. Bioorg Med Chem. 2020;28:115300

Keywords: Bortezomib and Carfilzomib, Neurotoxicity, Tubulin, Neuron cultures, In silico off-targets identification.

Poster No: 185 | Autoantibody screening in Guillain-Barré syndrome

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Introduction: Guillain-Barré Syndrome (GBS) is an acute inflammatory neuropathy with an heterogeneous presentation and pathogenesis. Serum antibodies against various gangliosides present in human nerves can be found in about half of all patients in the acute phase of GBS; but the target antigens remain unknown for most GBS patients. This study aims screen for autoantibodies targeting peripheral nerve tissue, cells and purified antigens in GBS.
Methods: Autoantibody screening was performed in serum samples from all GBS patients included in the International GBS Outcome study (IGOS) by 11 different Spanish centers. The screening included testing for anti-ganglioside antibodies, anti-nodo/paranodal antibodies, immunocytochemistry om neuroblastoma-derived human motor neurons and murine dorsal-root ganglia (DRG) neurons, and immunohistochemistry on monkey peripheral nerve sections. We analyzed the staining patterns of patients and controls. The prognostic value of anti-ganglioside antibodies was also analyzed.

Results: None of the GBS patients (n = 100) reacted against the nodo/paranodal proteins tested, and 61 (61%) were positive for, at least, one anti-ganglioside antibody. GBS sera reacted strongly against DRG neurons more frequently than controls both with IgG (6% vs 0%; $P = 0.03$) and IgM (11% vs 2.2%; $P = 0.02$) immunodetection. No differences were observed in the proportion of patients reacting against neuroblastoma-derived human motor neurons. Reactivity against monkey nerve tissue was frequently detected both in patients and controls, but specific patterns were only detected in GBS patients: IgG from 13 (13%) patients reacted strongly against Schwann cells. Finally, we confirmed that IgG anti-GM1 antibodies are associated with poorer outcomes independently of other known prognostic factors.

Conclusions: Our study confirms that (1) GBS patients display an heterogeneous repertoire of autoantibodies targeting nerve cells and structures, (2) gangliosides are the most frequent antigens in GBS patients and have a prognostic value, (3) further antigen-discovery experiments may elucidate other potential antigens in GBS.

Keywords: Guillain-Barré syndrome, autoantibodies.

Poster No: 186 | A novel surrogate marker of foot drop during gait in children with Charcot-Marie-Tooth disease

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Introduction: An observational study comparing timing of foot loading during gait barefoot and in different types of footwear in children with Charcot-Marie-Tooth (CMT) disease and typically developing (TD) controls.

Methods: Participants aged 4-17 years with CMT and age- and gender-matched controls walked over a 5.2 m electronic walkway barefoot and in different types of footwear - well-fitting athletic or school shoes (optimal) and slip-on type footwear (suboptimal). Six laps per footwear condition were recorded at self-selected pace per participant with a minimum of 30 footsteps per condition. Foot loading was measured as the difference between heel-on contact time and toe-on contact time. Footwear data from participants wearing ankle-foot orthotics were excluded.

Results: Sixty participants (30 CMT and 30 TD) were assessed; 42 males, mean age 11.5 (SD 3.7) years, CMT type 1A 57%; AFO n = 2. Foot loading in children with CMT was quicker barefoot and in all footwear types compared to TD controls, with a large effect size for barefoot and optimal footwear and moderate effect size for suboptimal footwear. Barefoot (mean difference [MD] 0.039, SE [SE] 0.001, 95% CI 0.036-0.042 second; $P < 0.001$, $d = -1.19$), optimal (MD 0.074, SE 0.004, 95% CI 0.067-0.081 second; $P < 0.001$, $d = -0.90$) and suboptimal (MD 0.033, SE 0.002, 95% CI 0.028-0.037 second; $P < 0.001$, $d = -0.58$).

Conclusions: This study found children with CMT exhibit faster foot loading than TD children irrespective of footwear worn. This may indicate dorsiflexor weakness in children with CMT, and therefore provide a surrogate measure of eccentric dorsiflexor strength and foot drop in this population. Future studies are required to validate timing of foot loading as a marker of dorsiflexor strength. Foot loading may be used to monitor effectiveness of disease-modifying interventions, including exercise and pharmaceutical agents.

Keywords: Charcot-Marie-Tooth disease, Gait, Foot loading, Dorsiflexor strength, Pediatric.

Poster No: 187 | Clinical characteristics of patients with transthyretin gene mutations and polyneuropathy manifestations of hereditary transthyretin amyloidosis

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Introduction: Hereditary transthyretin amyloidosis (hATTR or ATTRv [variant]) is a progressive and fatal disease caused by mutations in the transthyretin gene (TTR) that result in the deposition of misfolded TTR protein in major organs and systems, leading to multisystem dysfunction. Patients often experience a mixed phenotype of both cardiomyopathy and polyneuropathy. Early diagnosis, which can be facilitated with genetic testing, is key to achieving optimal patient outcomes.

Methods: This analysis utilized data from patients enrolled in the hATTR Compass program, a confidential genetic testing program offered in the United States (including Puerto Rico) and Canada for patients suspected of having hATTR with polyneuropathy or who have a family history of hATTR.

Results: Of 718 patients with a confirmed pathogenic TTR mutation, 345 had ≥1 symptom consistent with polyneuropathy. The mean age of these symptomatic patients was 69 years, most were male (59%) and African American (70%). A minority of patients reported a family history of hATTR (18%). Cardiologists and neurologists referred 65% and 8% of symptomatic patients to the hATTR Compass program, respectively. Patients who reported on pre-diagnosis experience (10%) saw an average of 2.4 doctors before genetic testing was performed. Patients presented with a variety of symptoms/manifestations including heart disease (53%), sensory dysfunction (44%), bilateral carpal tunnel syndrome (26%), motor dysfunction (26%), and autonomic dysfunction (24%). In this study, patients with the p.F53L mutation, generally considered a predominantly neurologic phenotype mutation, presented with heart disease along with neurologic symptoms.

Conclusions: Diagnosis of hATTR amyloidosis is challenging, as many patients see multiple doctors before being diagnosed, and many do not have a known family history of hATTR. Patients with hATTR often present with polyneuropathy and cardiomyopathy symptoms. Recognition of hATTR symptoms and performing genetic testing facilitates diagnosis of this debilitating and fatal disease.

Grant Support: This study was sponsored by Ionis Pharmaceuticals, Inc.

Keywords: Amyloidosis, Transthyretin, hATTR, ATTRv, Genetics.

Poster No: 188 | A novel gene-intergenic fusion identified in DHMN1: A new disease mechanism in motor neuron diseases?

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Introduction: Distal hereditary motor neuropathies (dHMN) are a group of neurodegenerative diseases with length-dependent axonal degeneration of the lower motor neurons leading to chronic disability. Our group has previously reported the pathogenic 1.35 Mb complex insertion mutation causing an autosomal dominant form of dHMN (DHMN1: OMIM % 182 960) in a large Australian family (Family-54). Here, we report a novel intergenic-gene fusion arising from the 1.35 Mb insertion. This finding represents a novel disease mechanism in motor neuron diseases.

Methods: In this project, we have generated induced pluripotent stem cell derived motor neurons (iPSC-MN) from DHMN1 patients (n = 3) and controls (n = 3) and have utilized RNA-sequencing to shed light on the patient transcriptome and potential functional pathways leading to axonal degeneration in DHMN1.

Results: Transcriptome data supported previous findings from our lab showing gene dysregulation caused by the 1.35 Mb insertion and has helped to further refine the list of potential causative candidate genes (MNX1, LMBR1, SHH, TMEM176B, LINC01006, UBE3C). Furthermore, we have identified a novel intergenic-gene fusion ("UBE3C-IntFus") involving the partial transcript of UBE3C (located in the DHMN1 insertion) fusing with upstream intergenic sequence within the DHMN1 locus. The presence of an in-frame canonical splice donor site within this intergenic sequence incorporated a pseudo-exon from the intergenic DNA sequence resulting in a novel aberrant fusion transcript being present in all the patients and absent from controls. This novel fusion transcript was validated in all patient iPSC-MN using Sanger sequencing of reverse transcribed template.

Conclusions: Although gene dysregulation cannot yet be excluded as a contributing factor of DHMN1 axonal degeneration, identification of this novel fusion transcript represents the primary pathogenic candidate for DHMN1. Follow-up studies using both in vivo (*C. elegans*) and in vitro systems will be essential for understanding the contribution of UBE3C-IntFus to DHMN1 pathogenesis. *Authors contributed equally to this work.

References

Drew AP, et al. A 1.35 Mb DNA fragment is inserted into the DHMN1 locus on chromosome 7q34-q36.2. Hum Genet. 2016;135(11): 1269-1278.

Keywords: RNA Sequencing, splicing, structural variation, iPSC, motor neurons.

Poster No: 189 | Correlation of fatigue and activity-dependent conduction block in neuromuscular disorders

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Introduction: Fatigue is one of the significant disabling problems in patients with neuromuscular disorders, such as demyelinating polyneuropathy and lower motor neuron disorders. Both nerve demyelination and increased axonal branching associated with collateral sprouting reduce the safety factor for impulse transmission and cause activity-dependent hyperpolarization and conduction block during voluntary contraction. Activity-dependent hyperpolarization and conduction block are assumed to be related with fatigue. The aim of this study was to investigate the correlation of activity-dependent conduction block induced by voluntary contraction and fatigue in demyelinating neuropathies and lower motor neuron disorders.

Methods: Seventeen patients with chronic inflammatory demyelinating polyneuropathy (CIDP), 14 with spinal and bulbar muscular atrophy (SBMA) and 16 healthy subjects were enrolled. Fatigue was assessed with the fatigue scale for motor and cognitive functions (FSMC). Compound muscle action potential (CMAP) recording after median nerve stimulation and nerve excitability testing were performed before and after maximal voluntary contractions in the abductor pollicis brevis (APB) muscle.

Results: CIDP and SBMA patients had prominent fatigue with higher FSMC motor scores ($P < 0.0001$), compared with controls. After voluntary contractions, CMAP amplitudes significantly decreased in 24% of CIDP and 7% of SBMA patients. The reduction of CMAP amplitudes was associated with the fatigue score on motor, but not on cognitive domains. After voluntary contraction, axonal hyperpolarization in the normal and CIDP/SBMA groups was disclosed by excitability testing.

Conclusions: In CIDP or SBMA, fatigue is caused by voluntary contraction-induced membrane hyperpolarization, when the safety factor is critically lowered due to demyelination or increased axonal branching, and this could be objectively assessed by CMAP amplitudes and excitability testing.

Keywords: fatigue, activity-dependent conduction block.

Poster No: 190 | **Comparison of patients with mutations associated with hereditary transthyretin amyloidosis and other neuromuscular diseases**

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Introduction: Hereditary transthyretin amyloidosis (hATTR or ATTRv [variant]) is a progressive, fatal disease caused by mutations in the transthyretin gene (TTR) and results in multisystem dysfunction. Early diagnosis, which can be facilitated with genetic testing, is key to achieving optimal patient outcomes.

Methods: This analysis utilized data from patients enrolled in hATTR Compass, a genetic testing program for patients in the United States and Canada suspected of having or who have a family history of hATTR with polyneuropathy. Next-generation sequencing was performed using an 81-gene panel associated with inherited neuromuscular disorders.

Results: 188 patients in the hATTR Compass program were referred by neurology specialists, tested positive for a gene mutation, and had no family history of hATTR. Of the 188 patients, 14 had a TTR mutation and 174 had non-TTR mutations. The most common TTR mutation was p.V142I (57%), which is typically associated with a cardiomyopathy phenotype. The most common non-TTR mutation was in the PMP22 gene (30%); this mutation is responsible for neuropathy arising from myelination errors in peripheral neurons. Compared to those with TTR mutations, the non-TTR mutation group had lower proportions of heart disease (29% vs 2%); bilateral carpal tunnel syndrome (43% vs 3%); and sensory (86% vs 21%), motor (64% vs 17%), and autonomic (43% vs 6%) dysfunction.

Conclusions: Diagnosis of hATTR is challenging because it can present similarly to other diseases. It is critical that clinicians recognize symptoms of hATTR and refer patients for genetic testing to facilitate diagnosis and initiate disease-modifying therapy for this fatal disease.

Grant Support: This study was sponsored by Ionis Pharmaceuticals, Inc.

Keywords: Amyloidosis, Transthyretin, hATTR, ATTRv, Genetics.

Poster No: 191 | **Siblings with hereditary transthyretin amyloidosis associated with F44S (p.Phe64Ser) transthyretin variant: A case report**

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Introduction: Hereditary transthyretin amyloidosis (hATTR or ATTRv [variant]), is a progressive, debilitating, and fatal disease. It is transmitted in an autosomal dominant manner and caused by mutations in the transthyretin (TTR) gene. TTR mutations result in the formation of insoluble amyloid fibrils that deposit in organs and tissues throughout the body. Patients often experience multisystem dysfunction including cardiomyopathy, polyneuropathy, and even oculoleptomeningeal manifestations. This case study describes siblings with amyloidosis arising from a pathogenic heterozygous mutation F44S in the TTR gene and who responded to inotersen treatment.

Methods: Patient 1 is a 31-year-old male who presented with a family history of hATTR and progressive dysesthesia at age 27. He initially experienced pain in both legs, bilateral handgrip and lower-limb weakness, vitreous opacificities, erectile dysfunction, gastrointestinal symptoms, and bilateral carpal tunnel syndrome (CTS). Patient 2, the brother of patient 1, is a 34-year-old male who initially experienced symptoms of progressive dysesthesia, vitreous opacificities, bilateral CTS, and diarrhea at age 31. Genetic testing, prompted by family history and symptomology, identified a heterozygous pathogenic TTR mutation F44S (p.Phe64Ser) in both patients. Abdominal fat pad biopsy demonstrated amyloid deposits.

Results: Since diagnosis, a multidisciplinary approach to care that includes a neurologist, geneticist, ophthalmologist, and cardiologist has been used. Their polyneuropathy was treated with diflunisal followed by inotersen ~2 years later. Since initiation of inotersen, patient 1 reported improvement in dysesthesia and strength, and patient 2 reported feeling "more hopeful" given the availability of treatment options. Both patients reported stabilization of disease, the ability to complete daily activities without limitations, and resolution of dysautonomia and gastrointestinal symptoms.

Conclusions: In siblings with the amyloidogenic mutation p.Phe64Ser, inotersen appeared to slow disease progression and subjectively improved select clinical parameters, suggesting that patients with this genotype may benefit from TTR gene-silencing treatment.

Grant Support: This study was sponsored by Ionis Pharmaceuticals, Inc.

Keywords: hATTR, ATTRv, amyloidosis, inotersen.

Poster No: 192 | **Anti-MAG antibody-related polyneuropathy: Clinical and electrophysiological characteristics of rapidly progressing cases**

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Introduction: Anti-myelin-associated glycoprotein antibody-related polyneuropathy (anti-MAG-PN) is characterized by IgM monoclonal gammopathy, IgM anti-MAG antibody, predominance in elderly men, and demyelinating polyneuropathy with a slowly progressive course. However, in recent years, clinical, immunological, and electrophysiological heterogeneity have been reported. The purpose of this study is to clarify clinical and electrophysiological characteristics of anti-MAG-PN patients with rapid progression which requires early therapeutic interventions.

Methods: Twenty anti-MAG-PN patients were retrospectively examined, including 16 males. The median age at initial evaluation was 69 years old. Progression rates (Overall Neuropathy Limitations Scale (ONLS) / disease duration (years)) at the time of the initial evaluation were calculated. The patients were classified into two groups by median of progression rate, and examined clinical, laboratory and electrophysiological findings at the initial evaluation.

Results: The median progression rate was 1.1 ONLS/year, and the patients were classified as a rapid progression group (progression rate≧1.1) and a slow progression group (<1.1). There were no differences between two groups in age at the symptom onset and initial evaluation, and gender. In the rapidly progressing group, a rate of patients with sensory impairment in the upper limbs was significantly higher ($P = 0.048$). There were no significant differences in anti-MAG antibody titer, serum IgM level, and cerebrospinal fluid protein level. Nerve conduction studies at the time of initial evaluation revealed no significant difference except for the terminal latency index of the ulnar nerve which was significantly lower in the rapidly progressing group ($P = 0.0066$).

Conclusions: Sensory impairments in the arm and progression of demyelination involving the nerve trunk at the initial evaluation suggest rapid disease progression and could be used as indicators for early therapeutic intervention. Rapid progression of demyelination from the nerve terminal to the nerve trunk can be associated with prognosis of anti-MAG-PN.

Keywords: anti-MAG antibody-related polyneuropathy, rapid progression, nerve conduction study, terminal latency index, nerve trunk.

Poster No: 193 | A study to establish the serological profile of Guillain-Barré syndrome following COVID-19

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Introduction: Reports have linked COVID-19 with Guillain-Barré syndrome (GBS). The overall UK GBS incidence did not increase as a consequence of the pandemic. The calculated maximum attributable risk was 1 GBS case per 62 500 COVID infections, much lower than for other infections(1). Another study reported a higher frequency of GBS in patients attending emergency departments with (0.15%) as opposed to without (0.02%) evidence of COVID-19 infection(2). Whether SARS-CoV-2 could potentially trigger GBS by inducing auto-antibodies or by generating a cytokine storm, leading to peripheral nerve injury, remains uncertain. Here, we aim to explore a possible immunological link between these pathologies.

Methods: Through UK-wide collaboration, we assembled a repository of GBS patients' biosamples ($n = 35$) linked to detailed clinical data. Control groups included patients with uncomplicated COVID-19 ($n = 40$) or chronic inflammatory neuropathies ($n = 41$). Samples were screened for auto-antibodies using ELISA, transfected-cell-based assays and myelinating co-cultures(3).

Results: Serological evidence of recent SARS-CoV-2 infection was more common in GBS (10/33, 30.3%) than in chronic neuropathy patients whose neurological disease onset preceded the pandemic (3/34, 8.8%). The frequencies of both ganglioside and nodal/paranodal antibodies in COVID/GBS and non-COVID/GBS were similar. We screened for novel peripheral-nerve-reactive antibodies using myelinating co-cultures, finding that 22.2% of the COVID/GBS patients presented IgG anti-nerve tissue antibodies, in comparison with a 12.5% of the non-COVID/GBS cases.

Conclusions: Evidence of recent SARS-CoV-2 infection was more common in incident GBS than in chronic neuropathy controls, and higher than contemporaneous estimates of population seroprevalence. However, this study is limited by the potential for ascertainment and recruitment biases and cannot reliably quantify risk or establish a mechanistic link. The clinical and serological profiles of COVID and non-COVID GBS patients were similar, and do not clearly establish the former as a distinct entity. The pathogenic relevance of peripheral-nerve-reactive IgG requires further investigation.

References

1. Stephen K, Julia P, Christina M, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome, Brain. 2020;awaa433. doi: 10.1093/brain/awaa433

2. Fragiel M, Miró Ò, Llorens P, et al. Incidence, clinical, risk factors and outcomes of Guillain-Barré in Covid-19. Ann Neurol. 2020. doi: 10.1002/ana.25987

3. Clark AJ, Kaller MS, Galino J, et al. Co-cultures with stem cell-derived human sensory neurons reveal regulators of peripheral myelination. Brain. 2017;140(4):898-913. doi: 10.1093/brain/awx012

Grant Support: COVID-19 Research Response Fund (University of Oxford).

Keywords: Guillain-Barré syndrome, COVID-19.

Poster No: 194 | Novel wearable sensors to examine physical activity in individuals with charcot marie tooth disease 1A

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Introduction: Background: Physical activity has been reported to be reduced in individuals with CMT and as a measure of function, it may

serve as an important endpoint for clinical trials. Physical activity has been measured using many different wearable devices that produce variables such as the time spent in various positions as well as the number of steps taken per day. The objective of this study was to examine physical activity and the relationships to measures of function and disease severity in individuals with Charcot Marie Tooth disease type 1A (CMT1A).

Methods: Participants were asked to wear BioStamp MC-10 sensors during assessments of mobility during an in-person research visit and then for the following 24 hours. These small, flexible sensors were applied using adhesive at the chest, thigh and lower leg. Data captured regarding the time spent resting, moving, and sleeping as well as the number of steps taken was recorded. Physical activity variables were compared to the CMT-Functional Outcome Measure (CMT-FOM) and measures of disease severity including strength and the CMT Exam Score (CMTES).

Results: 15 individuals (67% females) between the ages of 18-64 (mean age 37.3) participated in this study. Individuals moved a mean time of 150 minutes/day and rested a mean 781 minutes/day. Individuals took an average of 4416 steps/day. The number of steps was significantly correlated with the CMT-FOM ($\rho = -0.71$; $P = 0.003$) and overall lower extremity strength ($\rho = 0.54$; $P = 0.04$).

Conclusions: Physical activity, as measured by the number of steps taken, using adhesive wearable devices was associated with in-person measures of strength and function. Future studies of longer duration are needed to further examine physical activity as an endpoint for future clinical trials.

Grant Support: Charcot Marie Tooth Association.

Keywords: wearable sensors, physical activity, CMT.

Poster No: 195 | Small fiber onset neuropathy longitudinal impairments disability and mortality: A population-based case-controlled study

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Introduction: A population-based, case-controlled longitudinal study of neurological impairments, disability progression, and mortality in quantitative testing-confirmed small fiber neuropathy (SFN).

Methods: Patients with clinical SFN symptoms and abnormal quantitative SFN testing were compared to age and sex matched controls (January first, 1998 to December 31st, 2017).

Results: Ninety-four cases were identified, twenty-year average annual incidence 1.3/100000, prevalence 13.3/100000. All had onset neuropathic pain. Average follow-up was 6.1 years (0.7-43 years), mean onset 54 years (range 14-83). Female sex (67%), obesity (BMI average 30.4 vs 28.5), insomnia (86% vs 54%), analgesic-opioid prescriptions (72% vs 46%), and hypertriglyceridemia (180 mg/dL vs 147 mg/dL) were more common than controls ($P < 0.001$). Patients did not self-identify as disabled but had surrogate markers of disability with higher Charlson comorbidity indices (median 6, range 3-9). Classifications included: polygenic-idiopathic (70%); diabetes (15%); inflammatory-immune (9%); dysproteinemic (3%); AL-amyloidosis (1%); and genetic (2%). Onset median Composite Autonomic Severity Score (CASS) was 3, change/year 0.08 (range − 0-2.0). Onset median Neuropathy Impairment Score (NIS) was 2 (range 0-8), change/year 1.0 (range − 7.9-23.3). NIS and CASS change >1/year occurred in AL-amyloid, familial transthyretin amyloid, Fabry, uncontrolled diabetes, and Lewy body disease. Median age at death was 73 years vs controls 72 ($P > 0.05$) but death rates from symptom onset were higher in cases 19% (18/94) vs controls 12% (35/282) ($P < 0.001$) commonly linked to vascular diabetic complications, 50% (9/18).

Conclusions: Idiopathic SFN onset patients typically do not develop significant neurological impairments and disability but have multiple comorbidities needing attention with mortality implications. Specific causal forms develop greater neurological impairments and mortality and early diagnostic testing can facilitate interventional therapies, most commonly for diabetes.

Keywords: neuropathy, pain, disability, small-fiber, epidemiology.

Poster No: 196 | Investigating a candidate regulatory element in the GJB1 5' UTR

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Introduction: Mutations of GJB1 coding and non-coding regions cause the second most common form of Charcot-Marie-Tooth neuropathy, CMTX1. The non-coding GJB1 c.-103C > T mutation [chrX:71223249 (hg38)] is in exon 1b of the GJB1 P2 5′ untranslated region (5' UTR) and has been reported to cause CMTX1 in multiple unrelated families. GJB1 c.-103C > T is in an evolutionarily conserved region that is flanked by two non-pathogenic SNPs, c.-109C > T (rs746618959) and c.-102G > A (rs753207004).

Methods: To investigate whether the c.-108_-103 region is a regulatory element that may be disrupted by GJB1 c.-103C > T, a suite of luciferase constructs were generated. The GJB1 neural-specific P2 promoter and 5' UTR was inserted upstream of the firefly luciferase (FLuc) gene in the pGL4 vector, and the GJB1 3' UTR was inserted downstream of the FLuc gene. GJB1 c.-103C > T and GJB1 c.-108_-103del were then introduced separately into the GJB1-pGL4 vector. These vectors were separately transfected into the RT4 Rat Schwann cell line, using the pRLuc-TK vector as a transfection control. Relative expression was assessed by determining the ratio of FLuc:RLuc GJB1 c.-103C > T and GJB1 c.-108_-103del constructs and comparing this

to FLuc:RLuc ratios from the wild type GJB1 construct and an empty pGL4 vector.

Results: The GJB1 c.-108_-103del construct showed a 46% decrease (M = 0.54, SD = 0.19) in FLuc expression when compared to the wild type GJB1 construct ($P = .014$). The GJB1 c.-103C > T mutation resulted in an 88% decrease (M = 0.12, SD = 0.02) in FLuc expression when compared to the wild type GJB1 construct ($P < .00001$). Although GJB1 c.-108_-103del showed a significant decrease in expression, it remained significantly different to the c.-103C > T mutation ($P = .019$).

Conclusions: While this region may represent an important GJB1 regulatory element, the loss of expression due to the GJB1 c.-103C > T mutation requires further investigation to fully define a pathogenic mechanism that will enable suitable strategies for developing treatment therapies.

Keywords: Charcot-Marie-Tooth, CMTX1, GJB1, Connexin-32, Translation.

Poster No: 197 | Accelerate clinical trials in Charcot-Marie-Tooth disease (ACT-CMT)

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Introduction: With therapeutic trials on the horizon for Charcot Marie Tooth type 1A (CMT1A) reliable, valid, and responsive outcome measures of function are essential. The aims of the ACT-CMT study are to thoroughly validate and assess the responsiveness of 1. The Charcot-Marie-Tooth Functional Outcome Measure (CMT-FOM), 2. MRI of intramuscular fat accumulation (FF) as a lower limb motor biomarker and 3. in-vivo reflectance confocal microscopy (RCM) of Meissner corpuscle sensory receptor density, a sensory biomarker. The CMT-FOM is a reliable clinical outcome assessment developed to address the gap in clinically meaningful measurement of function in adults with CMT.

Methods: All sites in this multi-center, international clinical trial readiness study are actively recruiting and enrolling participants with CMT1A and unaffected controls. Serial assessments, up to 3 years, are being performed and include the CMT-FOM, 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.

Results: 169 individuals (136 CMT1A; 33 controls) have enrolled in the ACT-CMT study. The participants are 57% female with a mean age of 44.4 (range 19-72). The mean CMTES-R and CMT-FOM are 13.7 (range 1-25) and 23.9 (range of 7-43) respectively. The CMT-FOM is moderately correlated with the CMTES-R ($\rho = 0.62$, $P < 0.0001$), ONLS ($\rho = 0.52$; $P < 0.0001$), and the CMT-HI ($\rho = 0.62$; $P < 0.0001$).

Conclusions: Validated and responsive outcome measures for CMT1A are necessary for clinical trial readiness. Despite the challenges of the Covid-19 pandemic, individuals with CMT1A have enrolled and participated in ACT-CMT study visits. Summarized baseline data to date as well as correlation between the CMT-FOM, the CMTES and the CMT-HI will be presented.

Grant Support: Supported by NIH grant # NIH 1 U01 NS109403-02 to DNH.

Keywords: clinical trial readiness, outcome measures, Charcot Marie Tooth Diease, natural history.

Poster No: 198 | Optimal candidates of autologous stem cell transplantation for POEMS syndrome

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Introduction: Young patients with polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome are primarily treated with autologous stem cell transplantation (ASCT) because of its prompt and high efficacy. However, transplant-related mortality should be considered and there are some patients who can maintain long-term remission without ASCT. The aim of this study is to explore the optimal eligibility of ASCT for POEMS syndrome.

Methods: We evaluated patients with POEMS syndrome who were diagnosed at ≤70 years old, between 2000 and 2019. Overall survival (OS) were compared between patients treated with ASCT (ASCT group) and patients treated with other than ASCT (non-ASCT group) using a log-rank test. Stratified on prognostic factors, hazard ratio (HR) of ASCT group to non-ASCT group was estimated with Cox proportional hazards model. Referring to the results of previous reports, we included the following prognostic factors: age, performance status (PS), albumin level, estimated glomerular filtration rate, pleural effusion, pulmonary hypertension, complete hematologic response (defined as disappearance of M-protein) and complete VEGF response (defined as normalization of serum VEGF level) to the first-line therapy.

Results: A total of 104 POEMS patients (ASCT group, n = 57; non-ASCT group, n = 47) were evaluated. The 10-year OS were 77% in ASCT group and 66% in non-ASCT group ($P = 0.06$), respectively. ASCT group showed superior OS in patients with PS 3 or 4 (HR 0.07

[95% CI, 0.01-0.35]), non-hematologic response (HR 0.33 [95% CI, 0.13-0.85]), and non-VEGF response (HR 0.27 [95% CI, 0.10-0.73]).

Conclusions: Among young patients with POEMS syndrome, patients with poor PS or non-hematologic/VEGF response to the first-line therapy may be appropriate candidates for ASCT. The results of the present study can be useful in considering treatment strategies in POEMS syndrome.

Keywords: POEMS syndrome, autologous stem cell transplantation, overall survival.

Poster No: 199 | Examination of electrochemical skin conductance in chemotherapy-treated patients: Association with neuropathy status

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Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side-effect of neurotoxic chemotherapy treatment. It may induce small nerve fiber or autonomic symptoms which are difficult to measure objectively. Electrochemical skin conductance (ESC) may quantify sudomotor function and provide a surrogate marker of small fiber neuropathy. We aimed to identify the proportion of patients with ESC dysfunction and associations with CIPN characteristics.

Methods: 130 participants (mean age = 56.3 ± 13.2 years; F = 67%) were assessed cross-sectionally 9.3 ± 7.9 months post-neurotoxic chemotherapy. ESC was examined in the hands and feet using Sudoscan. CIPN severity was graded using patient-reported outcomes (EORTC-QLQ-CIPN20; PRO-CTCAE), a clinically graded scale (NCI-CTCAE), and a neurological examination score (Total Neuropathy Score-clinical version (TNSc)). Nerve conduction studies were completed for sural and tibial nerves. Rating scales were used to record pain (Pain Numeric Rating Scale [PNRS]) and autonomic symptoms (Survey of Autonomic Symptoms [SAS]). Patients were classified using Sudoscan normative ranges and differences in CIPN were investigated using Wilcoxon sign-rank tests.

Results: Among 130 participants (Taxane = 61%, Platinum-based = 24%, Bortezomib = 13%, Other = 2%), 42% recorded ESC dysfunction (n = 54). Patients with hand or feet ESC dysfunction demonstrated increased CIPN severity on NCI-CTCAE (dysfunction = 1.65 ± 0.91/no-dysfunction = 1 ± 0.89; $P < 0.0005$), PRO-CTCAE (dysfunction = 2.78 ± 2.07/no-dysfunction = 1.59 ± 1.69; $P = 0.001$), EORTC-QLQ-CIP20 (dysfunction = 16.9 ± 12.2/no-dysfunction = 9.02 ± 9.36; $P < 0.0005$) and TNSc (dysfunction = 4.94 ± 2.94/no-dysfunction = 3.45 ± 2.39; $P = 0.002$), but not with autonomic neuropathy (SAS) or pain measures (PNRS). Tibial amplitudes were reduced in patients with ESC dysfunction (dysfunction = 9.01 ± 3.95 mV/no-dysfunction = 11.63 ± 4.66 mV; $P = 0.008$) but not sural amplitudes (dysfunction = 10.97 ± 10.57uV/no-dysfunction = 12.3 ± 7.72uV; $P = 0.074$).

Conclusions: More than one-third of the participants presented with ESC dysfunction. Reduced ESC in the hands or feet was associated with increased CIPN severity but not autonomic neuropathy, highlighting the need for improved assessment tools to understand small nerve fiber dysfunction. Understanding CIPN phenotypes, including small nerve fiber and autonomic neuropathy, may inform suitable management strategies and minimize neuropathy burden.

Keywords: Electrochemical Skin Conductance (ESC), Sudoscan, sudomotor function, Chemotherapy-induced peripheral neuropathy (CIPN), Small nerve fiber.

Poster No: 200 | Electro-clinical profile of GDAP-1 related Charcot-Marie-Tooth disease

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Introduction: GDAP1 mutations have been associated with axonal Charcot-Marie-Tooth disease (CMT 2H,2 K), autosomal recessive demyelinating-CMT4A and autosomal recessive intermediate-CMTRIA.

Methods: Here we report the clinical and electrophysiological profile of 10 cases of genetically confirmed GDAP1-related CMT.

Results: Our patients (7 males, 3 females) had a mean age of 10.7 years (range 4-30 years). Disease onset was between 2 and 8 years, predominantly with walking difficulty and distal lower limb weakness. 6 cases had consanguineous parentage. Lower limb weakness was noted in all (distal-10, proximal-3) and upper limb weakness in 8 cases (all distal). Sensory examination was abnormal in 4 patients. All cases showed autosomal recessive inheritance. Nerve conduction study reports were available in 7 patients, of whom 3 had inelicitable potentials from all tested nerves. Among the remaining 4, axonal pattern was seen in 3 and an intermediate pattern in 1. Tibial and peroneal CMAPs were elicitable from only one (amplitude 1.2 mV) and two cases (amplitudes 1.3,0.1 mV) respectively, with mildly reduced velocity and mildly prolonged distal latencies. Upper limb CMAP amplitudes ranged from 1.3 to 8.3 mV and 2.7 to 5.3 mV while velocities ranged from 40.4 to 66.7 m/s and 50.0 to 64.3 m/s in median and ulnar nerves respectively. SNAP amplitudes ranged from 4.9 to 13.2micV, 4.7 to 13.6micV and 3.1 to 7.0micV and sensory conduction velocities ranged from 37.9 to 52.1 m/s, 36.0 to 51.3 m/s and 37.3 to 55.1 m/s in median, ulnar and sural nerves respectively.

Conclusions: Autosomal Recessive GDAP-1 CMT is an early onset, relatively severe hereditary neuropathy. Axonal sensori-motor neuropathy was the dominant electrophysiological pattern seen in our patients.

Keywords: Charcot-Marie-Tooth Disease, GDAP 1.

Poster No: 201 | **Intravenous immunoglobulin increases risk of thromboembolism in individuals with past history of cardiovascular disease: UK biobank cohort**

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Introduction: A risk prediction model including traditional cardiovascular risk factors for absolute risk of arterial and venous thromboembolic (TEE) event within the UK Biobank dataset established an association between IVIg exposure and prospective TEEs. We now investigate addition of past history of TEE as a predictor and whether treatment for the traditional risk factors mitigates the risk.
Methods: UK Biobank is a prospective study that recruited 502 647 individuals aged 40-69 from the UK between 2006 and 2010. Participants have been linked with Hospital Episode Statistics for England to obtain retrospective and prospective diagnosis and treatment data. Logistic regression was used to model the association between age, sex, hypercholesterolemia, hypertension, cancer diagnosis (excluding non-melanoma skin cancer), arterial or venous thromboembolism prior to recruitment, type 2 diabetes, smoking history (ever, never), IVIg exposure, current treatment with antiplatelets, statin, antihypertensive drugs, insulin, and oral hypoglycaemic medication, with prospective diagnosis of arterial or venous TEE.
Results: 17015 prospective cases of arterial or venous TEEs were identified. IVIg (n = 13) was associated with an increased risk in patients with a past history of any TEEs (n = 22 043). IVIg had the second strongest, statistically significant ($P < 0.05$) association (odds ratio (OR) =5.86) with the outcome. While being on IVIg and an antihypertensive or a statin were protective, this did not reach statistical significance.
Conclusions: In this large British prospective study, we identified an association between IVIg in patients with a past history of arterial or venous TEEs and future events. This study is limited by small numbers of patients on IVIg but did not show a mitigative effect of antiplatelets or a statistically significant protective effect of statins or antihypertensives. Future research into the mechanisms by which IVIg may be prothrombic in an already compromised state of endothelial dysfunction will help delineate the reason for the increased risk.
Keywords: inflammatory neuropathy, immunoglobulin, Risk, Thromboembolic Disease.

Poster No: 202 | **Investigating the pathogenic mechanism of the CMTX3 structural variation**

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Introduction: In 2016, a structural variation was identified as the cause of CMTX3. This mutation was characterized as an interchromosomal insertion whereby 78 kb of chromosome 8q24.3 was inserted into a gene desert at Xq27.1. However, the pathogenic consequence of this mutation remains unsolved. We hypothesize that this insertion may cause neuropathy via altering regulation of nearby genes. Our group has demonstrated that patient lymphoblasts display dysregulated expression of FGF13. However, given the tissue-specificity of transcriptional regulation, it is crucial that gene dysregulation is assessed within disease-relevant tissue. We have generated patient-derived peripheral nerve tissue to investigate the pathomechanism of CMTX3.
Methods: Patient fibroblasts were reprogrammed into induced pluripotent stem cells (iPSC). Immunofluorescence and quantitative PCR were utilized to confirm pluripotency. iPSC were then taken through a differentiation protocol to generate spinal motor neurons. An exploratory RNA-sequencing experiment was performed, comparing 1 patient sample to 3 controls, to search for genes that may show differential expression in neuronal cells.
Results: iPSC were positive for the common pluripotency markers, NANOG, OCT4 and SOX2. Differentiation of iPSC into spinal motor neurons was confirmed by the expression of HB9. Exploratory RNA-sequencing analysis did not reveal any clear candidate genes being dysregulated by the CMTX3 insertion. Interestingly, these preliminary results indicate that patient and control motor neurons display similar levels of FGF13 mRNA, in contrast to the FGF13 dysregulation previously observed in patient lymphoblasts.
Conclusions: CMTX3 has historically been classified as an intermediate CMT, although more recent evidence suggests a primarily demyelinating neuropathy. Therefore, to further investigate the pathomechanism of CMTX3, we are optimizing a protocol to generate patient-derived Schwann cells. CMTX3 is an excellent disease paradigm to enhance our understanding of the pathogenic consequences of intergenic structural variation, which is an important yet critically understudied mechanism of genetic disease.
Keywords: X-linked CMT, iPSC, Gene regulation.

Poster No: 203 | **Predictors of mechanical ventilation in the international Guillain-Barré syndrome outcome study (IGOS) cohort**

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Introduction: Guillain-Barré syndrome (GBS) is often complicated by respiratory insufficiency. We recently validated the Erasmus GBS Respiratory Insufficiency Score (EGRIS) in the International GBS Outcome Study (IGOS) cohort and showed that the model can be used in all patients with GBS or its variants to predict the risk of mechanical ventilation within the first week from hospital admission. The aim of this study was to (1) identify new predictors of mechanical ventilation, and (2) to determine if the EGRIS could be improved or simplified based on the IGOS data.

Methods: We used data from the IGOS-1500 cohort. Patients <6 years and patients from Bangladesh were excluded. We performed a univariate logistic regression analysis to define the relation between clinical factors, CSF features, nerve conduction study (NCS) subtypes and mechanical ventilation in GBS. We also attempted to simplify the EGRIS by including the sum of MRC scores for bilaterally measured individual muscles (score 0-10; MRC neck flexion 0-5) instead of the MRC sum score.

Results: We excluded 367 patients (n = 203 from Bangladesh, n = 40 aged <6 years, n = 124 because of protocol violations or other diagnosis). In the remaining 1133 patients 16% (n = 185) was ventilated. Factors related to ventilation in univariate analysis included the original EGRIS predictors, age, neck flexor strength and a demyelinating NCS. In multivariate analysis, individual muscle scores provided similar discriminative ability as the MRC sum score in the EGRIS: area under the curve (AUC) MRC sum score 0.852, shoulder abduction 0.838, hip flexion 0.842, neck flexion 0.833.

Conclusions: Inclusion of selected proximal muscles in the EGRIS provides similar discriminative ability and can improve clinical applicability. The IGOS data will be used to find other independent clinical and biological predictors of mechanical ventilation in GBS. Efforts to improve the existing EGRIS will be presented at the upcoming PNS meeting.

Grant Support: The IGOS is funded by the GBS-CIDP Foundation International, gain, Erasmus University Medical Center, Glasgow University, CSL Behring, Grifols, Annexon and Hansa Biopharma.

Keywords: Guillain-Barré syndrome, Respiratory insufficiency, Mechanical ventilation, Prognostic modeling.

Poster No: 204 | The ER stress transcription factor XBP1 modulates disease severity in Charcot-Marie-Tooth type 1B

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Introduction: Myelin protein zero (MPZ or P0) is the most abundant protein in the myelin of peripheral nerves. In humans, P0S63del and P0R98C mutations cause mild and severe Charcot-Marie-Tooth (CMT) type 1B, respectively. Similar demyelinating neuropathies occur in transgenic mice. Both mutant proteins are retained in the endoplasmic reticulum (ER), causing ER-stress resulting in an unfolded protein response (UPR). The UPR is characterized by the activation of PERK, ATF6 and IRE1 pathways. We have previously reported that the activation of downstream mediators of PERK is pathogenetic in P0S63del mice, but the role of the other UPR branches remains to be investigated.

Methods: To investigate the involvement of the IRE1 pathway in CMT1B, we generated new models of CMT1B mice 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 worsens hypomyelination as well as electrophysiological and locomotor parameters in young and adult P0S63del neuropathic animals. Interestingly, we observed strong upregulation of PERK and IRE1-mediated RIDD signaling in neuropathic animals lacking XBP1. This suggests that the activation of XBP1 targets plays a critical role in limiting P0S63del toxicity, which cannot be compensated by other stress responses. Similarly, ablation of XBP1 in P0R98C mice further worsens the dysmyelinating phenotype and neurophysiological parameters, proving our findings in another CMT1B model. Remarkably, in both P0S63del and P0R98C mice overexpressing XBP1, we observed an improvement of some disease parameters, such as myelin thickness and nerve conduction velocities.

Conclusions: Overall, these data demonstrate that the XBP1 pathway has an essential adaptive role in P0S63del and P0R98C neuropathies and suggest that activation of this pathway can attenuate the severity of CMT1B disease and could prove beneficial for other neuropathies characterized by UPR activation.

Keywords: XBP1, CMT, UPR, Myelin, Schwann cells.

Poster No: 205 | CMT Clinical Outcome Measures Training and Quality Assurance Protocol

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Introduction: Clinical outcome measures were validated to assess life-long disability in patients with Charcot-Marie-Tooth disease (CMT): CMT-Infant Scale [1], -Pediatric Scale [2] and -Functional Outcome Measure [3]. Clinical outcomes support clinical practice and research studies including the Inherited Neuropathy Consortium (INC). With disease-modifying trials imminent, clinical evaluators (CEs) need access to standardized training. Quality assurance must be ongoing, ensuring continual validity and reliability. We aimed to formalize a training and quality assurance program, facilitating standardized and reliable use of CMT clinical outcomes.

Methods: A training and quality assurance protocol was created, with users spanning global clinical and research practice through sponsored clinical trials. The protocol underwent nine rounds of review by eight experts. An online portal: www.clinicaloutcomemeasures.org was utilized to deliver the training program. Ten Master Trainers from Australia, USA, UK and Europe were identified, along with Co-Chairs for each of the clinical outcomes, to lead training workshops, Q&A sessions and certification of CEs.

Results: A 3-phase training and quality assurance plan was founded. Phase 1: "Self-directed learning" presents online clinical outcomes-related resources including training videos and protocols. Phase 2: "Training" was developed for INC CEs to receive in-person training and inter/intra-reliability testing with Master Trainers (conducted via video conference if necessary). Phase 3: "Monitoring" involves assessing CE's implementation of clinical outcomes and requires them to participate in refresher/annual training courses. Phases required for certification are contingent on the intended purpose of clinical outcomes use: Phase 1 for clinical practice/unfunded research studies; Phases 1-3 for INC-related studies; and individualized plans for sponsored clinical trials/funded research, specific to study needs (in consultation with clinical outcomes Co-Chairs).

Conclusions: The training and quality assurance protocol has been successfully launched to facilitate clinical trial readiness. Future work will focus on expanding the online portal to assist in automating quality assurance monitoring as our CE network grows.

References

1. Mandarakas MR, Menezes MP, Rose KJ, et al. Development and validation of the Charcot-Marie-Tooth Disease Infant Scale. Brain. 2018;141:3319-3330.

2. Burns J, Ouvrier R, Estilow T, et al. Validation of the Charcot-Marie-Tooth disease pediatric scale as an outcome measure of disability. Ann Neurol. 2012;71:642-652.

3. Eichinger K, Burns J, Cornett K, et al. The Charcot-Marie-Tooth Functional Outcome Measure (CMT-FOM). Neurology. 2018;91: e1381-e1384.

Keywords: Charcot-Marie-Tooth disease, Clinical outcome measures, Clinimetrics, Quality assurance, Clinical trials.

Poster No: 206 | Human patient SFPQ homozygous mutation is found deleterious for brain and motor development in a zebrafish model

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Introduction: SFPQ (Splicing factor proline- and glutamine-rich) is a DNA and RNA binding protein involved in transcription, pre-mRNA splicing, and DNA damage repair and it has been previously implicated in neurodegenerative disorders.

Methods: We used next generation sequencing (exome sequencing) to genetically investigate the patient. We then employed zebrafish modeling to run rescue experiments and examine the effect of the SFPQS660N mutant on the developing central nervous system (CNS).

Results: A homozygous p.Ser660Asn variant in SFPQ was identified through whole exome sequencing (WES) in an Italian woman presented a complex neurological phenotype with intellectual disability, peripheral neuropathy, bradykinesia, extrapyramidal rigidity and rest (heads) tremor and neuroradiological anomalies including thin dysplastic corpus callosum, hypomyelination and hypointensity of the globus pallidus and of the mesencephalic substantia nigra (resembling neurodegeneration with brain iron accumulation; NBIA). Using a zebrafish SFPQ genetic model we have showed that a rescue with this SFPQS660N mutant revealed robust defects in the developing central nervous system (CNS) of the embryos, including abnormal branching of the motor axons innervating body muscles and misfolding of the posterior brain neuroepithelium.

Conclusions: The defects hereby identified in the model organism indicate a potential contribution of the homozygous SFPQ p.Ser660Asn variant in some of the patient's neurodegenerative features, including the clinical parkinsonism and the NBIA-like pattern on brain imaging.

Keywords: SFPQ, cerebellar atrophy, zebrafish, motor diseases.

Poster No: 207 | Retrospective review of small fiber neuropathy in the pediatric population

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Introduction: Small fiber neuropathy (SFN) continues to remain underdiagnosed especially in pediatric population.

Methods: The aim of this study is to investigate various etiologies, clinical presentations, and laboratory findings in 16 pediatric patients referred to the neuromuscular clinic for the evaluation of chronic pain or autonomic symptoms. We retrospectively reviewed the medical records of 16 patients under the age of 18 years. Institutional review board approval was obtained.

Results: Out of the 16 patients, 69% were females with average age at diagnosis of 14 years. The mean duration of symptoms was 3.3 years. The course was chronic in all patients with 56% having non-length dependent presentation. The chief complaint was sensory symptoms in 81% and autonomic symptoms in the rest 19% patients. Overall, autonomic involvement including lightheadedness, dry eyes, dry mouth, hyper or hypohydrosis were seen in 75% patients. 25% of patients had Postural Orthostatic Tachycardia Syndrome (POTS) on the autonomic testing. All the 16 patients were clinically diagnosed with SFN based on the history and examination. Nerve conduction studies were performed in 75% patients and were normal. 81% patients had skin biopsy which were abnormal in all. Diagnostic work up showed immune mediated causes in 56% patients. The sensory neuropathy panel showed elevated IgM autoantibodies produced against trisulfated disaccharide IdoA2S-GlcNS-6 seconds (TS-HDS) antigen in 37.5% patients. The range of TS- HDS antibody in our patient population was 11 000-26 000 with normal values being less than 10 000. Concurrent EBV infection was found in 44% and oral HSV infection in 19%. Other causes were metabolic syndrome, diabetes, HPV vaccination and idiopathic.

Conclusions: Small fiber neuropathy should be in the differential for any patient presenting with pain or autonomic involvement. Early diagnosis will help in establishing etiology and appropriate treatment.

Keywords: Small fiber neuropathy, Postural orthostatic hypotension syndrome, autonomic symptoms, skin biospy, TS- HDS antibody.

Poster No: 208 | **High-resolution nerve ultrasound findings in hereditary neuropathy with liability to pressure palsies: phenotype-genotype correlations**

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Introduction: Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant demyelinating motor-sensory neuropathy characterized by recurrent peripheral nerve palsies at entrapment sites but may present as mild chronic sensory-motor polyneuropathy or entrapment neuropathy. Nerve high-resolution ultrasound (HRUS) documents focally enlarged nerves at entrapment sites, with some reports of enlarged nerves outside them, but studies are on small samples of patients with the classical PMP22 17p12 deletion.

Methods: We assessed 37 patients (27 families) with genetically confirmed HNPP harboring different PMP22 mutations, who underwent clinical assessment, nerve conduction study (NCS) and nerve HRUS of upper- and lower-limb nerves at various sites.

Results: The 17p12 deletion was found in 29 patients, the PMP22 p.Trp124Stop mutation was found in 3 patients, and the PMP22 c.78 + 1 g > c mutation in 5 patients. Nerve enlargement was mild and commonly found at classical entrapment sites, but very rare outside entrapment sites. HRUS findings significantly differed according to the PMP22 mutation, despite no NCS differences, but not to the clinical phenotype.

Conclusions: These findings offer a more complex view of the HRUS and NCS findings in HNPP patients, documenting the presence of phenotype-genotype correlations for HRUS but not NCS data. Enlargement was common at classical compression sites in PMP22 17p12 deletion, while HRUS findings differed for PMP22 point mutations.

Grant Support: N/A.

Keywords: inherited neuropathy, high resolution ultrasound (HRUS), nerve conduction study (NCS, genetics, phenotype.

Poster No: 209 | **Development and validation of an HSPB8 dual reporter system suitable for screenings**

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Introduction: Mutations in the small heat shock protein HSPB8 were identified as an underlying cause of CMT2L. The Hspb8_K141N knock-in mouse model mimics the CMT2L phenotype, whereas the knock-out model has no overt phenotype. Silencing of HSPB8 might therefore be a potential treatment strategy. To facilitate the development of therapeutic approaches, we generated a reporter cell line for HSPB8, allowing us to perform high-throughput screens to identify modulators of HSPB8 expression and stability.

Methods: A dual luciferase assay with deletion constructs of the human HSPB8 promoter region (−2616/+381) was used to identify the minimal promoter. This promoter was subsequently used to drive the expression of an HSPB8-GFP-P2A-mCherry construct. To validate its relevance, HeLa cells expressing the construct were subjected to different stresses and immunocytochemistry was used to assess the functional response.

Results: The full promoter region and different deletion constructs were assessed for their ability to drive luciferase expression. In combination with in silico analyses, we found two regions important for promoter activity which contained large enhancers and several putative transcription factor binding sites. By fusing these domains, we were able to halve the size of the promoter while remaining 90-95% activity. Rather than using a constitutive promoter, we used this truncated promoter to drive the expression of an HSPB8-GFP-P2A-mCherry construct, thereby more closely mimicking the endogenous situation. Upon induction of different stresses, responses one would expect for

HSPB8 were observed, validating its biological relevance and suitability as a screening platform.

Conclusions: We were able to narrow down the promoter of HSPB8 while remaining activity. This truncated promoter was used to drive the expression of an HSPB8-GFP-P2A-mCherry construct, which functionally behaved as expected. Because of the dual system, the reporter construct will allow us to identify both transcriptional inhibitors of HSPB8 as well as protein-destabilizers, which will be of great value for developing therapeutic approaches to treat CMT2L.

Keywords: Charcot-Marie-Tooth, small heat shock proteins, reporter cell line, screening.

Poster No: 210 | Myelopathy and polyneuropathy due to "laughing gas" inhalation

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Introduction: Nitrous oxide (N2O - commonly referred to as 'laughing gas') is a common medical inhalational anesthetic. However, recreational use via direct inhalation is becoming increasingly popular among the younger population. Abuse or long-term use can cause vitamin-B12 deficiency, and severe neural and psychiatric symptoms. We present 8 patients who developed subacute myelopathy and/or polyneuropathy after N2O overuse.

Methods: Case series.

Results: 7 men and 1 woman (19 to 35 years old). Time from the beginning of the symptoms to the admission at the hospital varied between 1 day and 2 months. All patients referred sensitive symptoms. All patients had walking difficulties with balance impairment. 5 also had a loss of strength. On examination, 7 patients had distal paresis. All patients had affected superficial and deep sensibility, and 3 also presented dysmetria. 3 patients had a recent COVID19 infection. EMG showed polyneuropathy in all the patients. Full-spine MRI showed subacute myelopathy located in the posterior columns in 4 patients. Blood test showed decreased vitamin B12 or high homocysteine and/or methilmalonic acid in 7 patients. Lumbar puncture was performed in 5 patients. 2 showed lightly increased proteins. Patients were treated with intramuscular vitamin B12 when it was low, and pregabalin for the sensory disturbances. One patient was also treated with intravenous immunoglobulins. The 4 patients who had a control visit 1 to 5 months after admission presented symptoms and abnormalities in the examination.

Conclusions: Recreational use of N2O has increased worldwide in the past 10 years, potentially due to its easy access and the false perception that it is completely innocuous. N2O exerts neurotoxicity though inactivation of cobalamin, leading to demyelination. Both central and peripheral nerve system affectation is increasingly reported. It is mandatory to raise awareness about the potential harm of the drug in order to reduce the number of cases.

Keywords: nitrous oxide, drug abuse, peripheral neuropathy, myelopathy, Vitamine b12.

Poster No: 211 | Nerve excitability and motor unit number estimation: Early biomarkers of nerve involvement in ATTRv

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Introduction: Gene silencing treatments for hereditary transthyretin amyloidosis (ATTRv) have recently been developed with dramatic improvements observed in patient outcomes. However, the optimal time to initiate treatment is not yet known. The aim of this study is to explore the pathophysiological progression of neuropathic features of ATTRv using nerve excitability and motor unit number estimation.

Methods: We prospectively recruited 14 symptomatic patients and 7 asymptomatic carriers with varied TTR mutations and compared these to 21 healthy controls. Nerve excitability properties of ulnar motor and sensory axons, and ulnar-ADM motor unit number estimation were collected.

Results: "Fanning in" of threshold electrotonus was observed in the motor axons of symptomatic ATTRv patients, suggestive of membrane depolarisation. Motor unit number estimation demonstrated a significant reduction in mean unit number between symptomatic and asymptomatic ATTRv patients ($P = 0.04$). Within the symptomatic cohort the mean unit number decreased with increasing FAP stage and PND score. Significantly increased hyperpolarising current/threshold gradients were seen in sensory axons between symptomatic ATTRv patients and healthy controls ($P = 0.002$), suggesting that upregulation of inwardly rectifying conductance may underlie sensory symptoms and neuropathic pain in ATTRv amyloidosis.

Conclusions: These findings suggest that ulnar nerve excitability and motor unit number estimation could be used as a tool to identify early nerve disease in ATTRv and monitor progression.

Keywords: Amyloidosis, Nerve excitability, Motor unit number estimation, biomarker.

Poster No: 212 | Exploiting allotypic determinants in the IgG1 constant domains to assess the pharmacokinetics of intravenous immunoglobulin treatment

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Introduction: Response to intravenous immunoglobulin (IVIg) treatment in patients with Guillain-Barré syndrome (GBS) is highly variable. Earlier reports indicate that serum immunoglobulin G (IgG) levels after IVIg are related to clinical outcome in GBS, yet these levels only partly reflect the true pharmacokinetics (PK) because IVIg cannot be distinguished from endogenous IgG. We aimed to address this limitation and developed new assays to differentiate between endogenous and IVIg-derived IgG in serum to specifically monitor the PK of IVIg in GBS patients.

Methods: ELISAs were developed that allow quantitative measurements of the polymorphic determinants G1m(a), G1m(f) and G1m (x) using monoclonal anti-allotype antibodies. IVIg-derived IgG was quantified in post-treatment serum from GBS patients via measurements of IgG1 allotypes in individuals not expressing this allotype. As a calibrator, an IVIg product was used.

Results: The specificity of anti-G1m(a), anti-G1m(x) and anti-G1m(f) antibody assays was sufficient to measure IVIg concentrations as low as 0.1 mg/mL in control sera from individuals not containing the respective markers. Out of 28 GBS patients who were serotyped, 27 patients were eligible for IVIg monitoring via one or two genetic markers, depending on the patient phenotype. Inter-run variability and background was low across the assays. The correlation between anti-G1m(a) and anti-G1m(x)-adjusted IgG levels (IVIg as reference) was high in 32 post-IVIg serum samples from 17 patients with the G1m(f, non-x, non-a) phenotype. Longitudinal monitoring of IVIg PK in five GBS patients showed differences in clearance of total IgG vs IVIg-derived IgG, indicating that in a subset of patients endogenous IgG production does not remain constant over time.

Conclusions: Anti-IgG1 allotype assays can discriminate between endogenous and IVIg-derived IgG in GBS patients treated with IVIg. These novel assays will be an imperative tool in understanding the variability in IVIg PK and treatment response of all patients treated with IVIg.

Grant Support: This study is funded by the Dutch Prinses Beatrix Spierfonds (grant application number: W.OR19-24).

Keywords: Guillian-Barré syndrome, IVIg, Pharmacokinetics, Allotype, Immunoglobulin G.

Poster No: 213 | Genetic and functional characterization of a novel HINT1 variant with a potential founder effect in Lithuania

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Introduction: Recessive loss-of-function variations in HINT1 are associated with a peculiar subtype of Charcot-Marie-Tooth disease: neuromyotonia and axonal neuropathy (NMAN; OMIM[137200]). With 24 causal variants identified all over the world, HINT1 is among the most common causes of recessive neuropathy. The majority of patients carry, in compound heterozygous or homozygous state, an ancient Slavic founder variant (c.110G > C, p.Arg37Pro) that spread through Europe and to the Americas.

Methods: In five Lithuanian patients from three families carrying a novel c.299A > G (p.Glu100Gly) HINT1 variant, we performed haplotyping analysis to determine a potential founder effect. Additionally, using yeast and cellular models, we investigated the effect of the missense variation on HINT1 protein stability and function.

Results: All patients and unaffected carriers share a common haplotype surrounding the c.299A > G HINT1 variant, suggesting that it originated from the same ancestral allele. Genetic complementation testing in HNT1 knockout yeast demonstrated that the p.Glu100Gly protein is (at least partially) stable in yeast and retains activity. However, in patient cells, the missense variant causes complete protein degradation, supporting a loss-of-function pathomechanism in line with known pathogenic variations.

Conclusions: Our findings broaden the genetic epidemiology of HINT1 neuropathy and have implications for the molecular diagnostics of inherited peripheral neuropathies in Lithuania and beyond. Moreover, the functional characterization in yeast provides mechanistic insights allowing patient stratification for future treatment strategies.

Grant Support: Research Foundation-Flanders (FWO): research grant #G049217N (to A.J.); postdoctoral fellowship to K.P.; pre-doctoral fellowship to S.A.B. and L.M.

Keywords: Charcot-Marie-Tooth disease (CMT), Neuromyotonia and axonal neuropathy (NMAN), HINT1, Lithuania, founder variant.

Poster No: 214 | Predictors of prolonged duration of mechanical ventilation and mortality in patients with Guillain-Barré syndrome from a tertiary hospital from south

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Introduction: Nearly one third of the patients with Guillain-Barré syndrome (GBS) require ventilatory assistance, the duration of which is variable. There are no studies from India to predict the duration of ventilatory requirement in patients with GBS which can direct the clinician to perform tracheostomy.

Methods: The aim is to study the predictors that determine the duration of mechanical ventilation(MV) and outcome of GBS patients requiring prolonged MV. Materials and Methods: This is a retrospective, observational study from a referral teaching hospital from South India. All consecutive patients with a diagnosis of GBS and requiring mechanical ventilation between 2009-2017 were included in the

study. The demographic, clinical parameters, electrophysiological data, complications and outcome of these patients were noted. Factors predicting prolonged MV(>2 weeks)were statistically assessed.

Results: Out of 79 patients requiring MV, 45(57%) patients needed prolonged MV and tracheostomy was performed in 29(37%).On multivariate regression analysis, sepsis($P = 0.02$;{95%CI 1.3-24.4}),MRC sum score($P = 0.01$;{95% CI 0.89-0.99}) and albumin levels within day 14($P = 0.004${95% CI 0.05-0.57}) correlated with prolonged duration of Moan univariate analysis, axonal GBS($P = 0.02$),presence of chronic renal disease($P = 0.03$) and pulmonary disease($P = 0.01$) were associated with significant mortality. On multivariate regression analysis, age (>60 years)($P = 0.001${95% CI 0.89-0.97}, MRC sum score ($P = 0.01${95% CI 1.01-1.1} correlated with poor outcome. Prolonged duration of MV ($P = 0.02${95%CI 0.88-0.99} also predicted a poorer outcome.

Conclusions: Sepsis and septic shock and not the choice of immunotherapy nor the electrophysiological subtypes of GBS determined prolonged duration of MV in our cohort.

Keywords: Prolonged mechanical ventilation, Guillian Barre syndrome, sepsis, tracheostomy, outcome.

Poster No: 215 | SARM1 knockout modestly rescues pathology of a Charcot-Marie-Tooth disease type 1A mouse model

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Introduction: Charcot-Marie-Tooth disease Type 1A (CMT1A) is caused by duplication of the PMP22 gene and is the most common inherited peripheral neuropathy. Although CMT1A is a dysmyelinating peripheral neuropathy, secondary axon degeneration has been suggested to be the leading cause of functional deficits in patients. The contribution of the programmed axon degeneration pathway to CMT1A pathogenesis has previously been evaluated by expressing the WldS transgene in CMT1A model rats. WldS expression delayed the modest axon degeneration observed in CMT1A model rats and resulted in moderate increases in nerve and potentially muscle function.

Methods: Given that SARM1 knockout is a more potent inhibitor of the programmed axon degeneration pathway, we determined whether SARM1 knockout rescues behavioral, electrophysiological and histological phenotypes in CMT1A model (C3-PMP) mice. Neuromuscular SHIRPA, rotarod, inverted hanging and forelimb grip strength assays were used to evaluate behavioral rescue at 3, 6 and 8 months.

Results: Significant rescue was not observed with SARM1 knockout at any time point. Sciatic nerve compound motor action potential (CMAP) was recorded from an intrinsic foot muscle after proximal and distal stimulation and sensory nerve action potential (SNAP) was recorded proximally in caudal nerve after distal stimulation. Electrophysiological rescue was minimal and the significant finding of SNAP amplitude rescue at 3 months was not supported by nerve morphometry. Muscle morphometry was also evaluated but revealed negligible effects.

Conclusions: These findings indicate that the programmed axonal degeneration pathway may modestly contribute to axon pathology early in the disease but is likely not the sole driver of axon dysfunction as the disease progresses. Additionally, our analysis supports previous reports demonstrating that CMT1A model mice poorly recapitulate the secondary axon degeneration observed in patients indicating that conduction block may contribute to functional deficits more than previously appreciated. These findings warrant more careful investigation into CMT1A pathomechanisms, particularly those causing dysmyelination.

Keywords: CMT1A, PMP22, SARM1, Axon Degeneration, Mouse Phenotype.

Poster No: 216 | A comprehensive update of the inherited neuropathies consortium of the rare diseases clinical research network

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Introduction: The Inherited Neuropathies Consortium is composed of 17 sites that evaluate patients with Charcot-Marie-Tooth Disease (CMT). All 17 sites are actively seeing and recruiting patients.

Methods: Data is collected from clinical visits in a standardized form, and the clinical information from patient visits is electronically submitted and maintained in a database housed at the University of Cincinnati at the Data Management and Coordination Center (DMCC). Current INC projects include: Natural History Evaluation of Charcot-Marie-Tooth disease (with particular emphasis on CMT1B, CMT2A, CMT4A, and CMT4C), Genetics of CMT, Creation and Validation of a CMT Pediatric Scale and Infant Scale, CMT Biomarker Discovery, and virtual evaluations. One INC site houses and researches DNA samples sent from other INC sites for testing on potential new forms of CMT and genetic modifiers of CMT1A.

Results: These projects have helped to create validated outcome measures to use in clinical trials. In addition, over the past five years, the INC has been able to identify over half of all the genes currently known to cause CMT.

Conclusions: The INC has evaluated 6275 patients overall, with a majority of patients enrolled patients for the Natural History Evaluation of CMT. The INC partners with patient advocacy groups in order to bring knowledge to patients establish connections between patients and researchers and physicians. These groups include the Muscular Dystrophy Association, the Charcot Marie Tooth Association, CMTUK, CMTA Australia, CMT-Rete and Telethon from Italy.

Grant Support: This consortium Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01).

Keywords: Charcot-Marie-Tooth, CMT, Inherited Neuropathies Consortium, INC.

Poster No: 217 | Guillain-Barré syndrome decreases in Singapore during the COVID-19 pandemic

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Introduction: A recent paper (1) suggested the absence of epidemiologic association between COVID-19 and Guillain-Barré syndrome (GBS). Previously, we had published the lack of national increase in GBS hospitalizations during Dengue (2) and Zika virus (3) outbreaks in Singapore. Using similar methodology, we asked if GBS hospitalizations have changed in 2020 during the COVID-19 outbreak.

Methods: All hospitalization episodes coded with discharge diagnosis of GBS (ICD-10: G61.0) from January 2019 to October 2020 were extracted from the Singapore Ministry of Health's inpatient administrative database. COVID-19 notification data were obtained from the Ministry's surveillance systems on infectious diseases. Association between monthly GBS hospitalization episodes and monthly number of COVID-19 notifications was examined by calculating the Spearman's correlation coefficient, after adjusting the time series data for stationarity.

Results: 57985 COVID-19 infections were notified from January 2020 to October 2020. Compared to 2019, there was a decrease in the number of GBS hospitalization from early 2020, from a high of 20/month in February 2019 to 4/month in February 2020. A relatively low level, 4-6 admissions /month, was maintained throughout the year whilst the outbreak was on-going. There was no association between GBS hospitalizations and COVID-19 (Spearman's correlation coefficient = 0.06). To date, we have only had one case of GBS, an acute motor sensory axonal variant, that developed in a patient 1 month into critical COVID-19 infection (4).

Conclusions: Our data suggests that COVID-19 may not be a significant antecedent infection of GBS. The decrease in GBS hospitalizations may be partly related to a few Singapore hospitals restricting non COVID-19 admissions during the second and third quarter of 2020. However, these cases would likely have been admitted to non COVID-19 designated hospitals. We believe the period of national lock-down, the social and physical isolation, emphasis on hygiene measures and mandatory mask-wearing were behind the general decrease in GBS cases.

References

1. Stephen K, Julia P, Christina M, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. Brain. 2020;awaa433.

2. Umapathi T, Lim CS, Ooi EE, et al. Asymptomatic dengue infection may trigger Guillain-Barré syndrome. J Peripher Nerv Syst. 2016; 21:375-377.

3. Umapathi T, Kam YW, Ohnmar O, Ng BCJ, Ng Y, Premikha M, Leo YS, Ng LFP. The 2016 Singapore Zika virus outbreak did not cause a surge in Guillain-Barré syndrome. J Peripher Nerv Syst. 2018; 23:197-201.

4.Umapathi T, Kam YW, Ohnmar O, Ng BCJ, Ng Y, Premikha M, Leo YS, Ng LFP. The 2016 Singapore Zika virus outbreak did not cause a surge in Guillain-Barré syndrome. J Peripher Nerv Syst. 2018; 23:197-201.

Keywords: COVID-19, Guillain-Barré syndrome.

Poster No: 218 | Distinct clinical profiles among ATTRv genotypes

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Introduction: Hereditary transthyretin amyloidosis is a progressive, debilitating, and ultimately fatal disease that results in multisystem dysfunction.

Methods: 56 cases (31 V122I, 12 late-onset V30M and 13 L58H) evaluated at JH between 2013 and 2020 were reviewed for peripheral nerve, GI and cardiac involvement.

Results: The age at onset were similar (V122I:71.5 + 8.0, V30M: 64.8 + 2.6 and L58H: 62.4 + 9.8) and a minority were female (26, 25, 31%). Only 10% of V122I and 17% of V30M patients had a family history suggestive for ATTRv, while 69% of L58H were. Peripheral neuropathy (PN) was present in all three variants at diagnosis (90, 100, 100%) with NIS values V122I:22 + 16, V30M:61 + 31 and L58H:57 + 25. Most points were attributed to strength followed by sensory and reflex deficits across all groups. Skin biopsies were Congo red positive 39/71 and 75% of cases. A positive Romberg sign was common while painless injuries were rare. Carpal tunnel syndrome was present among 97, 58 and 77% of cases (V122I/V30M/L58H) with CTS preceding ATTRv diagnosis by 7+ years in 30/29/30% of cases. ProBNP and IVSd were more elevated among V122I cases compared to V30M or L58H cases 5939 + 9621 vs 796 + 970 and 404 + 677 pg/mL and 1.70 + 0.29, 1.42 + 0.38 and 1.23 + 0.36 cm respectfully. AFib was present among 39% of V122I cases and only 8% of either V30M or L58H cases. GI symptoms were rare (6%) among V122I cases and common among V30M (42%) and L58H (38%) cases.

Conclusions: Important clinical differences exist between ATTRv genotypes. While V122I is widely believed to be a cardiac disease, PN consisting of both CTS and a distal sensory-predominant PN are very common. Most V30M and V122I patients were diagnosed de-novo and therefore require clinical suspicion for diagnosis. Skin biopsies were useful in confirming systemic amyloid.

Keywords: ATTRv, Skin Biopsy.

Poster No: 220 | **A longitudinal evaluation of chronic inflammatory demyelinating polyneuropathy and fatigue**

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Introduction: Fatigue is common in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) regardless of the disease activity status. Furthermore, use of sedating medications, increased severity of functional disability and a higher level of depression seem to contribute to increased levels of fatigue at a single time point of analysis. It would be helpful to understand the degree to which disability, chronic medical illness other than CIDP and medications influence fatigue over time.
Methods: 43 patients were evaluated at three tertiary health care centers and specialized neuromuscular clinics in Serbia. Inclusion criteria included meeting EFNS/PNS criteria for diagnosis and outcome measures collected included the Fatigue Severity Scale (FSS), Inflammatory Neuropathy Cause and Treatment (INCAT), Inflammatory Rasch-build Overall Disability Scale (iRODS), Chronic Acquired Polyneuropathy Patient-Reported Index (CAPPRI) and a quality of life questionnaire. Treatment regimens were collected at a baseline visit and at one year in follow up. Age, gender and comorbidity data was collected.
Results: Change in the FSS demonstrated that worse fatigue correlated with increased disability as reflected by iRODS ($P < 0.01$). Patients with more fatigue perceived CIDP was worse over the course of the year and this correlated with the interval change in the FSS ($P < 0.02$). Increased fatigue correlated to poor quality of life in CAPPRI ($P < 0.0001$). Additionally, fatigue was noted to be worse when a comorbidity was present ($P < 0.01$). INCAT score, age and gender did not demonstrate a significance with interval change in FSS.
Conclusions: Over the course of one year, worsening fatigue correlates with increased disability and worse quality of life. Fatigue correlates with an increasing number of comorbidities suggesting that fatigue in patients with CIDP may be influenced by chronic medical illness rather than CIDP alone. The influence of sedating medications and treatment effect over time needs further evaluation.
Keywords: CIDP, fatigue.

Poster No: 221 | **Enhanced CD4 and CD8 T cell responses in Chronic Inflammatory Demyelinating Polyneuropathy**

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Introduction: Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disorder of the peripheral nerves with an incompletely understood autoimmune mechanism. Earlier studies have demonstrated an increase in CD4 and CD8 T cells in CIDP patients; however, a comprehensive assessment of T cell phenotype and functional capacity has not been investigated in CIDP patients.
Methods: To address the role of CD4 and CD8 T cells in the development of CIDP, we performed a comprehensive T cell profile via high-dimensional flow cytometry. 25 CIDP patients meeting EFNS/PNS criteria and 25 healthy controls were recruited to the study and blood was collected for peripheral blood mononuclear cells (PBMCs) isolation for cellular analysis. Cytokine production was measured using intracellular cytokine staining and an in-vitro suppression assay was performed to measure and compare the suppressive capacity of Tregs from CIDP patients and healthy controls.
Results: In CIDP patients, the maturation status of both CD4 and CD8 T cells were skewed toward central memory (CD45RA-CCR7+) T cells ($P = 0.007$ and $P = 0.018$, respectively). CD4 and CD8 T cells demonstrated an enhanced capacity to produce inflammatory cytokines. Compared to healthy controls, CD4 T cells from CIDP patients produced greater levels of TNF-alpha ($P < 0.01$), IL-2 ($P = 0.008$), and IL-21 ($P = 0.007$), while CD8 T cells were higher in IFN-gamma ($P = 0.043$), TNF-alpha ($P = 0.006$), and IL-2 ($P = 0.046$). In parallel, we observed a defect in the ability of Tregs to suppress effector CD4 T cell proliferation in CIDP patients.
Conclusions: Overall, our study revealed disparities within CD4 and CD8 T cells from CIDP patients that is shifted toward a Th1 response. Our data suggest that Treg dysfunction may contribute to the enhancement of pro-inflammatory cytokines. Compounding the inflammatory environment is the increased frequency of IFN-gamma +, TNF-alpha+, IL-2+ polyfunctional CD8 T cells. Future work will focus on identifying mechanisms to suppress inflammation via Th1-specific targets.
Grant Support: GBS/CIDP Foundation grant funded.
Keywords: CIDP, T cell profile, CD8 T cells, cytokines.

Poster No: 222 | **Anti-nerve antibodies in CIDP: Clinical correlates and treatment response. Data from the Italian CIDP database**

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Introduction: To investigate the frequency and clinical-therapeutic correlates of anti-nerve autoantibodies in a large unselected population of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Methods: Sera from 202 CIDP cases fulfilling the EFNS/PNS criteria were included in the present analysis and screened for anti-nerve autoantibodies. Results were compared to retrospectively retrieved clinical features collected in a national database.

Results: Among anti-paranodal IgG antibodies, the recorded positivity rate was 4% (8/202) for anti-Neurofascin 155 antibodies and 2% (4/202) for anti-Contactin 1 antibodies, while no reactivity was identified against neither Gliomedin nor Neurofascin 186. IgG isotype class was tested in 9 patients revealing IgG4 predominance in 7. All antibody positive patients had a diagnosis of definite typical CIDP as defined by the EFNS/PNS criteria. Compared to the antibody negative cohort, Neurofascin-155 antibody positive patients were characterized by a higher prevalence of ataxia and of prolonged distal motor latencies on nerve conduction studies; CSF analysis revealed a higher mean protein concentration. Anti-CNTN1 positive patients presented more frequently a GBS-like onset and had a more severe motor impairment reflected by a higher mean ONLS and lower mean MRC at inclusion. There was no difference in the frequency of overall response to therapy even if patients with anti -CNT1 more frequently received plasmapheresis ($P = 0.024$) possibly reflecting a more frequent unsatisfactory response to IVIg or steroids.

Conclusions: The demonstrated differences in the analyzed cohort identify two subgroups of patients with specific clinical features. These findings support the hypothesis that the disease might be a syndrome that includes different forms endorsing the idea that a pathogenic-oriented approach that integrates serological analysis may be used in future studies aimed to the adoption of personalized treatment strategies.

Keywords: Chronic inflammatory demyelinating neuropathy, CIDP, Peripheral neuropathy, anti-nerve antibodies, nodal/paranodopathy.

Poster No: 223 | A mouse knockin allele of Sptlc1-C133W to model hereditary autonomic and sensory neuropathy 1 (HSAN1)

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Introduction: Hereditary autonomic and sensory neuropathy (HSAN1) is caused by dominant mutations in serine palmitoyltransferase long chain 1 or 2 (SPTLC1/2), which charges serine onto palmitoylate as a first step in sphingolipid biosynthesis. Mutations in SPTLC1 alter the enzyme's substrate specificity, creating deoxysphingoid base intermediates (DSBs) that are toxic to neurons.

Methods: We used CRISPR genome editing to create a precision mouse model of HSAN1 by engineering a knockin allele of the disease-associated Sptlc1-C133W mutation. Previous transgenic mice overexpressing the C133W allele recapitulate many aspects of the human disease; whereas homozygous null (knockout) mice are lethal, and heterozygous nulls have no phenotype.

Results: To determine if the Sptlc1-C133W mice provide a better preclinical model for HSAN1, we performed genetic, biochemical, behavioral, neurophysiological and histopathological analyses. Interestingly, the mice do not survive as homozygotes, suggesting that not only is the substrate specificity of SPTLC1 altered, but also that the normal, essential function of SPTLC1 is reduced or lost. Heterozygous mice do develop elevated levels of DSB intermediates in several organs and in plasma by three-months-of-age. Dietary supplementation with serine suppressed the DSB levels, as anticipated. However, the mice performed normally in tests of sensory and motor performance, had normal nerve conduction velocities and compound muscle action potential amplitudes, and showed no evidence of axon degeneration in the femoral or caudal nerves, or in the small sensory fibers of the hind paw epidermis, even at one-year-of-age. We are currently assaying molecular biomarkers of axon degeneration.

Conclusions: The Sptlc1-C133W knockin mice have elevated DSB levels, but not neuropathy. Therefore, they will be useful for testing approaches to lower DSB levels, but not for testing approaches to prevent axonopathy. We are testing whether DSB levels are lower than those produced by transgenic overexpression of mutant Sptlc1.

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Keywords: hereditary autonomic and sensory neuropathy 1, serine palmitoyltransferase long chain 1, deoxysphingoid base intermediates, Sptlc1-C133W.

Poster No: 224 | **Bringing together racial and ethnic categories for the RDCRC inherited neuropathy consortium: A proposed framework for international data collection**

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Introduction: Categorization of people by race and ethnicity has a controversial history originating from the eugenics movement(1). It has been a historically difficult endeavor as races are not genetically distinct subspecies and poor markers for underlying genotypic, structural and cultural characteristics(2). There is a recognition, however, of societal diversity and there is a call to include people from different backgrounds in research for biomedical and socio-political equity(3). As an international collaboration, the Inherited Neuropathy Consortium (INC) faces challenges as racial and ethnic categories collected by the countries of the consortium differ according to the socio-political status, indigenous or migrant groups.

Methods: The Diversity Committee of the INC aimed to standardize the nationally recognized racial/ethnic categories for the four main countries represented in the consortium. Nationally collected race and ethnicity categories were identified for the USA (NIH categories), UK (Office of National Statistics), Italy (2019 census categories), and Australia (2019 census categories). Common categories were identified between each source then grouped under broad categories and sub-categories. Next, categories specific to one country were grouped under the broad and sub-categories. This early framework was presented to the INC diversity committee to reach consensus and check appropriate wording.

Results: We present a framework with 8 broad categories: White, Black, Asian, Americas, Middle East/North Africa, Oceania, Mixed/Multiple Ethnic Groups, Any Other Ethnic Background. Each broad group has sub-groups (eg, South Asian) with further options for that sub-group (eg, Pakistani).

Conclusions: The INC diversity committee presents a combined race and ethnicity framework for data collection for its program of research. This will be available to clinical evaluators as a tick box form with an accompanying manual of category descriptors. Future research plans to validate these categories from the participant's perspective will serve as a model for other large-scale international studies.

References

1. Saini *A. Superior*: The Return of Race Science. 2019. Harper Collins, London, UK

2. Ellison GTH, Smart A, Tutton R, Outram SM, Ashcroft R, Martin P. Racial categories in medicine: a failure of evidence-based practice? PLoS Med. 2007;4(9):1434-1436

3.National Institute for Health Research. Improving inclusion of under-served groups in clinical research: Guidance from INCLUDE project. 2020. https://www.nihr.ac.uk/documents/improving-inclusion-of-under-served-groups-in-clinical-research-guidance-fro

Keywords: Inherited neuropathy, Diversity, Inclusion, Race and ethnicity categories.

Poster No: 225 | **Antibodies targeting both Caspr1 and CNTN1 in two CIDP patients**

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Introduction: Antibodies anti-Caspr1 or anti-CNTN1 are present in a subset of patients with aggressive-onset CIDP with early axonal involvement and poor response to IVIg. Recently, anti-paranodal antibodies targeting both Caspr1 and CNTN1 were reported in two patients with acute-onset immune-mediated neuropathy.

Methods: We tested anti-Caspr1 antibodies in sera from a cohort of 18 CIDP patients with anti-CNTN1 antibodies. Anti-Caspr1 and anti-CNTN1 IgG were tested by CBA and ELISA, and also IgG subclasses were investigated by ELISA. Clinical data were retrospectively collected.

Results: We identified two CIDP patients with antibodies reacting against both CNTN1 and Caspr1 separately. Patient 1 was a 54 y/o man with a subacute-onset neuropathy with moderate asymmetric tetraparesis, ataxia, dysphonia, early axonal involvement and good clinical response to steroids. At onset anti-Caspr1 and anti-CNTN1 antibodies were IgG4 predominant but also anti-Caspr1 and anti-CNTN1 IgG3 were detected. After treatment, IgG4 targeting only Caspr1 were detected. Patient 2 was a 74 y/o man with a subacute-onset neuropathy with a relapsing-remitting course with ophthalmoparesis, ataxia, tetraparesis and dysphagia that required mechanical ventilation. He responded to plasma exchange. Anti-Caspr1 and anti-CNTN1 antibodies were IgG4 predominant and also anti-CNTN1 IgG3 were detected. Antibodies were not detected after treatment. Full clinical and immunological data from these patients will be presented at the meeting.

Conclusions: Our observations suggest that anti-paranodal antibodies targeting both Caspr1 and CNTN1 epitopes are present in a small number of patients with CIDP. Studies in larger cohorts of CIDP are required to validate these observations.

Keywords: CNTN1, Caspr1, Paranode, CIDP, Antibodies.

Poster No: 226 | **Functional interaction of PMP22 with the PI3K/AKT/mTOR signaling cascade - novel targets to treat CMT diseases?**

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Introduction: Previous studies from our group have shown that one of the major growth pathways in myelination, the PI3K/AKT/mTOR pathway, is PMP22 gene-dosage dependently altered in animal models of Charcot-Marie-Tooth disease 1A (CMT1A) and, vice versa, hereditary neuropathy with liability to pressure palsies (HNPP). The major inhibitor of the pathway is Phosphatase and Tensin homolog (PTEN), and PTEN knockout in Schwann cells leads to an over-activation of the PI3K/AKT/mTOR pathway and tomacula formation, a phenotype similar to HNPP.

Methods: Genetic mouse models, behavior, electrophysiology, in vitro myelination, immunohistochemistry, HEK cell transfection.

Results: We observed increased PTEN protein levels in CMT1A and decreased levels in HNPP. In HNPP, the PI3K/AKT/mTOR pathway is upregulated and inhibition of mTOR with Rapamycin was sufficient to reduce myelin outfoldings in vitro. Moreover, treating HNPP mice in vivo reduced tomacula formation and improved behavioral and electrophysiological phenotype in the mice. To counteract the downregulated PI3K/AKT/mTOR pathway in CMT1A we used a pharmacologic and a genetic approach to reduce PTEN activity in Schwann cell-DRG co-cultures. Both strategies revealed increased myelination in vitro. In vivo, genetic reduction of PTEN in CMT1A Schwann cells was beneficial to increase myelin sheath thickness early in development, but not in adult mice. Transient PMP22 overexpression in HEK cells resulted in an acute perturbation of both AKT phosphorylation and PTEN levels, resembling the signaling phenotype in CMT1A.

Conclusions: These findings indicate that interference with growth signaling is a general function of PMP22, not exclusive to Schwann cells. The functional link between PMP22 and the PI3K/AKT/mTOR pathway can provide a useful target for therapeutical strategies in PMP22 gene-dosage related diseases and will give insight into the molecular function of PMP22.

References

1. Fledrich R, Stassart R, Klink A, et al. Soluble neuregulin-1 modulates disease pathogenesis in rodent models of Charcot-Marie-Tooth disease 1A. Nat Med. 2014;20:1055-1061. doi: 10.1038/nm.3664

Keywords: PMP22, CMT1A, HNPP, PI3K/AKT/mTOR signaling, Schwann cell.

Poster No: 227 | **Altered Metabolics in CMT1A rats**

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Introduction: Glial cells support axons not only by myelination but guarantee a supply of metabolites and trophic factors. In Charcot-Marie-Tooth disease type 1A (CMT1A), caused by an overexpression of PMP22 in Schwann cells (SC), patients present with severely reduced nerve conduction velocities and eventually loss of compound muscle action potentials. Previous studies in animal studies have reported that reduced axonal numbers and alterations in mRNA expression of the metabolic machinery correlate with disease severity.

Methods: We combined metabolomics, qRT-PCR analysis with FLIM analysis of FRET sensors in nerve lysates of Pmp22tg animals.

Results: When comparing wildtype and CMT1A rats, glucose was enriched and a downregulation of the polyol pathway along with reduced sorbitol levels was observed. Glycogen storages or glycolysis machinery was not altered. Protein levels of glucose transporter1 were increased and could be localized to Schmidt-Lanterman Incisures as well as the ab- and adaxonal SC surface. ATP levels of axons were maintained but decreased in old Pmp22tg animals when compared to wild type animals.

Conclusions: We hypothesize that free glucose fuel the axonal metabolism in peripheral nerves of CMT rats. Failing metabolic support of axons may lead to axonal dysfunction, neuromuscular junction degeneration and muscle atrophy. Understanding of axo-glial metabolic coupling may promote novel therapeutic targets in CMT1A.

References

1. Fledrich R, Schlotter-Weigel B, Schnizer TJ, et al. A rat model of Charcot-Marie-Tooth disease 1A recapitulates disease vari. 2012.

Keywords: CMT1A, Schwann Cell, Metabolic Support.

Poster No: 228 | **Altered ubiquitination of mutant TRPV4 ion channels may contribute to CMT2C/dSMA disease pathogenesis**

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Introduction: Precise regulation of ion channel activity is essential for cellular homeostasis. We have previously shown that dominant missense mutations of the calcium-permeable cation channel Transient receptor potential vanilloid 4 (TRPV4) cause a gain-of-channel function resulting in Charcot-Marie-Tooth disease type 2C and forms of distal spinal muscular atrophy. Little is known currently about how the activity of wild type (WT) TRPV4 is regulated at the plasma membrane, or whether neuropathy-causing mutations disrupt these regulatory processes. Ubiquitination is a protein post-translational modification known to modify the activity of numerous ion channels by triggering their endocytosis.

Methods: Using mass spectrometry, we determined that both exogenously expressed and endogenous TRPV4 is mono-ubiquitinated at specific lysine residues in the intracellular, N-terminal intrinsically disordered region (N-IDR). Site-directed mutagenesis of these lysine residues to arginine (to conserve the positive charge but prevent ubiquitination) resulted in increased cellular calcium influx via TRPV4, suggesting that N-IDR ubiquitination suppresses TRPV4 channel activity. We further demonstrate that members of the NEDD4 family of ubiquitin ligases (eg, NEDD4) interact with TRPV4, increase ubiquitination of the N-IDR, and reduce channel activation in response to pharmacological agonists. Mono-ubiquitination of the TRPV4 N-IDR appears to regulate channel activity without altering cell surface localization.

Results: Strikingly, neuropathy-causing TRPV4 mutants exhibit reduced levels of ubiquitination relative to the WT channel, consistent with an impairment of this negative regulatory process. Further supporting this concept, the gain-of-channel function characteristic of TRPV4 mutants can be abrogated by exogenous overexpression of NEDD4.

Conclusions: Together, these data implicate mono-ubiquitination as a key negative regulator of TRPV4 channel activity at the plasma membrane and suggest that disruptions in channel ubiquitination may contribute to the pathogenesis of TRPV4 channelopathies.

Grant Support: F31-NS-105404-2.

Keywords: CMT2C, Ubiquitin, Ion Channel, Calcium.

Poster No: 229 | Genetic evidence for the most common risk factors of chronic axonal polyneuropathy in the general population

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Introduction: Chronic axonal polyneuropathy is a common disease of which the etiology is only partially understood. Most studies have focused on environmental risk factors, however, genetic studies may help to determine causal associations and provide insight in the etiology. We used polygenic scores (PGS) containing multiple genetic variants of the clinically established risk factors diabetes mellitus, body mass index (BMI), vitamin B12 levels and alcohol intake, to investigate if there is genetic evidence for the associations between these risk factors and chronic axonal polyneuropathy.

Methods: This study was performed within the population-based Rotterdam Study and we included 1565 participants. PGS for different risk factors were calculated at multiple significant thresholds ($P < 5x10\text{-}8$, $P < 5x10\text{-}6$, $P < 5x10\text{-}4$, $P < 5x10\text{-}2$, $P < 1.0$) based on previous performed GWA-studies.

Results: Median age was 73.6 years (IQR 64.6-78.8) and 53.5% was female. Polyneuropathy was present in 215 participants (13.7%). Higher PGS for diabetes mellitus, BMI and alcohol intake were associated with higher risk for chronic axonal polyneuropathy, whereas higher PGS for vitamin B12 levels was associated with lower risk for polyneuropathy. These effects were most pronounced in PGS with lenient significance thresholds for diabetes mellitus and BMI (OR[diabetes, $P < 1.0$] = 1.21, 95% CI 1.05-1.39 and OR[BMI, $P < 1.0$] = 1.21, 95% CI 1.04-1.41), whereas the effects for vitamin B12 levels and alcohol intake were most pronounced for PGS with strictest significant thresholds (OR[vitaminB12, $P < 5e\text{-}8$] = 0.79, 95% CI 0.68-0.92 and OR[alcohol, $P < 5e\text{-}8$] = 1.17, 95% CI 1.02-1.35). We did not find an association between different PGS and sural SNAP amplitude, nor between the individual variants of PGS[$P < 5e\text{-}8$] and polyneuropathy.

Conclusions: This study presents genetic evidence for the associations between the clinically identified risk factors and chronic axonal polyneuropathy, namely diabetes mellitus, BMI, vitamin B12 levels and alcohol intake. This supports the hypotheses of causal associations between these known clinical risk factors and polyneuropathy, and provides insight in the etiology of chronic axonal polyneuropathy.

Grant Support: Prinses Beatrix Spierfonds W.OR17-10.

Keywords: polyneuropathy, neuropathy, genetics, polygenic scores, risk factors.

Poster No: 230 | Clinical and electrophysiological characterization of CMT type 4C with SH3TC2 mutation

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Introduction: Autosomal recessive Charcot-Marie-Tooth (CMT) type 4C (CMT4C) is demyelinating neuropathy caused by SH3TC2 mutations. Aim of this study was to characterize clinical and electrophysiological features of CMT with SH3TC2 mutation in Indian population.

Methods: 112 patients with CMT, including 50 autosomal recessive form underwent clinical exome sequencing. Clinical and demographic profile along with CMAPs of median, ulnar, common peroneal and

tibial motor nerves; SNAPs of median, ulnar and sural nerves were studied.

Results: Twelve (M:F = 1:1) had SH3TC2 mutation. Consanguinity was found in four patients with positive family history in two. Mean age of onset was 11.18 ± 11.5 years (range: 2-38 years). Most common presenting symptom was difficulty in walking. Lower limb weakness (distal-12, proximal-7) was present in all patients, upper limb weakness in half (distal-6, proximal-2),wasting and impaired sensation each in 8 patients. Facial weakness (n = 4), ptosis (n = 3), hearing impairment (n = 2), tongue wasting (n = 2), ophthalmoparesis (n = 1), pes cavus (n = 5), hammer toes (n = 4), scoliosis (n = 4) and kyphosis (n = 1) were noted. Ten patients were ambulatory at presentation and two were wheel chair bound. Electrophysiological testing was available in ten patients. Demyelinating sensorimotor neuropathy was noted in all ten patients. Common peroneal nerve (absent CMAP-8, severe demyelination-2) was more affected compared to median and ulnar nerves (absent CMAP-2, demyelination-7, normal-1). Distal motor latencies ranged from 8.9-20.5 ms, 6-13 ms, 14-19.1 ms, while velocities ranged from 10.89-28.2 m/s, 13.4-31.2 m/s and 7.9-12.2 m/s in median (n = 7), ulnar (n = 7) and common peroneal (n = 2) nerves respectively. Tibial nerve was not elicitable in all patients tested (5/5). SNAP of sural (absent-8, demyelination-2) and ulnar nerves (absent-7, demyelinating-3) were more affected than median nerve (absent-4, demyelinating-5, normal-1).

Conclusions: CMT 4C is demyelinating neuropathy affecting lower limb earlier and more severe than upper limb. Hearing impairment and spine deformities were less frequent compared to previous reports indicating wider spectrum of disorder.

Keywords: CMT 4C, demyelinating neuropathy, SH3TC2.

Poster No: 231 | CMT4G mutation in the 5'-UTR of Hexokinase I modifies its binding to VDAC and leads to dysfunction in mitochondrial calcium buffering

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Introduction: CMT4G results from recessive mutation in the 5'UTR of HKI gene that leads to an altered mRNA splicing. However, as the mutation does not affect the protein size, expression or enzymatic activity, the pathomechanism remains unclear. We recently reported that mitochondrial calcium release is a key event of Schwann cell demyelination. We hypothetized that alternative splicing induced the expression of a HK1 protein missing its Nterminal PBD domain. As PBD allows HKI binding to mitochondrial VDAC, HK1 mutation would impair its inhibitory effect on the calcium release from mitochondria, therefore promoting demyelination.

Methods: We recruited 22 patients diagnosed with CMT4G, the first cohort of this disease in the French gypsy population. This cohort was characterized by a childhood onset, an intermediate demyelinating pattern, a slow degradation leading to be wheelchair bound by the fifth decade of life. We collected peripheral blood mononuclear cells (PBMC) from 3 of these patients and one sural nerve biopsy.

Results: VDAC immunoprecipitation with HKI was significantly decreased in patient's PBMC compared to control's suggesting that CMT4G mutation impairs the binding of HK1 to VDAC. A similar result was obtained in the sural nerve sample. Co-immunoprecipitation studies performed in HEK293-T cells transfected with wild-type or mutated HKI confirmed that the mutation reduced the enzyme interaction with VDAC. Using a calcium probe targeted to mitochondria, we observed that wild-type HKI expression decreased mitochondrial calcium release while mutated CMT4G had no effect. Displacing endogenous HK1 from VDAC resulted in mitochondrial calcium release in cells. This release was blocked by a peptide comprising the 15 aa of the wild-type HKI. However, a peptide comprising the 15 aa of the mutated HKI was unable to block mitochondrial calcium release.

Conclusions: Taken together these data show that the CMT4G-induced modification of the HK1 Nterminus alters mitochondrial calcium buffering thereby promoting demyelination.

References

1. Schwann cell demyelination is triggered by a transient mitochondrial calcium release through Voltage Dependent Anion Channel 1 Nicolas Tricaud, Benoit Gautier, Gerben Van Hameren, Jade Berthelot, Sergio Gonzalez, Roman Chrast bioRxiv 581157.

Keywords: CMT4G, hexokinase, mitochondria.

Poster No: 232 | Assessing deterioration in CIDP patients upon treatment withdrawal using impairment and functional outcome measures

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Introduction: Currently it is unclear whether cut offs for minimal clinically important differences (MCIDs) for continuous outcome measures can accurately identify meaningful deterioration in chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods: Post-hoc analysis using data from the IOC trial, in which sixty patients with CIDP were randomized to IVIg withdrawal or continuation of IVIg-treatment. Change scores from baseline to the final visit (end of study at 24 weeks or if an early endpoint was reached) of the Inflammatory Rasch-Built Overall Disability Scale (iRODS), grip strength, and MRC sum score (MRCss) were calculated. Early endpoint was defined as a deterioration on the iRODS (≥1.96 SE) or deterioration as judged by patients and/or physician warranting stopping of study treatment. For this study, patients were classified into "deteriorated" and "not deteriorated", based on two anchors: the patient impression of change scale (5-point Likert scale), and a treatment anchor (decision to restart/increase treatment after reaching an early endpoint). Using these two anchors as reference standards, the area under the curve (AUC) of each outcome measure was calculated, as well as the sensitivity and specificity of MCIDs as defined in literature.

Results: An early endpoint was reached in 30 patients, 28/56 patients deteriorated according to the patient anchor and 24/60 patients deteriorated according to the treatment anchor. The AUC of the iRODS based on the individual standard errors of the change was 0.87 and 0.90 and based on centiles 0.86 and 0.90, using the treatment or patient anchor, respectively. The AUC for grip strength was 0.74 and 0.65 and 0.69 and 0.68 for the MRCss. Varying sensitivity and specificity rates were found, depending of the used cut-offs.

Conclusions: In CIDP patients starting treatment withdrawal, changes in iRODS showed better discriminatory potential than changes in grip strength and MRCss to assess clinical relevant deterioration, but sensitivity and specificity varied substantially among different iRODS cut-off values.

Keywords: chronic inflammatory demyelinating polyneuropathy, outcome measures.

Poster No: 233 | A potential role of endocannabinoid system in the pathogenesis of bortezomib-induced neuropathic pain model

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Introduction: The critical problem we want to address is the lack of preventive measures or treatment for chemotherapy-induced peripheral neuropathy (CIPN), which is a common dose-limiting side effect of several chemotherapeutic agents. In particular, we have focussed on bortezomib, a first-in-class proteasome inhibitor used for the treatment of multiple myeloma, which is associated with a relatively high incidence occurrence of CIPN. Currently there are no effective therapies for CIPN prevention, and symptomatic treatment is frequently ineffective. Among possible pharmacological treatments of CIPN, modulation of the endocannabinoid system might be particularly promising.

Methods: To test this hypothesis, we performed electrophysiological, behavioral and pathological analyses in a rat model of painful CIPN induced by the administration of chronic bortezomib. The animals were intravenously treated with bortezomib 0.20 mg/kg, 3 times a week for 8 weeks. In addition, neuroinflammation in the peripheral nerve as well as CB1R and CB2R expressions and distribution in the DRG and spinal cord were investigated.

Results: After administration of bortezomib, the rats showed mechanical and thermal allodynia associated with macrophages infiltration in rats after 8 weeks of treatment. In addition, bortezomib induced an increase in the number of CB1R- and CB2R-positive DRG neurons in comparison to untreated controls, as well as a significant increase in CB1R expression. Slight changes regarding CB1R distribution were observed also in the spinal cord.

Conclusions: The results suggest that the alteration of the endocannabinoid levels in peripheral and central nervous tissues could have a significant influence on neuroinflammation. Therefore, we have concluded endocannabinoid system modulation through effective pharmacological intervention might be one of the principal mechanisms of the therapy in CIPN patients.

Keywords: Endocannabinoid system, Bortezomib, neuropathic pain, peripheral neuropathy, preclinical study.

Poster No: 234 | The integrated stress response is activated in multiple mouse models of tRNA-synthetase-associated peripheral neuropathy

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Introduction: Dominant mutations in at least six aminoacyl-tRNA synthetases genes cause forms of Charcot-Marie-Tooth disease. This is the largest gene family associated with CMT and suggests a shared mechanism. Mutations in glycyl-tRNA synthetase (Gars) activate the integrated stress response (ISR), which contributes to disease severity in mouse models.

Methods: We have examined gene expression signatures in mouse models carrying disease-associated mutations in two other tRNA synthetase genes, Yars-E196K and Hars-P134H. Spinal cords were examined by RNA sequencing, Q-RT-PCR, and in situ hybridization to detect changes indicative of ISR activation.

Results: Activation of the ISR was observed in both the Yars-E196K and Hars-P134H mice. In Yars mice, heterozygous animals showed low-level induction of the ISR, and a stronger induction was observed in homozygous mice. In situ hybridization revealed that, in both genotypes, ISR activation was restricted to alpha-motor neurons, and no other cell types in the spinal cord were affected. Gene expression changes were confirmed and quantified by RNA sequencing and Q-

RT-PCR from whole spinal cord mRNA. Interestingly, Yars-E196K homozygous mice show neuropathy-relevant phenotypes by four-months-of-age, whereas heterozygous animals are phenotypically normal. Hars-P134H/+ mice have gene expression changes consistent with ISR activation in Q-RT-PCR assays, and results parallel changes in Gars and Yars mutant mice, but at a lower magnitude. Analysis of in situ hybridization is ongoing. Despite these gene expression changes, the Hars-P134H/+ mice do not have a neuropathy phenotype, even at greater than one-year-of-age, based on preliminary analyses.

Conclusions: The Yars and Hars mutant mice show indications of ISR activation that are consistent with changes seen in Gars mutant mice, suggesting ISR activation may be a shared mechanism across these mutations. Also, ISR activation is an early, primary problem that is seen even without discernable neuropathy phenotypes.

Grant Support: R37 NS054154, R24 NS098523, U54 OD020351, R01 NS113583.

Keywords: axonal neuropathy, CMT2D, diCMTC, tRNA synthetase, GCN2.

Poster No: 235 | Exploring in vivo neural imaging as a readout for HDAC6 rescue of axonal transport after oxaliplatin-induced peripheral neuropathy

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Introduction: We hypothesized that loss of axonal transport is an early event in the development of neuropathy. The goal of this study is to use an in vivo neural imaging biomarker as a readout for axonal transport, to assess the effect of HDAC6 inhibition (ACY-1083) on axonal transport upon oxaliplatin induced neuropathy.

Methods: We used a 2x2 factorial design: oxaliplatin vs vehicle x ACY-1083 vs vehicle on 20 female SKH1 mice. A fluorescently labeled neural imaging biomarker (TTc-790) was injected in the calf muscle of each animal followed by in vivo imaging after injection.

Results: At the conclusion of the study, after 2 weeks of no treatment, oxaliplatin significantly reduced TTc-790 transport in the oxaliplatin treated group ($P = 0.03$) and showed no significant difference from the control or ACY-1083 alone group. ACY-1083 rescues the loss of IENFs of oxaliplatin treated mice where the two-way ANOVA showed a significant interaction ($P < 0.005$) and a paired *t* test revealed significant differences between oxaliplatin vs control, ACY-1083 and ACY1083/oxaliplatin groups ($P < 0.005$).

Conclusions: In vivo TTc-790 transport can be successfully used to track the effect of neuroprotective agents on chemotherapy-induced deficits in axonal transport. The HDAC6 inhibitor, ACY-1083, showed imaging evidence of efficacy as a neural protectant for oxaliplatin-induced neuropathy.

Grant Support: Neurodegeneration Consortium at MD Anderson Cancer Center.

Keywords: Axonal transport, neural imaging probe, chemotherapy, HDAC6 inhibitor, in vivo imaging.

Poster No: 236 | Transforming growth factor-β1 (−509C/T and +869C/T) polymorphisms in patients with Guillain-Barré syndrome in Bangladesh

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Introduction: Guillain-Barré syndrome is the most common but serious autoimmune disorder of peripheral nervous system after the cessation of poliomyelitis. The pathogenesis and its etiology still remain partially unidentified or unclear. In order to comprehend whether some hosts are more susceptible to develop the disease than others, the distribution of certain genetic polymorphism in TGFβ1 -509C/T and TGFβ1 + 869C/T were studied in association with susceptibility and severity of patients with GBS compared to healthy individual in Bangladesh.

Methods: The genotyping of the TGFβ1 -509C/T and TGFβ1 + 869C/T polymorphisms were performed using tetra amplification refractory mutation system, sequence specific PCR (T-ARMS PCR) in 145 patients with GBS and 149 ethnically matched healthy individual of Bangladesh. Statistical analyses were carried out using Fisher's exact test with Yates' continuity correction. Allele and genotype frequencies were reported as P values, odds ratios (ORs) and 95% confidence intervals (CIs). A P value less than 0.05 were considered statistically significant.

Results: No significant association was found with TGFβ1 -509C/T and TGFβ1 + 869C/T polymorphisms and susceptibility to GBS. Clinical subgroup analysis revealed TGFβ1 -509 T allele was prevalent in axonal subtype of GBS compared to demyelinating subtype before Bonferroni correction ($P = 0.04$, OR = 2.12, 95% CI = 1.03-4.33; Pc = 0.08). TT genotype of TGFβ1 (−509) was predominantly present in axonal variant of GBS compared to demyelinating subtype but result was not significant (21.1% vs 7.7%). Patients with positive anti-GM1 antibody and recent *Campylobacter jejuni* infection showed no significant association with TGFβ1polymorphisms. The frequency of TGFβ1 (-509C/T and + 869C/T) genotype was not significant at any stage of disease prognosis and were not evident in mild and severe cases.

Conclusions: Our study revealed that TGFβ1 (-509C/T and + 869C/T) polymorphism is not risky for the susceptibility and severity of GBS but TGFβ1 -509 T allele may play a pivotal role in axonal subtype of GBS.

Grant Support: icddrb, Bangladesh.

Keywords: Guillain-Barré syndrome, Transforming Growth Factor-β1, Polymorphism, Genotype, allele.

Poster No: 237 | Bioassay-confirmed pathogenic de novo mutations expand the genotype-phenotype spectrum of ATP1A1

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Introduction: ATP1A1 encodes a sodium-potassium-ATPase that is highly expressed in both peripheral nerve and central nervous system. Pathogenic mutations in ATP1A1 have so far been associated with an autosomal dominant Charcot-Marie-Tooth (CMT) phenotype as well as with hypomagnesemia, mental retardation, and seizures (OMIM). According to the GnomAD constraint metrics, ATP1A1 appears to have a low tolerance to missense ($Z = 6.22$) and loss of function ($pLI = 1$) mutations.

Methods: We herein describe five novel heterozygous variants in ATP1A1: p.Gln225Arg, p.Gly335Cys, p.Gly509Asp, p.Gly718Ser, and p.Phe923Tyr.

Results: All mutations occurred de novo in five unrelated children of Dutch, Polish, Italian, and US American descent. None of the variants was found in healthy control populations (GnomAD). The age at onset was early infancy in all cases. As signs of neuropathy, the most abundant clinical features included foot deformities (3/4), delayed motor development (3/4), and sensory deficits (1/4). Additional features were intellectual disability (4/4), spasticity (2/4), and seizures (1/4). Hypomagnesemia was not detected in any of the probands. Variant pathogenicity was assessed via ouabain survival assay. U2OS cells were transfected with ouabain-resistant plasmids encoding the three variants p.Gln225Arg, p.Gly335Cys, and p.Phe923Tyr. Cells were treated for 72 hours with the ATPase inhibitor ouabain at a concentration of 0.5 μM, and cell survival was measured by luciferase assay. Compared to control, cell viability was significantly reduced in all three mutants, confirming a relevant reduction of ATPase function.

Conclusions: In summary, we confirmed the pathogenicity of the three novel variants. Besides CMT, the phenotypic spectrum associated with pathogenic ATP1A1 mutations seems to be broader than previously thought, including central nervous system manifestations such as spasticity and developmental delay.

References

1. Lassuthova P, Adriana PR, Gianina R, et al. Mutations in ATP1A1 cause dominant Charcot-Marie-Tooth type 2. Am J Hum Genet. 2018;102(3).

Grant Support: NIH (R01NS105755), DFG (DO 2386/1-1).

Keywords: Charcot-Marie-Tooth disease, Ouabain survival assay, ATP1A1, Genotype-phenotype correlation, De novo mutations.

Poster No: 238 | Biallelic Expansion of an Intronic Repeat in the RFC1 Gene in a Sample of Brazilian Citizens: a Genetic Study

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Introduction: Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) is a late-onset, slowly progressive neurological disorder. Despite recently described, its etiopathogenesis is still in the process of elucidation due to the identification of a biallelic intronic AAGGG repeat expansion in the RFC1 gene as the genetic cause of the disease. Distinguished nonpathogenic expansion configurations have also been described, such as: AAAAG and AAAGG. Based on these findings, this study evaluated all three mutation's prevalence in Brazilians with late-onset ataxia associated or not with the other known manifestations of the syndrome.

Methods: The control group was included 100 health individual with no family history of neurological disorder while the ataxic group included 50 patients. In order to genetically identify these expansion carriers, flanking polymerase chain reaction (PCR) and repeat-primed PCRs (RP-PCR) for the three allele expansion configurations in RFC1 were performed. If flanking PCR did not show any product, the DNA sample would undergo RP-PCR.

Results: Biallelic AAGGG expansion was found in eleven patients of the sample group (22%). Two of these patients had also presented extrapyramidal signs and migraine. Six patients (12%) had AAGGG and AAAAG expansions, and two patients (4%) had AAAGG and AAGGG expansions. One patient did not show a product by flanking PCR, and yet it also did not show any products by RP-PCR.

Conclusions: Two patients had all the CANVAS main symptoms and both had AAGGG biallelic expansion. There were no clinical distinctions among patients with and without the pathogenic expansions. In the control group, no flanking product was observed in 7 patients. Ultimately this study aims to contribute to the understanding of the most frequent genetic expansion configurations that cause CANVAS in the Brazilian population.

References

1. Cortese A. et al. Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia. Nat Genet. 2019;51:649-658.

Grant Support: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).

Keywords: Inherited Neuropathy, Late-Onset Ataxia, Genetics.

Poster No: 239 | **A Retrospective Descriptive Analysis of 103 Patients Presenting with Symptoms Consistent with Small Fiber Neuropathy**

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Introduction: Rational: Little is published on the symptoms and testing for small fiber neuropathy (SFN) in adolescents. Objectives: A retrospective analysis of 103 patients presenting with symptoms consistent with small fiber neuropathy to describe common patient characteristics, and elucidate clinical findings associated small fiber neuropathy.

Methods: Methods: Patient demographic and clinical characteristics were summarized according to diagnosis of small fiber neuropathy using standard descriptive statistics. Differences in variable distribution by SFN were evaluated using Fisher's exact-test for categorical variables and ANOVA or the Kruskal-Wallis test for continuous variables.

Results: Results: We present the distribution of patient age, clinical symptoms, and lab values according to SFN diagnosis. The median age of patients with SFN (16 years, IQR = 13-17) did not significantly differ from patients without SFN (16 years, IRQ = 15-18). However, more patients with SFN had joint pain compared to patients without SFN. Patients with SFN also had statistically significant higher median values of Rheumatology ACE (39 [IQR = 30-61] vs 27 [IQR = 17-32], $P = 0.004$) and Thyroid Free T4 (106 [0.98-1.21] vs 0.97 [0.86-1.11], $P = 0.019$). Primary analysis evaluating the association between number of symptoms and SFN patients who had 4 symptoms compared to who had <3 symptoms, had 1.56 times the odds of SFN in unadjusted analysis. Patients who had 5 to 6 symptoms also did not have increased odds of SFN compared to patients with <3 symptoms. Evaluating the association between SFN and symptomatology and we found the odds of SFN was higher among patients who have headaches or migraines and among patients with Dysautonomia.

Conclusions: Conclusions: Of the 103 patients tested 52% have skin biopsy documented small fiber neuropathy. The high prevalence of negative biopsies in patients with similar phenotypes needs to be further evaluated. Although not statistically significantly the symptom profile and laboratory findings are consistent with other studies of small fiber neuropathy1, 2.

References

1. NeuropathyTreister R, Lodahl M, Lang M, Tworoger SS, Sawilowsky S, Oaklander AL. Initial development and validation of a patient-reported symptom survey for small-fiber polyneuropathy. J Pain. 2017;18(5):556-563. doi: 10.1016/j.jpain.2016.12.014

2. Lang M, Treister R, Oaklander AL. Diagnostic value of blood tests for occult causes of initially idiopathic small-fiber polyneuropathy. J Neurol. 2016;263(12):2515-2527. doi: 10.1007/s00415-016-8270-5

Keywords: neuropathy, pain, dysautonomia.

Poster No: 240 | **Mutational profile in patients with anti-MAG antibody neuropathy identifies new potential therapeutic target**

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Introduction: Anti-myelin-associated glycoprotein (MAG) antibody neuropathy is associated with IgM monoclonal gammopathy of undetermined significance (MGUS) or lymphoproliferative disorder (Waldenstrom's Macroglobulinemia [WM], marginal zone lymphoma [MZL] or chronic lymphocytic leukemia [CLL]). Rituximab is currently used in anti-MAG antibodies 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 WM, especially with MYD88L265P mutated and CXCR4S338X wild-type.

Methods: We assessed the mutational profile of the MYD88 and CXCR4 genes in 48 patients (33 men, mean age 72 ± 9.6 years) with anti-MAG antibody neuropathy. Of them, 27 (56.2%) had IgM-MGUS, 17 (35.4%) WM, 4 (8.3%) CLL/MZL. Molecular analysis was performed from bone marrow mononuclear cells, using allele specific-PCR in 35/48 patients and in circulating cell-free tumor DNA in 13/48. All the patients were assessed with INCAT (Inflammatory Neuropathy Cause and Treatment) Disability Score, INCAT Sensory Sum Score, Medical Research Council sum score.

Results: Thirty-three patients (68.7%) carried the MYD88L265P mutation: all the 17 WM patients, 15/27 (55.5%) MGUS and 1/4 (25%) CLL/MZL. All the patients were CXCR4S338X wild-type. Eleven of the 33 MYD88L265P mutated patients (33.3%) were treated with rituximab; of them, 7/11 (63.6%) relapsed. Thirteen of the 15 (86.6%) of the unmutated MYD88 patients were treated with rituximab and 7/13 (53.8%) relapsed, with no significant difference in relapse rate depending on the mutational profile ($P = 0.63$). Three patients (all WM, MYD88L265P mutated, 2 previously treated with rituximab) were treated with ibrutinib 420 mg/die orally, with early and progressive improvement, especially of the sensory symptoms as shown by improvement of clinical scales.

Conclusions: In conclusion, we confirm the high prevalence of the MYD88L265P mutation also in patients with IgM MGUS. As a mutational target for ibrutinib, a new and potential effective therapy for anti-MAG antibody neuropathy, the MYD88L265P mutation should be always searched for.

Keywords: anti-MAG neuropathy, MYD88 mutation, ibrutinib.

Poster No: 241 | **MAVERICK: Variant prioritization for Mendelian diseases using deep learning**

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Introduction: Thousands of genes have been discovered to cause Mendelian-inherited diseases, according to current data from OMIM. Yet, a sizable proportion of patients with many Mendelian disorders do not currently receive a genetic diagnosis. Identifying the causal variants in these unsolved cases is an important and challenging task.
Methods: We developed MAVERICK, a transformer-based neural network, to differentiate among Mendelian disease-causing dominant variants, recessive variants and all others. MAVERICK is able to classify non-synonymous SNVs and protein altering indels simply by comparing the referent and altered amino acid sequences.
Results: Patient exomes typically contain hundreds of rare, protein altering SNVs and Indels. We developed MAVERICK to filter those results down to a more manageable number of probable causal variants. Using only genotype information to rank all the variants in a patient, this approach gave the causal variant top prioritization over 77% of the time for known disease genes and over 50% of the time for novel disease genes. Furthermore, the causal variant fell within the top five ranked variants over 90% of the time for both known and novel disease genes. This novel disease gene set included several recently discovered CMT genes. In these test cases, the method considered both dominant and recessive inheritance patterns and scored all possible monogenic compound heterozygous pairs in addition to single heterozygous or homozygous variant solutions. MAVERICK additionally supports the incorporation of phenotype information as HPO terms and inheritance information, which can often improve performance considerably.
Conclusions: Here, we introduce MAVERICK: a Mendelian approach to variant effect prediction. We believe this approach will greatly reduce the time and effort required to solve cases with novel variations and even help elucidate new disease genes. MAVERICK is currently in open beta testing on the GENESIS platform, which hosts genomic data from over 1600 CMT patients.
Keywords: Deep Learning, Variant Prioritization, CMT, Genetic Diagnosis, Mendelian Inheritance.

Poster No: 242 | **Contribution of Kv1.6 to modulation of neuropathic pain in vivo and spontaneous activity in vitro**

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Introduction: Neuropathic pain following peripheral nerve injury is associated with hyperexcitability in damaged myelinated sensory axons, which partially normalizes overtime. Belatedly following nerve injury, axonal Kv1 channels switch the expression of its α-subunits, downregulating Kv1.1 and 1.2, and overexpressing Kv1.6. This coincides with a marked reduction in exacerbated spontaneous activity in injured spinal nerves, and diminished mechanical pain behavior. Blocking Kv1 channels with α-DTX reinstates damaged-triggered hyperexcitability. Aim: to further investigate Kv1.6 involvement in dampening hyperexcitability following severe sensory axon damage.
Methods: We determined mechanical allodynia (MA) in a sciatic nerve neuroma model in adult Sprague Dawley male rats. MA was evaluated by paw-withdrawal assay for up to 5 weeks after surgery in the presence or absence of 30 μM CPY-Fe1 (conopeptide Kv1.6 blocker). We cultured embryonic rat DRG explants in myelinating conditions. We determined Kv1.2 and Kv1.6 channels expression change after in vitro axotomy through Western Blot and immunofluorescence. Spontaneous and 30 mM KCl-evoked activity was recorded in axons in control conditions or with 30 μM CPY-Fe1.
Results: Rats developed MA after surgery, which recovered overtime. CPY-Fe1 treatment abolished this recovery. Undamaged DRG cell cultures express Kv1.6 at paranodes and juxtaparanodes; following axotomy Kv1.6 increases in myelinated axons. DRG culture axons express both Kv1.2 and Kv1.6 channels in control conditions. In vitro axotomy reduced Kv1.2 and increased Kv1.6 expression in Ranvier nodes of axotomized axons. Ca2+ influx was induced by KCl stimuli, both before and after axotomy. Action currents(AC) under voltage-clamp axon-attached mode occur at a rate of 1.6 AC/min on single undamaged axons($n = 9$). KCl stimulation increases this up to 9.2 AC/min($P = 0.0313$;$n = 6$). Acutely after axotomy, basal firing rate rises to 5.5 AC/min($P < 0.01$;$n = 5$), which tends to normalize overtime.
Conclusions: We are studying the effect of blocking Kv1.6 on axotomized axons and the use of lentiviral-mediated Kv1.6 overexpression on the electrical activity of DRG explant axons.
References
1. Calvo M, Richards N, Schmid AB, et al. Altered potassium channel distribution and composition in myelinated axons suppresses hyperexcitability following injury. Elife. 201.
2. González A, Ugarte G, Restrepo C, et al. Role of the excitability brake potassium current IKD in cold allodynia induced by chronic peripheral nerve injury. J Neurosci. 2017;37(12):3109-3126.
Grant Support: ANID National PhD Scholarship FONDECYT 1161019 MiNuSPain Millenium Nucleus for the Study of Pain.
Keywords: Neuropathic Pain, Electrophysiology, Potassium Channles, Kv1.6, Behavior.

Poster No: 243 | **Nutritional status in patients with Guillain-Barré syndrome: an observational study in Bangladesh**

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Introduction: Host nutritional status has effects on immune response that are implicated in the pathogenesis of autoimmune diseases including Guillain-Barré syndrome (GBS). We examined the association of nutritional status with disease progression and outcome of GBS in Bangladesh.

Methods: A total of 43 GBS patients were enrolled from a prospective study in Bangladesh. Socio-demographic information was collected using a standard questionnaire. Baseline anthropometric measurement such as body mass index (BMI), waist circumference (WC), hip circumference (HC), mid-upper arm circumference (MUAC) was taken. GBS severity and outcome were assessed by GBS disability score (GBS-DS). Routine blood parameters were measured using automated analyzer. Logistic regression was performed to see the association between nutritional status and disease progression and outcome.

Results: The median age of the patients was 31 years (IQR: 21-40) with male predominance (70%). We found mean ± SD of BMI (22.05 ± 5.01), WC (78.51 ± 15.2), HC (84.56 ± 15.5) and MUAC (25.19 ± 5.1) and hemoglobin (g/dL) (13.18 ± 2.02). Around 20% patients were undernourished, and more than 70% patients were in poor and middle-wealth quintiles. About 35% patients drank water from unimproved water sources and 12% used poor sanitation facilities. Increased hemoglobin was associated with lower risk of developing severe disease (OR: 0.46, 95% CI: 0.23-0.90, $P < 0.05$) and significantly associated with good outcome (GBS-DS < 3) at 4 weeks (OR: 0.54, 95% CI: 0.32-0.90, $P < 0.05$). Patients with low BMI had two times higher risk of having poor outcome at 4 weeks (OR: 2.18, 95% CI: 0.22-21.79). No significant association was found between disease severity and socio-economic status.

Conclusions: The study found hemoglobin and BMI are significantly associated with disease severity and poor outcome. These suggest that nutritional status may affect the clinical course and prognosis of GBS. However, further large-scale studies are required to confirm the findings.

References

1. Ding M, Markon A, Wolpert B, Chavarro JE. Associations of body mass index and waist circumference with risk of Guillain-Barré syndrome in women and men: A prospective analysis of three cohort studies. PLoS One. 2020;15(12):e0239099.

Grant Support: NIH-K43 Grant.

Keywords: Nutritional status, Guillain-Barré syndrome, waist circumference (WC), Body mass index.

Poster No: 244 | A RARE CAUSE OF MONONEUROPATHY MULTIPLEX

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Introduction: While rare, Lymphomatoid granulomatosis (LyG) is a mimic of other systemic vasculitidies given its multiorgan involvement and histological features of angiocentric inflammation. Given its association with dysregulated immune surveillance and immunosuppression, accurate diagnosis is important as treatment varies from other systemic vasculitities.

Methods: Case Report.

Results: A 58-year-old male presented with a 4-month history of progressive, multifocal sensory disturbances in all extremities and acute onset right foot drop without systemic symptoms. Examination showed multifocal loss of pinprick sensation, distal weakness in the left upper extremity and right ankle dorsiflexion and plantarflexion weakness. Electrodiagnostic testing confirmed an asymmetric sensorimotor axonal polyneuropathy consistent with MNM. Neuroimaging of the brain and lumbar spine were unremarkable. Vasculitic, infectious, nutritional and immunologic laboratory studies were unrevealing to include negative myeloperoxidase (MPO) and serine protease 3 (PR3) antibody testing. Cerebrospinal fluid analysis was unremarkable. A fat pad biopsy was negative. Full body PET scan revealed hypermetabolic lesions in the left upper and lower lobes and a right lower lobe pleural based mass. Tissue biopsies were performed of the lung and right peroneus brevis muscle and sural nerve. Empiric treatment with corticosteroids and mycophenolate mofetil was discontinued within 1 month due to side effects and concerns related to the COVID-19 pandemic. Lung pathology results were ultimately diagnostic of lymphomatoid granulomatosis (LyG) with complementary findings of an inflammatory neuropathy with poorly formed, non-caseating granulomas on the sural nerve biopsy. Fite stain on the sural nerve biopsy was negative for *Mycobacterium leprae*.

Conclusions: LyG is an extremely rare angiodestructive lymphoproliferative disease. Only one other published case report describes mononeuopathy multiplex in a patient with lymphomatoid granulomatosis which was diagnosed post-mortem. In patients with pulmonary lesions and multifocal sensorimotor symptoms, LyG should be suspected as a cause of granulomatous mononeuropathy multiplex.

References

1. Song JY, Pittaluga S, Dunleavy K, et al. Lymphomatoid granulomatosis-a single institute experience: pathologic findings and clinical correlations. Am J Surg Pathol. 2015; 39(2):141-156.

2. Melani C, Jaffe ES, Wilson WH. Pathobiology and treatment of lymphomatoid granulomatosis, a rare EBV-driven disorder. Blood 2020;135 (16):1344-1352.

3. Elavarasi A, George J, Sharma MC, et al. Multiple neurologic deficits and cognitive decline in a young woman. Ann Indian Acad Neurol. 2019;22(4):506-512.

4. Gibbs AR. Lymphomatoid granulomatosis-a condition with affinities to Wegener's granulomatosis and lymphoma. Thorax 1977; 32:71-79.

5. O'Brian S, Schmidt P. Lymphomatoid granulomatosis with paraneoplastic polymyositis: A rare malignancy with rare complication.

Keywords: Mononeuropathy Multiplex, Vasculitic Neuropathy, Lymphomatoid Granulomatosis.

Poster No: 245 | **NADPH oxidase activation underlies MMP-13-dependent paclitaxel-induced neurotoxicity**

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Introduction: Paclitaxel is an anti-cancer agent that leads to a distal, symmetric, sensory-dominant neuropathy (PIPN) in approximately 70% of patients. Underlying mechanisms are unknown and primarily suspected to be neuron-intrinsic, however, the Rieger lab has previously uncovered that epidermal damage is a major underlying factor in PIPN. More specifically, that inhibition of the extracellular matrix-degrading enzyme, matrix-metalloproteinase 13 (MMP-13), prevents neuropathy-like symptoms and axon degeneration in rodents and zebrafish, respectively. While our previous studies have demonstrated different sources of hydrogen peroxide (H2O2) regulate MMP-13 activity and expression, the exact source of H2O2 and upstream regulatory mechanisms remain elusive.

Methods: Insights into the mechanisms underlying MMP-13 regulation will allow for the development of precision-targeted therapies to improve patient quality of life. Here we investigated possible sources of H2O2.

Results: Our lab's recent findings using in vivo quantitative imaging analysis in zebrafish show paclitaxel treatment causes increased mitochondrial H2O2 in the epidermis, further supporting our previous data suggesting mitochondrial dysregulation in the presence of paclitaxel underlies reactive oxygen species (ROS)/H2O2 formation and MMP-13 upregulation. However, we further investigated additional sources of H2O2 production, such as microtubule(MT) stretch-dependent mechanisms. We hypothesized that paclitaxel's MT-stabilizing activity increases epidermal H2O2 through activation of membrane NADPH oxidases tethered to MTs. Our recent RNAseq and qPCR data in mice and zebrafish support these findings.

Conclusions: We are currently investigating further the potential involvement epithelial NADPH oxidases using mutant and imaging analyses. Future studies will investigate potential mechanisms underlying increased NADPH oxidase activity.

Grant Support: Research reported in this presentation was supported by the National Cancer Institute of the National Institutes of Health under award number 7R01CA215973-02.

Keywords: Axon Degeneration, Oxidative Stress, Toxic Neuropathy, Chemotherapy Induced Peripheral Neuropathy, RNAseq.

Poster No: 246 | **Development of an algorithm to support the differential diagnostic process in peripheral neuropathies: ALADDIN project**

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Introduction: The diagnostic process in peripheral nerve diseases may be changeling. However, achieving rapidly the correct diagnosis is essential for treatment and prognosis. The aim of our work is to elaborate an algorithm, which can be a support to neurologists in the diagnostic process of peripheral neuropathies, even for those not specialized in peripheral nerves diseases.

Methods: To elaborate the algorithm, data were collected from the most recent and updated scientific literature. We focused on those neuropathies that most often can be included in the differential diagnosis of each other: chronic inflammatory demyelinating polyradiculoneuropathy, anti-MAG neuropathy, multifocal motor neuropathy, familial amyloid polyneuropathy, AL amyloidosis neuropathy, POEMS syndrome, diabetic neuropathy, the most common variants of hereditary neuropathies, vasculitic and paraneoplastic neuropathies. For each of them, suggestive signs and symptoms, blood chemistry, associated systemic signs, characteristics of the neurophysiological study, CSF examination and MRI data were collected. These data were then entered into a computer algorithm thanks to which each type of neuropathy corresponds to a set of signs, symptoms and instrumental tests.

Results: A web application was therefore created. Neurologists can easily select, from a list of numerous data, those reported by their patients. Once entered all data requested, diagnostic suggestions appear, listed in order from the most to the least probable. Subsequently, the selection of the most probable diagnostic suggestion allow to view a card with advices on any further investigation useful for diagnosis confirmation and for possible therapeutic strategies. The algorithm has been tested retrospectively on 138 cases with a known diagnosis. Neurologists and algorithm diagnosis matched in 84.8% of cases.

Conclusions: Considering the high number of increasingly available therapies for peripheral nerve diseases, the rapid achievement of a correct diagnosis has become always more changeling. In this way, our web application can become a useful tool.

Keywords: Differential diagnosis, Inflammatory neuropathies, Hereditary neuropathies.

Poster No: 247 | **Deep brain stimulation for tremor in chronic inflammatory demyelinating polyneuropathy: A series of three cases**

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Introduction: Tremor is a symptom of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and other neuropathies. Deep Brain Stimulation (DBS) is a therapy for tremor of various etiologies. Little is known on the efficacy of DBS in tremor due to CIDP.
Methods: We report all CIDP patients treated with DBS in our center. DBS was targeted at the dentatorubrothalamic tract (DRT) during its course in the posterior subthalamic area (PSA). To determine the location for DBS electrode implantation diffusion tension imaging tractography and intraoperative clinical response to macrostimulation were used. Tremor was assessed with the Fahn-Tolosa-Marin tremor rating scale (FTM-TRS, range 0 to 156). Neuropathy associated disability was measured with the Inflammatory Rash-built Overall Disability Scale (I-RODS, range 0 to 48). Assessments were performed pre-operatively and up to 12 months post-operatively. Additional clinical information was available up to 24 months.
Results: Three CIPD patients (all males, age range 65-69 years) with neuropathic tremor were treated with bilateral DBS of the DRT/PSA. Tremor severity improved in all patients according to the FTM-TRS scores: preoperative and follow-up (FU) scores were 52 and 31 for case 1 (10 months FU), 58 and 18 for case 2 (12 months FU). Despite a slight FTM-TRS improvement in case 3 (76 to 65; 6 months FU); impairments due to tremor remained unchanged. Neuropathy associated disability improved in case 1 (I-RODS 20 to 23) and case 2 (I-RODS 35 to 45), and deteriorated in case 3 (clinical assessment). Two years after DBS surgery, case 1 and 2 had an increase in symptoms and disability, mainly attributable to intention tremor.
Conclusions: DBS of the DRT/PSA effectively improved neuropathic tremor and disability in two out of three CIDP patients, but the long-term response was suboptimal. Follow-up of a larger group of patients is needed to further substantiate the findings.
Keywords: Tremor, Deep brain stimulation, Demyelinating diseases, Polyradiculoneuropathy.

Poster No: 248 | **Pediatric chronic inflammatory demyelinating polyneuropathy: Clinical description of three cases with poor therapeutic response to steroids**

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Introduction: Chronic inflammatory demyelinating polyneuropathy (CIDP) in pediatric population is uncommon. They present with acute/subacute/chronic onset making diagnosis challenging and there are few studies on therapeutic response.
Methods: Retrospective case study.
Results: Age at onset ranged from 4-15 years (P1 - 10y, P2 - 4y, P3 - 15y). M:F was 1:2. Two patients had acute onset typical of GBS followed by relapses while one had chronic onset. Duration of illness was 5 days in P1, 15 days in P2 and 2 months in P3. Motor symptoms were dominant in P1 & P2 while distal sensorimotor symptoms in P3. Proximal>distal lower limb weakness with falls followed by upper limb, neck and truncal weakness in P1, P2 while P3 had distal weakness & numbness. All had areflexia. P1 had 4 relapses while P2 had 3 relapses. Bulbar weakness was seen during relapse in P1. Demyelination - prolonged distal latencies, reduced conduction velocities, conduction block, temporal dispersion was observed in all. MRI brachial, lumbosacral plexus -thickened and enhancing in P1 and P2. CSF showed albuminocytologic dissociation in all. Clinical exome sequencing in P1 and P2 was negative. All were treated with pulse steroids followed by oral however, they continued to worsen. Hence, mycophenolate was started. P1 has follow-up of 2.5 years with only mild distal weakness and P3 after 2 years has completely recovered. P2 was recently started on second-line immunomodulation after third relapse.
Conclusions: Pediatric CIDP is a rare disease. Studies by Silwal et al, 2018 on 21 cases and McMillan et al, 2013 on 30 cases which are the largest case series- suggested chronic presentations were frequent and good response to IVIG/steroids. We describe clinical challenges faced due to GBS-like presentation at onset of CIDP and need for other immunomodulatory agents as response to steroids was poor in our cases.
Keywords: Pediatric CIDP, GBS, Steroids.

Poster No: 249 | **Argonaute autoantibodies as biomarkers for a dysimmune context in peripheral neuropathies**

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Introduction: The identification of autoantibody biomarkers in peripheral neuropathies (PN) can assist clinicians to establish a diagnosis and choose an appropriate treatment. However, for many patients, no biomarker is detected, although it appears that some idiopathic PN are linked to a dysimmune context. To reveal a potentially undetected dysimmune context of PN, novel autoantibodies (Abs) are of major importance. In this study we aimed to describe Abs against the family of Argonaute (AGO) proteins (mainly AGO1 and AGO2) as a serum biomarker for a dysimmune context in PN.

Methods: Protein microarrays were applied for antibody identification in PN patients. Enzyme-linked immunosorbent assay was used to validate the sensitivity/specificity of the serum Abs and to determine their titer, IgG subclass, and conformation specificity. We used 116 healthy controls (HC), 230 subjects having systemic autoimmune diseases (SAD) already known to be associated with AGO Abs (formerly anti-Su) in 8-20% of the cases as a positive control cohort, and 350 patients with different NP.

Results: We found AGO Abs in 0/116 HC and in 14/200 (7.0%) SAD, comprising 5/95 (5.3%) Sjögren's syndrome, 7/65 (10.8%) systemic lupus erythematosus, 0/19 (0%) primary biliary cholangitis, and 2/51 (3.9%) other SAD. Among the PN, we found 28/350 patients (8.0%) with AGO Abs, comprising 19/133 (14.3%) sensory neuronopathy, 2/68 (2.9%) small fiber neuropathy, 2/58 (3.4%) chronic inflammatory demyelinating polyneuropathy, and 5/91 (5.5%) other PN. For 8/28 seropositive PN patients (28.6%), the AGO Abs were the only known biomarker of a dysimmune context. Antibody titers were between 1:100 and 1:100000, subclass IgG1 was dominating, but also IgG2-4 were detected in some patients. Furthermore, 3/28 had cancer and in 27/28 the AGO Abs were conformation specific.

Conclusions: We suggest that AGO Abs are biomarkers of a dysimmune context in patients with PN and may hence present a clinical benefit in diagnosis and treatment decision.

Grant Support: This work has been developed within the BETPSY project, which is supported by a public grant overseen by the French National Research Agency (ANR), as part of the "Investissements d'Avenir" program (reference ANR-18-RHUS-0012) and ANR-10-INBS-08-01 ProFi.

Keywords: Argonaute antibodies, Biomarker, Autoantibody, Autoimmunity, Sensory neuronopathy.

Poster No: 250 | Epidermal axon changes in patients with prediabetes: The PACMAN study

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Introduction: Understanding the progression of neuropathy is important as the incidence of prediabetes increases. The societal and biologic risk factors driving neuropathy progression are critically important to identify. We report on an ongoing clinical study with subjects recruited into 3 groups based on metabolic status: 1) normal (N), 2) prediabetes with no neuropathy (PD-N), 3) prediabetes with neuropathy (PD + N). Our goal is to identify biomarkers relevant to neuropathy in prediabetes and identify potential changes in axonal subpopulations.

Methods: Subjects with and without diabetes and no other cause for neuropathy were enrolled. All subjects underwent an initial visit to determine metabolic health. Demographic information, health history, social/lifestyle history was obtained. Physical and neuropathy assessments were performed on all subjects. Lipid profile and other metabolic laboratory tests were obtained. Subjects were categorized into subgroups based on clinical examination and ADA Guidelines for A1c, fasting glucose, and oral glucose tolerance. Distal leg skin biopsies were performed on all subjects. IENFD assessments include antibodies to PGP9.5, TrkA to identify a subpopulation of peptidergic axons, and langerin to identify Langerhans cells.

Results: To date, 72 subjects have been screened and 22 subjects have completed the study. Subjects with prediabetes have impaired glucose tolerance, elevated HOMA-IR and hyperinsulinemia. Prediabetic subjects with neuropathy have significant decreases in IENFD (N = 11.03, PD-N = 11.94, PD + N = 4.27 fibers/mm, $P < 0.5$) compared to normal and prediabetic subjects without neuropathy. Importantly, no differences were noted related to axon fiber type or Langerhans cells. Also, prediabetic subjects with neuropathy have significantly lower LDL levels than normal or prediabetic subjects without neuropathy (N = 97.0, PD-N = 124.3, PD + N = 84.0, $P < 0.5$).

Conclusions: Our preliminary results suggest that unlike rodents, subjects with prediabetes have IENFD loss across all epidermal fiber types. Interestingly, LDL levels differ among prediabetics, suggesting that LDL levels may play a role in neuropathy in prediabetes.

Grant Support: 5 R01 NS043314-15.

Keywords: Prediabetes, Neuropathy, epidermal nerve fiber density, LDL.

Poster No: 251 | Intravenous administration of ANX005, an anti-C1q therapy, inhibits CSF antibody-driven complement activity in early stage Guillain-Barré syndrome

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Introduction: We hypothesize that in early Guillain-Barré Syndrome (GBS), pathological changes in blood-CSF permeability allows leakage of autoreactive antibodies and complement components into the CSF, that can drive classical complement-mediated peripheral nerve root damage.

Methods: CSF was collected from GBS patients participating in a randomized placebo-controlled Phase 1b study, before and 5-12 days after intravenous administration of a single dose of ANX005 or

placebo. CSF samples from 50 patients were screened for IgM and IgG antibodies against GM1 ganglioside, a known target of autoreactive antibodies in GBS. Positive samples were examined for their ability to activate the classical complement cascade on plates coated with GM1 vs control gangliosides, as measured by deposition of C3 and C4 on plates in an ex vivo assay. The assay relied on antibody and complement components already present within the CSF.

Results: All GBS patients had elevated levels of immunoglobulin as well as complement proteins in their CSF (20-100x above controls), which correlated with the degree of blood-CSF barrier permeability measured by the CSF/serum quotient of albumin. IgG and / or IgM antibodies against GM1 were observed in 30% of patients, but not in CSF samples from patient controls. Pretreatment samples from the majority of these patients triggered complement deposition specifically on GM1-coated plates, with the highest degree of activation in samples that had both IgG and IgM anti-GM1 antibodies. In samples taken after treatment with ANX005, unlike placebo, complement activation was inhibited, consistent with full engagement of C1q by the anti-C1q therapy.

Conclusions: These findings support the hypothesis of IgG and IgM autoantibody-driven complement damage at the level of peripheral nerve roots, which is amenable to classical complement inhibition.

Keywords: Autoreactive IgM and IgG antibodies, Guillain-Barré Syndrome, Peripheral nerve root, Blood-CSF barrier, Complement inhibition.

Poster No: 252 | **Itch in lichen simplex chronicus is associated with localized small fiber neuropathy**

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Introduction: Lichen simplex chronicus (LSC), is a common pruritic condition of unknown pathophysiology. Sensory innervation of the skin consists of a dermal plexus formed by myelinated and unmyelinated fibers. The epidermis only contains unmyelinated fibers, which signal temperature, pain and/or itch. Damage to these intraepidermal fibers can produce neuropathic itch, pain or both. We hypothesized that itch in LSC could have a significant neuropathic component if chronic skin inflammation leads to intraepidermal fiber dysfunction.

Methods: -We prospectively enrolled 33 patients with histological diagnosis of LSC. -We determined the sensory profile of patients' lesional and uninvolved skin using Quantitative sensory testing (QST). -We obtained skin punch biopsies from lesional and uninvolved sites and immunostained with PGP9.5 -We used 5% lidocaine plaster to cover the lesion for 12 hours daily for 1 month.

Results: We enrolled 33 patients. Mean itch intensity was 6.3 ± 2.2. Pain was present in 44% with a mean intensity of 4.6 ± 1.6. We observed a reduced sensitivity to warm and cool stimuli, as well as increased thermal sensory limen. Mechanical sensitivity was unchanged. 22% of LSC patients presented allokinesis at the lesion site. We observed a reduction in the intraepidermal nerve fiber density at the lesional site (1.8 ± 2.3 fibers/mm) compared to control (11 ± 2.4 fibers/mm, $P < 0.0001$). We temporarily block itch sensation, using a 5% lidocaine plaster for 1 month. Itch and pain were reduced. Thermal sensory function was significantly improved. Epidermal thickness was reduced by 31%, innervation of the epidermis improved with treatment, although most patients did not reach normal values (before: 0.37 ± 0.3 fibers/mm, after: 3.55 ± 3 fibers/mm, $P = 0.03$).

Conclusions: We have demonstrated that LSC skin is associated with a localized SFN evidenced by loss in thermal sensitivity and decrease in intraepidermal fibers. Silencing damaged intraepidermal fibers with lidocaine led to healing of the skin together with initial reinnervation and reinstatement of thermal sensitivity.

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Keywords: small fiber neuropathy, neuropathic itch, lichen simplex chronicus.

Poster No: 253 | **Muscle MRI as a novel outcome measure of hereditary transthyretin amyloidosis: A cross-sectional cohort study**

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Introduction: The development of reliable outcome measures correlating with patient functional deficits and sensitive to early disease stages has proven challenging in hereditary transthyretin (hATTR) amyloidosis. Recently, magnetic resonance imaging (MRI) quantification of intramuscular fat showed high responsiveness in patients carrying Charcot-Marie-Tooth 1A. The aim was to assess the role of quantitative muscle MRI (qMRI) as an outcome measure by cross-sectional correlation against functionally relevant clinical measures in hATTR amyloidosis.

Methods: Twenty-four patients with hATTR amyloidosis (18 males, median age 63, range 45-76) attending the Amyloidosis Research and

Treatment Center (Pavia) were enrolled. Most frequent mutations were Val30Met (6; 25%) and Phe64Leu (4; 17%). Twenty-one/24 (87.5%) patients were receiving treatment. Extent of disability and neurological functional impairment were quantified by Polyneuropathy Disability (PND) scoring system and Neurological Impairment Score (NIS) and NIS-lower limb, respectively. Participants underwent lower limb 3 T-MRI of thigh and calf muscles. Muscle fat fraction (FF), indicating the degree of fat replacement of degenerated muscle fibers, was quantified by Fatty Riot algorithm from a 6-point multi-echo gradient-echo acquisitions.

Results: Median NIS was 20 (range 4-170.5). Widespread changes at both thigh and calf level were seen without any selective pattern of muscle involvement. Mean FF at thigh and calf level was 10 ± 4% and 12 ± 10%, respectively, which is higher compared with mean FF of healthy controls of previous reports (~1.5%). We identified a significant correlation between mean FF and both PND score and NIS/NIS-LL ($P < 0.01$). This positive association was independent from age, sex, mutation and treatment in a multivariable regression model.

Conclusions: This cross-sectional pilot study showed correlation between muscle qMRI measures and disease stage and clinical severity in hATTR amyloidosis, thus paving the way for the assessment of qMRI role in pre-symptomatic carriers and its responsiveness to change over time.

Keywords: Hereditary transthyretin amyloidosis, Quantitative muscle MRI, Fat fraction, NIS.

Poster No: 254 | Loss-of-function SARM1 coding variation is present in the human population

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Introduction: Sterile alpha and TIR motif containing 1 (SARM1) is a central executioner of axon death which plays a major role especially in the early stage of various neurological diseases. Its intrinsic enzymatic NADase function, which resides within the Toll/interleukin-1 receptor (TIR) domain, is essential for inducing pathological axon loss. Interestingly, axonal damage varies widely between individuals even when upstream causes are closely matched. We are trying to understand why that is the case and hypothesize that variants in the pro-degenerative gene SARM1 can have a disease-modifying effect, thereby contributing to a spectrum of axon vulnerability in the human population.

Methods: In this study, we selected a total of 18 missense variants within the coding region of human SARM1. All mutations reside within the protein's sterile α motif (SAM) or TIR domain and were chosen from the dbSNP and the gnomAD databases. We then went on to investigate the function of these naturally-ocuring mutations looking at consequences on NAD+ metabolism and injury-induced axon degeneration.

Results: Our data demonstrate the presence of loss-of-function (LoF) SARM1 coding variation within the general human population. Some of these novel variants, especially those in close proximity to the binding pocket of the NADase, translate to altered NAD+ levels, ATP levels, SARM1 NADase activity and axon susceptibility in vitro. This implies a role in protecting axons in neuropathies consistent with the idea that the Wallerian degeneration pathway is relevant to human physiology and disease.

Conclusions: We propose that genetic variation in human SARM1 may act as modifiers of human axonopathies and neurodegenerative disorders.

Grant Support: Thompson Family Foundation Grant.

Keywords: Wallerian degeneration, human Sarm1, axon vulnerability, peripheral neuropathies.

Poster No: 255 | Chronic inflammatory neuropathies associated with COVID-19: Case-descriptions of unique phenotype

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Introduction: With present COVID-19 pandemic its association with onset of Guillain-Barré syndrome has received interest in several reports, but has been limited to the notion of exacerbations in only a few patients with chronic inflammatory demyelinating polyneuropathy (CIDP). We here present 2 cases with complex CIDP phenotypes associated with COVID-19.

Methods: A 37-years old male and 48-years old female presented with subacute onset of distal limb paresthesia following confirmed COVID-19 infections, initially with slow progression over months with more diffuse sensory deficits and subsequent rapid course of diffuse muscle weakness and cranial nerve involvement. Neurologic examination showed tetraparesis, diffuse hypoesthesia, areflexia and multiple cranial nerve involvement.

Results: They underwent all relevant ancillary investigations, including nerve conduction studies and fulfilled the EFNS/PNS electrodiagnostic criteria for CIDP, but lacked anti-ganglioside and nodal antibodies nor showed evidence for other systemic disorders. Subsequent treatment resulted improvement, but required combined immune-modulating strategies in the first case.

Conclusions: Our 2 cases indicate that COVID-19 infections may lead to unique presentations of complex CIDP phenotypes. The lack of established antibodies, related to distinct clinical presentations of inflammatory neuropathies, in combination with responsiveness to immune-modulating treatment suggest that these could belong to yet undetermined spectrum of antibody mediated chronic inflammatory neuropathies.

Keywords: COVID-19, CIDP, Inflammatory neuropathy, Antibodies, EMG.

Poster No: 256 | **Update on the international CIDP outcome study (ICOS): A prospective observational study**

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Introduction: Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare immune-mediated polyneuropathy with considerable heterogeneity in clinical presentation, electrodiagnostic features, treatment response and long-term outcome. This heterogeneity complicates the diagnostic process, and counseling of patients regarding treatment efficacy. Improved description of CIDP and its variants, 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. Follow-up visits are scheduled every 6 months for a minimum of 2 years, after which visits can be continued annually. In treatment-naïve patients, an additional follow-up visit is scheduled at 6 weeks. ICOS contains clinical, diagnostic and treatment data, as well as biomaterials (DNA, cerebrospinal fluid, and serial serum samples at each visit). Outcome measures include validated disability scales along with patient reported outcomes, such as RODS, R-FSS, and EQ-5D-5L.
Results: Since November 2015, 259 patients have been enrolled in three Dutch academic hospitals (67% men, median age at diagnosis of 59 years). Of all included patients, 83% have completed 12 months of follow-up, and 75% have completed 24 months of follow-up. Acute onset, which is either GBS-like or acute-onset CIDP, is reported in 30% of all patients. Of the patients currently included in the ICOS cohort, 70% are diagnosed with typical CIDP, while 29% of patients have a CIDP variant (asymmetric 18%, predominant motor 6%, −sensory 3% or predominant distal involvement 2%).
Conclusions: ICOS aims to include at least 1000 CIDP patients. Our aim is to improve the diagnostic process and choice of treatment, and to obtain more insight in determinants of long-term outcome of CIDP. Harmonization of study protocols will allow close collaboration of ICOS with other registries, such as INCbase.
Keywords: CIDP, Outcome, Prediction.

Poster No: 257 | **Disentangling the enzymatic functions of HINT1 and their connection to CMT neuropathy**

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Introduction: Mutations in HINT1 cause axonal neuropathy with neuromyotonia (NMAN). Besides its known nucleotide phosphoramidase function, HINT1 was found to exhibit cysteine protease activity, removing SUMO from a variety of signaling proteins in vitro. The SUMOylation activity of HINT1 in vivo and its involvement in NMAN is yet to be determined.
Methods: We introduced an artificial missense variation in HINT1 (p.Cys84Ser) targeting the key residue for SUMOylation activity and tested it by genetic complementation in a yeast strain deficient for the yeast orthologue (HNT1). We also created yeast strains deficient for two yeast SUMOylases (Slx5, Uls1) by homologous recombination.
Results: The HINT1-p.Cys84Ser genetically complemented the growth deficiency in the HNT1 knockout yeast model, suggesting that the SUMOylase activity is not as conserved as the HINT1 phosphoramidase activity. Indeed, multiple sequence alignment showed that p.Cys84 is only conserved in mammals and zebrafish but not in yeast. Importantly, a systematic assessment of all reported NMAN-causing HINT1 variants demonstrated that two of them fully complement the growth defect when expressed in the HNT1 knockout yeast. While this proves that they both retain their phosporamidase activity, we cannot draw conclusions about the SUMOylase activity with the current model. Therefore, we set out to develop a novel yeast model to assess HINT1 SUMOylation function. We created knockout strains targeting Slx5 and Uls1, and we are validating their SUMOylation state. Subsequently, we will repeat the genetic complementation assay in the yeast strains that are SUMOylation deficient, to determine whether they can serve as a model for HINT1 SUMOylation activity.
Conclusions: Our pilot studies on the newly reported SUMOylation activity of HINT1 indicate that the initially established yeast model only partially recapitulates the enzymatic activities of HINT1. The development of new tools is therefore crucial to discriminate which HINT1 function(s) are affected by the disease-causing variations and are thus linked to neuropathy.
Keywords: HINT1, Axonal Neuropathy, CMT2, Yeast.

Poster No: 258 | **Problematic of the diagnosis and management of peripheral neuropathy in a limited-resources setting (Mali)**

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Introduction: Peripheral neuropathy (PN) is a common and heterogeneous group of neurological disorders. Despite its high prevalence elsewhere, PN have been overtaken by central nervous system disorders in developing countries, probably due to limited resources to characterize them. The recent acquisition of an electromyograph has improved the clinical refinement of our PN patients. Thus, we performed this study with the aim to clinically characterize patients with PN and identify their etiologies.

Methods: This is a hospital-based study conducted from January 2019 to December 2020. Only in-patients with a suspicion of PN were included. After clinical evaluation, laboratory testing including vitamin B12, creatinine, blood glucose level and cell count, HIV serology, and CSF analysis, and nerve conductions studies (NCS) were done. In addition, genetic testing is planned for cases with suspected genetic origin.

Results: Sixteen patients (9 males and 7 females) were enrolled. The mean age at diagnosis was 38.9 years (ranging from 19-62 years). Distal muscle weakness was the main reason for consultation, and paraparesis the starting symptom. NCS performed in 10 patients confirmed the sensorimotor demyelinating type in six patients, three axonal and one undetermined. There were eight cases of Guillain-Barré syndrome of which six had CSF albuminocytologic dissociation, three cases of diabetic polyneuropathy, one case of HIV-related polyneuropathy and one case of dominant Charcot-Marie-Tooth phenotype. In four cases, no etiologies were found. All patients benefitted of some standard treatment except Guillain-Barré patients due to the lack immunoglobulin in Mali. Progression was favorable except for one patient who passed away. Further investigations are ongoing for the unknown and suspected CMT cases.

Conclusions: In this study, Guillain-Barré syndrome was the most common type of peripheral neuropathy in in-patients, suggesting the necessity to conduct a larger study to identify its etiologies for better management.

Keywords: Polyneuropathies, Guillain Barré syndrome, Mali, West-Africa.

Poster No: 259 | The use of remote measures for charcot marie tooth type 1A (CMT1A), a pilot study

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Introduction: 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. Grip dynamometry and the 9-hole peg test (9HPT) measure upper limb function and the timed up and go (TUG) assesses gait and balance function - deficits in these areas commonly cause disability in CMT1A. Remote administration of these assessments, if found reliable, can reduce participant burden, increase participation of those living further from research centers, and provide frequent monitoring during clinical trials.

Methods: Methods: After an in-person visit, participants were sent home with a Jamar Plus digital hand dynamometer, 9HPT, and 3-m tape for the TUG. Within one week of the in-person visit, a remote assessment was performed by the clinical evaluator via synchronous HIPPA compliant video conferencing. Time to complete the 9HPT and TUG was recorded, as well as 3 trials of grip dynamometry. Feasibility was assessed and results of the in-person and remote assessments were compared.

Results: Results: Fifteen participants (ages 18-64) completed all of the remote assessments, which took 5-10 minutes. Both the TUG and 9HPT demonstrated a 0.91 ICC (0.75-0.97 CI; $P < 0.0001$). Hand grip dynamometry had an ICC of 0.87 (0.64-0.96 CI; $P < 0.0001$).

Conclusions: Conclusion: Remote assessments took minimal time to complete and were feasible in this pilot study. The TUG and 9HPT demonstrate excellent reliability and grip dynamometry shows good reliability. Reliability of the handgrip may have been limited by the use of two different dynamometers. Examining the feasibility and reliability of remote assessments in a larger population and over time is necessary to determine the utility in clinical trials.

Grant Support: CMTA funding.

Keywords: CMT, Remote Measure, Remote Assessment, Functional Assessment.

Poster No: 260 | The Charcot-Marie-Tooth disease gene curation expert panel (ClinGen)

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Introduction: The genetic spectrum of Charcot-Marie-Tooth (CMT) disease currently spans more than 90 reported genes, and that number continues to rise with advances in genome sequencing technology. 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 16 CMT genes: 11 genes have been classified as definitive (DNM2, FGD4, GDAP1, GJB1, MPZ, MTMR2, NEFH, TTR, INF2 SLC25A46, and YARS1), 2 genes as moderate (GNB4 and LITAF), 2 genes as limited (ARHGF10 and MARS1) 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.

Keywords: CMT, ClinGen, disease genes, variants.

Poster No: 261 | Mitochondria regulatory genes protect against cisplatin neurotoxicity in a *Drosophila melanogaster* model

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Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) is a critical, often dose-limiting side effect of platinum-based anti-cancer drugs such as cisplatin. 30% of patients treated with cisplatin develop lifelong toxic neuropathy. Few known risk factors reliably identify vulnerable patients, and effective treatments or preventive measures are not available. Cisplatin causes cell death by forming platinum-DNA adducts, damaging the mitochondria, and increasing levels of damaging reactive oxygen species, leading to cell death by apoptosis. Further research into the mechanism of neuronal cell death and identification of factors, such as genetics, that contribute to cisplatin neurotoxicity are critical to improving disease outcomes in patients.

Methods: Here, we present an in vivo model of CIPN in *Drosophila melanogaster* in which cisplatin treatment causes toxic neuropathy that can be assessed using behavioral analysis such as negative geotaxis climbing assays, imaging of apoptotic neurons, and biochemical analysis of mitochondria health and function.

Results: We have identified a Drosophila strain in which genetic reduction of mitochondria complex I subunits is protective against cisplatin neurotoxicity. This strain exhibits improved climbing, reduced neuronal apoptosis, and maintained mitochondrial health with cisplatin treatment, as compared to control strains. We also show that mitochondria regulatory pathway genes PGC1-α and Sirt1 are necessary for this protection against cisplatin.

Conclusions: Altered mitochondria regulation and function are a likely mechanism of resistance to cisplatin neurotoxicity in our model. These findings in a Drosophila model of CIPN have translational potential for CIPN prevention and identification of at-risk patients through a focus on preservation of mitochondria health and function.

References

1. Podratz JL, Staff NP, Froemel D, et al. *Drosophila melanogaster*: a new model to study cisplatin-induced neurotoxicity. Neurobiol Dis. 2011;43:330-337.

2. Groen CM, Podratz JL, Treb K, Windebank AJ. Drosophila strain specific response to cisplatin neurotoxicity. Fly (Austin). 2019;12:174-182.

Keywords: Chemotherapy Peripheral Neuropathy, Mitochondria, Drosophila.

Poster No: 262 | Early amyloidosis detection in asymptomatic carriers of ATTRv mutations with normal electroneuromyography

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Introduction: In the last decade, four disease modifying therapies have been proposed for ATTRv, a life-threatening disease. It is essential to screen for ATTRv onset as early as possible. We describe clinical and paraclinical data from ATTRv asymptomatic carriers with normal electromyography, as a baseline assessment to detect disease onset and progression.

Methods: We retrospectively collected data of ATTRv carriers with normal electroneuromyography, between March first 2015 and January 31st 2019, including: demographics, symptoms, physical exam, electroneuromyography (initial and in follow-up obtained in

73 patients, 56.2%), neurovegetative tests, skin biopsy (amyloid deposition, denervation), cardiac evaluation (multimodal imaging, cardiac denervation and arrhythmias).

Results: We included 130 patients, aged 43.6 years (±13.5), selected in family of a proband with an age of onset of 52.7 years (±15.7), 40.8% male, carrying 20 different variants of the transthyretin gene, including 83 Val30Met. Amyloid deposits on skin biopsy (11 patients) and/or cardiac.

Conclusions: Clinical and paraclinical assessment of asymptomatic carriers of ATTRv mutations show that skin or cardiac amyloid in.

Keywords: Inherited neuropathies, Amyloidosis, Transthyretin, Carriers, Genetic.

Poster No: 263 | A pipeline for streamlining repeat expansion discovery

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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). Expansions of short tandem repeats (TRs) are responsible for over 40 known diseases, most of which primarily affect the nervous system. We hypothesize these represent only a fraction of the pathogenic repeat expansions that exist and that they may be responsible for explaining a proportion of the missing heritability of rare monogenic neurodegenerative diseases.

Methods: ExpansionHunter Denovo was used to identify large TRs genome-wide in 1115 control genomes as well as a replication cohort of 2504 samples from the 1000 Genomes Project. This TR profile was compared to positive control samples with known repeat expansion disorders to develop a method for identifying and filtering expanded TRs in undiagnosed disease genomes.

Results: After investigating 102 genomes with amyotrophic lateral sclerosis (ALS), Friedrich's ataxia, fragile-X, and CANVAS among others, we found that there were statistically significant differences in the ExpansionHunter Denovo output between negative and positive controls. Thus, we created pipelines for streamlining the discovery of novel repeat expansions through both case-control and outlier analysis using filters based on population allele frequency, genomic locus, and distribution of expansion size in the control cohorts.

Conclusions: We ran ~600 undiagnosed whole genome sequence samples from axonopathies, including Charcot-Marie-Tooth (CMT) disease, through these pipelines and found numerous cases that could be solved for known repeat expansion genes, including RFC1 (see abstract by Danique Beijer). We are also currently analyzing the results to identify novel pathogenic repeat expansions. It is likely that unsolved cases with peripheral neuropathies such as CMT may be explained by repeat expansions.

References

1. Cortese A, et al. Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia. Nat Genet. 2019;51:649-658.

Keywords: Neuropathy, Genetics, Structural variation.

Poster No: 264 | Uniform drosophila models for four CMT-related aminoacyl-tRNA synthetases reveal common signs of toxicity

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Introduction: Aminoacyl-tRNA synthetases (aaRS) represent the largest cluster of proteins implicated in the etiology of Charcot-Marie-Tooth disease (CMT). Dominant mutations in six aaRS cause different subtypes of CMT which share common clinical characteristics. Our strategic goal is to investigate whether there is a common neurotoxic pathway triggered by the CMT mutations in aaRS.

Methods: New CMT-aaRS fly models were generated in a standardized manner using a modified GeneSwitch (TM) technology. Transgene insertion was verified by Sanger sequencing and aaRS protein expression levels were assessed by immunoblotting. General toxicity and locomotor function were evaluated by developmental lethality and negative geotaxis climbing assays, respectively.

Results: We modeled in Drosophila in a uniform manner CMT-causing mutations in four aaRS. For each synthetase, two mutations, one that alters and one that does not affect catalytic activity were selected. Transgenes were integrated into a modified GeneSwitch(TM)-UAS-vector and injected into the same landing sites of the fly genome. Lines with comparable protein expression were selected for further analysis. Strong ubiquitous overexpression of mutant aaRS induced developmental lethality in all four aaRS models. Reducing mutant transgene expression restored fly viability, suggesting that developmental lethality is dosage dependent. The toxicity phenotype demonstrated gender specific characteristics with male flies being more affected than females. Aging flies pan-neuronally expressing mutant aaRS displayed reduced locomotion in negative geotaxis assays, mimicking the progressive walking impairment characteristic for CMT patients. Overall, our findings are similar to previously described phenotypes in YARS and GARS fly models, confirming that phenotype expressivity does not correlate with aminoacylation activity of aaRS.

Conclusions: We report the successful generation of unified fly models for four CMT-related aaRS. Expression of CMT-causing mutations caused similar signs of toxicity, rendering our models a valid platform for investigating putative shared toxic pathway(s). The knowledge gained might contribute to common treatment strategies for this group of neuropathies.

Keywords: Charcot-Marie-Tooth, tRNA-synthetases, *D. melanogaster*, Disease modeling.

Poster No: 265 | **NEURO-TTRansform: Phase 3 study to evaluate AKCEA-TTR-LRx in patients with hATTR-PN**

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Introduction: Assess the efficacy and safety of AKCEA-TTR-LRx for treatment of hereditary transthyretin (TTR)-mediated amyloid polyneuropathy (hATTR-PN), a progressive, fatal axonal sensorimotor and autonomic neuropathy caused by misfolding/aggregation of TTR. Inotersen is an antisense oligonucleotide (ASO) approved to treat hATTR-PN by reducing TTR production by the liver. AKCEA-TTR-LRx, an ASO with the same sequence as inotersen, is conjugated to triantennary N-acetyl galactosamine for enhanced uptake by the asialoglycoprotein receptor on hepatocytes. In a phase 1 healthy volunteer study, 45 mg subcutaneous injection (SC) of AKCEA-TTR-LRx every four weeks (Q4W) achieved a mean reduction of 86% in serum TTR compared to baseline.

Methods: NEURO-TTRansform is a Phase 3 global, open-label study, with a historical control (placebo arm in NEURO-TTR) and an active reference arm (inotersen). Approximately 140 hATTR-PN patients will be randomized to receive either AKCEA-TTR-LRx (n ~ 120; 45 mg SC Q4W) or inotersen (n ~ 20; 300 mg SC weekly). Key inclusion criteria include preserved ambulatory status (stage 1 or stage 2), confirmed TTR mutation, and Neuropathy Impairment Score (NIS) between 10 and 130. Key exclusion criteria include estimated glomerular filtration rate <45 mL/min/1.73 m2, platelets <=125 $\times$ 10 ̂9/L and urine protein/creatinine ratio ≥ 1000 mg/g. At Week 35, an interim efficacy analysis will be performed and those assigned to receive inotersen will move to treatment with AKCEA-TTR-LRx. Outcome measures at Week 66 include percent change from baseline in serum TTR concentration and change from baseline in the modified NIS + 7 composite score and Norfolk Quality of Life-Diabetic Neuropathy Questionnaire score.

Results: This study is ongoing (ClinicalTrials.gov NCT04136184; EudraCT 2019-001698-10).

Conclusions: NEURO-TTRansform is a phase 3 study designed to evaluate the efficacy and safety of AKCEA-TTR-LRx compared to the placebo arm in NEURO-TTR for the treatment of hATTR-PN.

Keywords: Hereditary, Amyloidosis, Polyneuropathy, transthyretin-mediated, antisense oligonucleotide.

Poster No: 266 | **Screening of SORD mutations in a CMT cohort expands the clinical spectrum of SORD-related neuropathy**

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Introduction: Mutations in SORD have been recently identified as a frequent cause of autosomal recessive Charcot-Marie-Tooth disease (CMT). In light of this discovery, we aimed to evaluate the impact of SORD mutations in an in-house cohort of unsolved individuals with CMT.

Methods: We analyzed 720 unrelated patients predominantly of South-Eastern European and Turkish ancestry. The cohort consisted of individuals with sporadic or recessive neuropathy of various CMT types that remain unsolved after targeted re-sequencing of the most common CMT genes. All probands were screened initially for mutations in exon 7 of SORD by Sanger sequencing. Targeted sequencing of all coding exons of SORD was performed in cases where only one heterozygous pathogenic variant was found in exon 7.

Results: We identified 12 individuals from 10 families who carried in homozygous state the c.757delG (p.Ala253GlnfsTer27) variant previously reported. Five of them were diagnosed with axonal CMT, while three were classified as having demyelinating CMT. Only one patient presented the intermediate form of CMT. A Turkish family consisting of three adult siblings carrying the c.757delG homozygous variant showed phenotypic variability as only one of them suffered mild motor impairment in the upper limbs whereas the others were reported to be asymptomatic. Interestingly, one Bulgarian patient with axonal CMT experienced pyramidal and cerebellar symptoms. We identified 10 additional individuals heterozygous for the c.757delG mutation. In one of them, subsequent Sanger analysis of the entire coding region of SORD revealed a missense variant (c.951 T > G, p. Asn317Lys) of unknown significance.

Conclusions: This work confirms the relevance of SORD as a causal gene for CMT disease and expands the phenotypic spectrum of SORD neuropathy.

References

1. Cortese A, Zhu Y, Rebelo AP, et al. Biallelic mutations in SORD cause a common and potentially treatable hereditary neuropathy with implications for diabetes. Nat Genet. 2020;52:473-481. doi: 10.1038/s41588-020-0615-4.

Keywords: CMT, SORD.

Poster No: 267 | **Data sharing and advanced genome analysis of inherited neuropathies on the GENESIS platform**

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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, less 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.

Methods: An example of recent success is the SORD gene neuropathy, which represent up to 10% of all patients with CMT2/dHMN phenotypes and was only recently discovered. 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.

Results: This GENESIS platform is used by many active investigators in the field from all continents. With now nearly 13 000 exomes/genomes from rare neurodegenerative disorders, GENESIS presents one of the largest data aggregations in this area. This has aided over 80 gene discoveries (25 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 synched 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.

Keywords: genomics, CMT, data sharing, gene discovery.

Poster No: 268 | **Multimodal evaluation of carpal tunnel syndrome in a pre-symptomatic TTR mutation carrier**

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Introduction: Carpal tunnel syndrome (CTS) is a common manifestation of hereditary transthyretin amyloidosis (ATTRv). CTS is very common also in the general population (idiopathic CTS) where cross-sectional area (CSA) of median nerve, at ultrasound (US) evaluation, is enlarged according with the severity of CTS. We have recently demonstrated in large population of pre-symptomatic ATTRv carriers a mismatch between the severity of CTS and median nerve CSA, which remains within normal range. Here we report on a pre-symptomatic carrier affected with severe CTS who underwent a comprehensive evaluation: clinical, neurophysiological, US, magnetic resonance (MR) of both median nerve and ligaments and biopsy.

Methods: A 55-years old woman, pre-symptomatic carrier with Phe64Leu mutations affected with severe right CTS underwent clinical and neurophysiological examination (Hi-Ob and Padua Scale were assessed), median nerve US, 3 T MR of the wrist. Subsequently she underwent surgical median nerve release and biopsy of transverse carpal ligament was collected and a Congo-red staining was performed.

Results: CTS resulted severe due to absence of sensory response and abnormal distal motor latency (6.8 ms). Median nerve US at wrist was normal and measured 10 mm2. MR of carpal tunnel showed a normal transverse carpal ligament, an increased signal intensity of median nerve and an increase of connective tissue within the finger flexor tendons. Transverse carpal ligament was positive for Congo-red staining. After surgery the patients partially recovered.

Conclusions: This is the first multimodal examination (clinical, neurophysiology, US, MRI and biopsy) of a CTS in a TTR pre-symptomatic carrier. This case may help understand the peculiar physiopathology of CTS in TTR mutation carriers.

Keywords: Amyloidosis, Transthyretin, Carpal Tunnel syndrome, Ultrasound, Magnetic resonance.

Poster No: 269 | **Clinical and electrophysiological features of hereditary sensory and autonomic neuropathy in a Malian girl**

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Introduction: Hereditary sensory and autonomic neuropathy (HSAN) is a rare heterogeneous group of disorders characterized by axonal atrophy and degeneration leading to a loss of pain and temperature perception, and autonomic dysfunction. It is classified into five groups based on clinical features and the inheritance pattern. Although few cases have been reported worldwide, the global prevalence of this

disease is unknown. We report here the case of a 2-year-old girl from Mali.

Methods: After parental consent, a two-year-old girl was enrolled in our study approved by our Institutional Ethics Committee. Familial and personal past medical history were recorded. Patient was examined by neurologists and dermatologists, and bone X-ray and nerve conduction studies were performed. Peripheral blood was collected to extract DNA for candidate gene testing (WNK1 and RETREG1).

Results: A two-year-old girl from a consanguineous relationship was referred in our clinic for scalable ulcerative mutilating acropathy. The age of onset was around 14 months consistent with self-mutilation and a certain insensitivity to pain as reported by parents. Neurological examination revealed open sores in hands and feet and distal sensory loss in pinprick. In addition, she had a much reduced communication. NCS found a severe loss of sensory nerve conduction velocities and an absent sensory nerve action potentials. However, hand and feet X-rays were normal. These clinical and electrophysiological features are consistent with HSAN type II. Testing of WNK1 and RETREG1 genes is underway.

Conclusions: The diagnosis of HSAN type II on the basis of clinical trophic aspects remains challenging to many clinicians, specifically for those form developing countries where this entity can be taken for other ulcerating infectious diseases. This could be the very first case of HSAN II reported in Mali and the first step into establishing its genetic basis in the region.

Keywords: HSAN, Genetic, Mali, West-Africa.

Poster No: 270 | Telemedicine By tablet: Neurogenetic counseling pilot study

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Introduction: Telemedicine use has soared during the pandemic. New service delivery models for genetic counseling are rapidly expanding and require validation. Patient use of tablet device for neurology genetic counseling services has not been studied.

Methods: Twenty patients suspected to have a hereditary neuropathy and referred to pre-test genetic counseling will be divided into two groups. Ten will have the genetic counseling session provided through telemedicine by tablet at the time of referral. Ten patients will have the genetic counseling session provided in person at the time of the referral. Each patient will be asked to complete a survey after the visit.

Results: Results of the patient responses to a Genetic Counseling Satisfaction Likert Scale survey and computer literacy questions drawn from Computer-Email-Web Fluency Scale.

Conclusions: In this pilot study we will evaluate if patients show a difference in satisfaction between genetic counseling services received in-person vs by telemedicine on a computer tablet during a pandemic at a University Medical Center. In the future, if shown to be consistent with in-person services, this may allow increased access to genetic counseling services for neurology based multidisciplinary clinics.

Keywords: Telemedicine, Tablet, Neurology.

Poster No: 271 | Improving diagnosis of small-fiber neuropathy in children

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Introduction: Small-fiber neuropathy (SFN) is confirmed by PGP9.5-immunolabeled lower-leg skin-biopsies epidermal neurite density (END) ≤5% of predicted. Ectopic firing/degeneration of small sensory/autonomic/trophic axons underlies symptoms. Absent pediatric data, most young patients remain undiagnosed, potentially disrupting emotional and educational development. Given diagnostic ENDs reported in 53% of juvenile fibromyalgia patients, and potential treatability of pediatric SFN's common causes-dysimmune and genomic-pediatric SFN characterization is overdue.

Methods: The validated Massachusetts General Hospital (MGH) Neuropathy Exam Tool (MAGNET) captures neuromuscular abnormalities including vital signs, appearance, pin, touch, vibration, position sensation, great-toe strength, and reflexes, and the validated Small-fiber Symptom Survey (SSS) captures patient-reported symptoms. We analyzed results from all MGH patients <18y at biopsy, comparing data between those with vs without confirmatory biopsies and screened healthy children.

Results: The 93 patients studied so far were aged 14.2 ± 3.8y (3.5-17.9y), 64.5% female, 93.5% Caucasian, 2.2% Hispanic. 47.3% had diagnostic biopsies. Age at onset averaged 9.8 ± 5.1y, with earlier onset in END-confirmed patients (8.9y vs 10.5y). Analyzing 62 MAGNETs revealed 39.1% prevalence of neuropathic foot appearance (eg, hyperemia) in confirmed vs 44.7% in unconfirmed patients. 58.3% of END-confirmed had reduced, absent, or abnormal sensitivity to pinprick and touch compared to 36.8% of unconfirmed; 41.7% had great-toe sensory dysfunction and/or reduced strength vs 21.1% in unconfirmed. Both had ~17.5% prevalence of Achilles hyporeflexia. SSS scores ($n = 86$) were moderately high; 48.4 ± 24.3 (full scale = 136). The most prevalent symptoms ("sometimes/often/always" present) were physical and/or mental fatigue, sleep difficulties, headaches, orthostatic dizziness/faintness, pins and needles, and restless legs. Both groups reported equally less-frequent hyper−/hyposensitive, burning, or discolored skin. Frequency-not presence-of gastrointestinal distress distinguished confirmed from unconfirmed patients.

Conclusions: Sensory abnormalities correlated better with diagnostic skin biopsy than symptoms or other exam findings. These analyses demonstrate need for a pediatric case definition to improve diagnosis and for evaluating the relative roles of skin biopsy, SSS, and MAGNET in diagnosis.

Grant Support: NIH R01NS093653, The Mayday Fund foundation.
Keywords: pediatrics, small-fiber.

Poster No: 272 | **Role of macrophage monocarboxylate transporter 1 (MCT1) in diabetic peripheral neuropathy**

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Introduction: Diabetic peripheral neuropathy (DPN) is one of the most common complications of a highly prevalent disease. The pathogenesis of DPN is not well understood, but likely involves altered metabolism in several different cell types. A recent publications from our laboratory demonstrated that reducing monocarboxylate transporter 1 (MCT1 or SLC16a1), which is a bidirectional proton-linked transporter of pyruvate, lactate, and ketone bodies, in transgenic mice in all cells led to more severe DPN in the streptozotocin (STZ)-induced model of diabetes.
Methods: To better understand the cell types most important for the function of MCT1 in DPN, we evaluated STZ-induced peripheral neuropathy in conditional MCT1 knockout mice, in which the transporter was ablated in Schwann cells, endothelial cells, dorsal root ganglion (DRG) neurons, or macrophages. DPN was quantified by sensory and motor nerve electrophysiologic recordings, sural sensory nerve axon number/ myelin thickness, and behavioral testing for thermal pain sensitivity and mechanosensitivity.
Results: Our results show that MCT1 ablation in endothelial cells, Schwann cells, or DRG neurons led to no significant alterations in nerve electorphysiology or behavioral testing in the STZ model of DPN. In contrast, macrophage-specific MCT1 deletion led to significantly greater nerve injury, as measured by sensory electrophysiology, histology of toluidine blue-stained semithin sections, and thermal pain sensitivity.
Conclusions: Several cell types have been shown to contribute to the pathogensis of DPN, particularly DRG neurons, Schwann cells, and endothelial cells. Surprisingly, our results suggest that the impact of global MCT1 reduction on DPN is not through any of these cell types, but rather through its impact on macrophages. Though less studied than other cell types, prior research has suggested a role for macrophages in DPN, and our studies suggest that MCT1 contributes to this function. Future studies will evaluate the specific metabolic impact, both globally and intracellularly, of deleting MCT1 from macrophages.
References
1. Jha MK, et al. Reducing monocarboxylate transporter MCT1 worsens experimental diabetic peripheral neuropathy. Exp Neurol. 2020;333:113415.
2. Morrison BM., Patrick RH, John HM. Determinants of neuronal vulnerability in neurodegenerative diseases. Ann Neurol. 1998;44(S1): S32-S44.
3. Jha MK, et al. Monocarboxylate transporter 1 in Schwann cells contributes to maintenance of sensory nerve myelination during aging. Glia. 2020;68(1):161-177.
Grant Support: NINDS (NIH) R01NS086818.
Keywords: Monocarboxylate transporter, Diabetes, Streptozotocin, Macrophage, Peripheral neuropathy.

Poster No: 273 | **Carpal tunnel syndrome and amyloidosis: clinical comments in electrodiagnostic study reports lead to screening in one third of patients**

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Introduction: Carpal tunnel syndrome (CTS) is the most common compressive mononeuropathy and a common reason for referral for electrodiagnostic studies (EDX). It is also an early manifestation of amyloidosis. Recent evidence indicates that amyloid deposits are present in 10.2% of selected patients undergoing carpal tunnel release (CTR). In cases of hereditary transthyretin amyloidosis (hATTR), symptoms of CTS occur an average of 10.4 years before the diagnosis of hATTR. We sought to determine if clinical comments in EDX reports increase screening for amyloidosis.
Methods: From September 2020 to January 2021, for men older than 50 years and women older than 60 years diagnosed with bilateral CTS in our laboratory, we introduced a clinical comment in EDX reports that alerted the referring provider of the possibility of amyloidosis, offered a stepwise approach for further evaluation, and provided contact information in case additional guidance was necessary. We then reviewed the charts to determine if an action had been taken. Acceptable actions included screening for light chain amyloidosis, for cardiac amyloidosis and/or for hATTR, as well as referrals to Neurology or Cardiology.
Results: During the study period 175 EDX were performed. Forty-seven patients (27%) were diagnosed with bilateral CTS and 29 (17%) met the predefined criteria. Of those, there were 19 men (66%) and 10 women (34%). Median age was 65 years (Range 53-88). In 10 patients (34%) and action was taken to screen for amyloidosis. No cases have been detected thus far. Seven patients (24%) had CTR but none had tenosynovial tissue biopsy for Congo red staining.
Conclusions: The introduction of clinical comments in EDX reports led to screening for amyloidosis in one third of patients. Further directions include the implementation of a standardized protocol for screening and obtaining tissue biopsies in patients undergoing CTR.
References
1. Sperry BW, Reyes BA, Ikram A, et al. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release.
2. Karam C, Dimitrova D, Christ M, Heitner SB. Carpal tunnel syndrome and associated symptoms as first manifestation of hATTR amyloidosis. Neurol Clin Pract. 2019;9:309-313.
Grant Support: None.
Keywords: Carpal tunnel syndrome, Amyloidosis, Electrodiagostic study, Diagnosis.

Poster No: 274 | **Arsenic trioxide-induced peripheral neuropathy: Prospective evaluation in a cohort of patients with acute promyelocytic leukemia**

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Introduction: Arsenic trioxide (ATO), effective in acute promyelocytic leukemia (APL), has cardiac and hepatic side effects, but less is known on peripheral neurotoxicity.
Methods: With the aim to assess the characteristics of ATO-related peripheral neurotoxicity, we prospectively evaluated 19 patients with APL (11 men, mean age 54.9 ± 13.5, range 35-81 years) at 3 data points (baseline, induction, consolidation). The Total Neuropathy Score clinical version (TNSc) was used, with TNSc>2 considered significant for neuropathy.
Results: At baseline, all patients had TNSc 0, except for one who presented with distal sensory symptoms and ankle areflexia (TNSc 3) for an overlooked hereditary neuropathy. After induction, median TNSc was 3 (range 0-8), with 10/19 patients (52.6%) presenting TNSc>2. Distal sensory symptoms at lower limbs resulted the most common complaint. After consolidation, median TNSc was 2 (range 0-8), with 7/19 (36.8%) presenting TNSc>2. At 1-year follow-up after the end of consolidation, median TNSc was 1 (range 0-8), with 3/19 patients (15.8%) presenting TNS > 2, in addition to the patient with neuropathy at baseline. Neurophysiology after induction (available in 17/19) disclosed an axonal neuropathy in 7/17 that persisted in 4 patients one year after consolidation. No significant differences were observed in ATO cumulative dose in patients who developed or not neuropathy (1237.5 mg vs 1072.5, $P = 0.44$). No correlation was found between ATO cumulative dose and TNSc ($r = 0.06$, $P = 0.7$). No changes in neurophysiology were observed in the patient with hereditary neuropathy and TNS 3 at baseline.
Conclusions: In conclusion, up to 41% of patients undergoing ATO for APL may present sensory axonal neuropathy in the early stages of induction therapy followed by progressive improvement, suggesting that peripheral neurotoxicity may be a reversible side effect. A quarter (26%) of patients however had persisting peripheral neuropathy at 1-year follow-up.
Keywords: peripheral neurotoxicity.

Poster No: 275 | **Pre-clinical treatment studies of SORD neuropathy with novel aldose reductase inhibitors AT-001 and AT-007**

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Introduction: SORD neuropathy is a newly identified frequent cause of axonal peripheral neuropathy. Loss of function mutations in SORD have been shown to cause a complete loss of sorbitol dehydrogenase, a key enzyme in the polyol pathway. The polyol pathway is a 2-step alternative glucose metabolism pathway, comprised of aldose reductase, which converts glucose to sorbitol, and SORD, which converts sorbitol to fructose. The consequences of SORD loss are a 10-100-fold increase in sorbitol levels in patient peripheral blood and fibroblasts.
Methods: Reducing the high sorbitol levels using aldose reductase inhibitors (ARI) epalrestat and ranirestat has been shown by us to rescue the behavioral neurodegenerative phenotype in a drosophila model. Given that no ARI is currently clinically available in the US and Europe, we partnered with Applied Therapeutics to test a new type of highly selective ARI (AT-007, AT-001) in our models. These drugs are currently in phase II and III trials for rare diseases and diabetic complications, respectively.
Results: Treatment with AT-007 and AT-001 substantially reduced sorbitol levels in SORD patient fibroblasts, providing proof of concept data for further clinical investigation.
Conclusions: Detailed results on various doses and treatment durations will be presented, including results from ongoing studies in drosophila. Of note, orally given AT-007 is CNS penetrant and thus of special interest for neuropathy treatment.
Keywords: CMT, SORD, sorbitol, aldose reductase inhibitor.

Poster No: 276 | **Inflammatory neuropathies related to Covid-19: two electrophysiological observations from tertiary referral hospital in Lithuania**

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Introduction: There have been numerous reports of neurological complications of Covid-19, including inflammatory neuropathies. We report clinical and electrophysiological features of two cases, diagnosed during the second wave of the pandemic. The first case was a variant of Guillain-Barré syndrome; meanwhile, the second case was a small fiber neuropathy.
Methods: Clinical examination was performed and medical history was collected. Electrophysiological evaluation included nerve

conduction studies (NCS) and needle electromyography (EMG). Covid-19 infection was confirmed by polymerase chain reaction (PCR).

Results: Patient number one (75y, man) had ascending sensory loss and weakness two weeks after a mild Covid-19 infection. Flaccid tetraparesis and stocking-glove type sensory loss was observed with areflexia in lower limbs and hyporeflexia in upper limbs. On electrophysiological examination, sensory nerve action potentials (SNAPs) were absent in lower limbs. Radial superficial SNAPs were lower in amplitude and prolonged in duration. Motor NCS revealed prolongation of distal latencies and M response durations, decreases in amplitudes and conduction velocities. F-waves were of prolonged latencies/absent. Needle EMG (C8-Th1;C5-C6;L2-L5 myotomes on the left) did not show any denervation potentials, but poor MUP recruitment pattern was observed. Electrophysiological picture was consistent with a sensory-motor variant of Guillain-Barré syndrome. Second patient (61y, woman) twelve days after the first symptoms of Covid-19 infection felt dysesthesias of the limbs and tongue, as well as loss of smell. Tendon reflexes and muscle strength were normal. On electrophysiological examination, sensory and motor NCS were normal except for signs of mild carpal tunnel syndrome on the right. Silent cutaneous period (tibialis anterior - sural nerve) showed prolonged durations consistent with small fiber dysfunction. Needle EMG (L3-S1;C6-C8 myotomes bilaterally) was normal.

Conclusions: Future studies should include more patients with Covid-19 associated inflammatory neuropathies to determine clinical and electrophysiological patterns. Clinicians should be aware of possible neurological complications even after a mild infection.

Keywords: Covid-19, Guillain-Barré, Small fiber neuropathy.

Poster No: 278 | Genotype and phenotype spectrum of SORD neuropathy

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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.

Methods: This global natural course observatory study aims at reporting the full genotype-phenotype spectrum of SORD neuropathy and at defining valid outcome parameters for future clinical trials.

Results: Through an international network of neuropathy experts, we have so far identified 79 individuals from 71 unrelated families with biallelic mutations in SORD, including 35 previously unreported cases. Sixty-seven cases (85%) carried the common c.753delG; p.(Ala253GlnfsTer27) variant in a homozygous state. In 13 cases, the c.753delG variant was found in compound-heterozygosity with a second missense or nonsense variant,. Clinical data were available in 64 patients of Caucasian (68%), Middle-eastern (16%), Asian (12%), or Mixed (3%) origin. 62% of cases were sporadic. Patients were diagnosed with axonal CMT (51%), dHMN (37%), and intermediate CMT (9%). The mean age of symptom onset, mostly difficulty walking, was 16 ± 7 years. Delayed motor milestones were uncommon, but 75% of the patients had foot deformities and 20% reported a poor sport performance in school. After 20 years of disease duration, the neuropathy was still mild in 62%, moderate in 25%, and severe in 12%; 42% needed ankle-foot orthosis, 11% used a stick, and 2 patients were wheelchair-dependent. In all patients, the fasting serum sorbitol level was elevated to 14.8 ± 2.5 mg/L (normal 0.05 ± 0.02 mg/L), while normal levels led to re-interpretation of the previously reported c.964G > A;p.(Val322Ile) variant as likely benign in a patient with a compound-heterozygous haplotype.

Conclusions: We demonstrate biallelic mutations in SORD as a frequent recessive form of axonal, motor predominant neuropathy across different ethnicities. The ongoing multi-center natural history study is still recruiting new patients and will hopefully lead to the identification of sensitive outcome measures for future clinical trials.

References

1. Cortese A, Zhu Y, Rebelo AP, et al. Biallelic mutations in SORD cause a common and potentially treatable hereditary neuropathy with implications for diabetes.

Keywords: SORD, sorbitol, diabetes, CMT, natural history study.

Poster No: 279 | DNA-based therapeutic approach to CMT2E molecular phenotype reversal in a human induced pluripotent stem cell (iPSC)-derived motor neuron model

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Introduction: Charcot-Marie-Tooth disease type 2E has been attributed to missense mutations in NEFL, encoding neurofilament light chain (NF-L). NF-L, exclusively found in neuronal tissue, is an essential

component of the cytoskeletal axonal structure, contributing to axonal radial growth, stability, and nerve conduction velocity. Various studies have solidified increased levels of plasma and CSF NF-L as a biomarker for axonal degeneration. Intracellular, toxic NF-L positive aggregates in induced pluripotent stem cell (iPSC)-derived motor neuron cultures and a knock in mouse model have been reported as a potential molecular phenotype for CMT2E.

Methods: Our study aims to develop an antisense oligonucleotide (ASO) mediated genetic treatment strategy to mitigate NF-L aggregate formation by targeting allele-specific knockdown of the mutant NEFL transcripts. ASOs were designed with 2'-O-methyl modifications flanking 5 base pairs on each end or using locked nucleic acid modifications, and phosphorothioate modifications between all 16-20 base pairs. Patient and control iPSC-derived spinal spheroids (SpS) with radially projecting axonal neurites were grown from iPSC-differentiated motor neurons. Using a CX5 high content screening platform, SpS were analyzed for NF-L positive aggregate formation and clearance post-ASO treatment.

Results: Initial results indicate a proximal to distal axonal clearance of NF-L positive aggregates after allele-specific knockdown of NEFL (N98S) mutant RNA transcripts. To further investigate NF-L aggregate clearance after treatment, imaging was performed at various time points during axonal neurite growth, up to 50 days post-treatment. Supernatant NF-L was measured at corresponding imaging time points using a SIMOA assay to determine axonal degeneration. Using iPSC-derived 2D motor neurons, RT-PCR and cDNA sequencing was performed to assess transcript knockdown efficiency.

Conclusions: Our results continue to suggest a viable strategy for genetically based therapeutic development in autosomal dominant disorders where no current treatment exists. Further enhancing this approach using patient tissue and established molecular phenotypes is a vital approach in pre-clinical therapy development per current FDA guidelines.

Keywords: CMT, Inherited Neuropathy, Neurofilament, ASO, ipsc.

Poster No: 280 | Using human genetics to link programmed axon death regulators SARM1 and NMNAT2 to human disease

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Introduction: Two decades of research into programmed axon death (Wallerian degeneration) in mouse, fly and other animal models has extensively characterized this degenerative mechanism and identified many ways to block it. It is driven by SARM1, a prodegenerative NADase. Its upstream negative regulator, the NAD-synthesizing enzyme NMNAT2, is short-lived and essential for axon survival. When NMNAT2 is absent, concurrent absence of SARM1 completely rescues the otherwise lethal phenotype. Blocking programmed axon death protects axons in models of many disorders including some peripheral neuropathies, motor neuron disorders, glaucoma and Parkinson's disease. Aberrant activation of the pathway also causes disease, especially polyneuropathies.

Methods: However, all models have limitations, which limit knowledge of which human disorders actually involve programmed axon death, and which specific patients may respond best to SARM1-blocking drugs. We are addressing these questions using human genetics followed by functional testing of associated variants in mouse and human neurons and enzyme kinetics.

Results: Rare biallelic hNMNAT2 loss-of-function (LoF) variants associate with varying degrees of polyneuropathy resembling corresponding mouse mutants. There are many distinct SARM1 LoF variants in humans, mostly in heterozygotes, and our work in Sarm1 haploinsufficient mice show this partially protects axons from disease-relevant stresses. We also find evidence of SARM1 gain-of-function in humans whose pathogenic consequences remain to be clarified.

Conclusions: Together, these findings indicate a spectrum of intrinsic axon vulnerability in the human population. By testing disease association of variants confirmed to enhance or impair SARM1 or NMNAT2 protein function, our ongoing study will test for involvement of programmed axon death in rare, inherited neuropathies and in more common, acquired and metabolic disorders such as chemotherapy-induced and diabetic neuropathies.

Keywords: Axon degeneration, SARM1, NAD, Polyneuropathy, Axonopathy.

Poster No: 281 | Cholesterol-added antigens can enhance anti-GM1 antibody activity: Application to antibody testing

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Introduction: The binding activity of anti-glycolipid antibodies is affected by the lipid environment around the target antigen. The purpose of this study is to verify the effect of adding cholesterol to glycolipid antigens on the antigen-antibody reaction.

Methods: The participants consisted of 113 patients with Guillain-Barré syndrome (GBS), 25 patients with Miller Fisher syndrome (MFS), and two patients with Bickerstaff brainstem encephalitis, only 40 (35.4%) of whom had IgG anti-GM1 antibodies. We examined their sera for antibody activity against cholesterol-added GM1 antigens by using enzyme-linked immunosorbent assay. Various amounts of cholesterol were used (30 ng-16 μg per 100 ng of GM1). When the corrected optical density (cOD) value increased by 0.1 or more, the serum was judged to have a cholesterol-enhancing effect. The antibody activity-enhancing effect of cholesterol addition and clinical features were analyzed.

Results: The use of cholesterol-added antigens enhanced anti-GM1 antibody activity. The antibody activity-enhancing effect of cholesterol addition was enhanced in a dose-dependent manner up to 2 μg per 100 ng GM1 in 19 anti-GM1-positive GBS patients (the enhancement group). The enhancement group (n = 19) had no specific features, whereas anti-GQ1b antibodies were significantly more frequent in the nonenhancement group (n = 21) ($P = 0.037$) than in the enhancement group. Five anti-GM1-negative sera became anti-GM1 antibody-positive by adding cholesterol to GM1 antigens.

Conclusions: The use of cholesterol-added glycolipid antigens results in increased detection of anti-glycolipid antibodies. By approximating the lipid environment around the target antigen to the biological membrane in the antibody screening, it may be possible to accurately evaluate the anti-glycolipid antibody activity in vivo.

Keywords: Guillain-Barré syndrome, Antibody, Ganglioside, Cholesterol, Lipid environment.

Poster No: 282 | Prevalence of RLS in histologically proven small fiber neuropathy

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Introduction: Associations between peripheral neuropathy (PN) and restless legs syndrome (RLS) are described but exact correlation remains inconsistent. Specifically, prevalence of RLS in histologically proven small fiber neuropathy (SFN) or correlation of RLS severity to SFN severity remains unknown. Dopaminergic dysfunction in RLS leads to loss of supraspinal inhibition and enhanced excitability of propriospinal mechanisms. Additionally, abnormal sensory inputs in SFN could worsen this inhibition secondary to altered dorsal horn physiology contributing to RLS. This study aims to address this void and improve quality of life (QOL) by identifying treatable comorbidity of RLS in SFN.

Methods: A prospective single center study to assess prevalence of RLS in SFN is underway. We present preliminary results. 13 patients diagnosed with SFN showing reduced intradermal nerve fiber (IDNF) density were screened for RLS using standardized questionnaire based on International RLS study group diagnostic criteria (IRLSRS). All patients who answered yes to three or four questions were considered screen-positive and further analysis regarding RLS severity was performed. We plan to study correlation of SFN severity based upon IDNF to IRLSRS severity.

Results: Out of 13 patients with histologically proven SFN, 2 patients did not address all 4 questions. 9 patients endorsed 3 or 4, and 2 patients endorsed 1 or 2 symptoms displaying RLS in 81.82% SFN. All 13 (100%) admitted unpleasant sensations combined with urge to move legs and 10 (90.91%) noticed symptoms at rest or periods of inactivity. 6 (54.55%) admitted sensations improved with movements and symptoms worse at night or evenings. The mean severity score of 26.33 and median of 29 suggested severe RLS per IRLSRS criteria.

Conclusions: This study demonstrates that RLS is associated with SFN and could have significant impact on QOL. Exploration of correlation between severity of SFN based on IDNF density to severity of RLS will enhance understanding of these comorbidities.

Grant Support: N/A.

Keywords: Small Fiber Neuropathy, Restless Leg Syndrome, Severity, IDNF, Quality of Life.

Poster No: 283 | Using drosophila mutations in DCTN1 to dissect the neuron cell-type specificity of peripheral neuropathy and related neurodegenerative diseases

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Introduction: The gene DCTN1 encodes the p150/Glued subunit of dynactin and is required for all dynein-mediated microtubule-based organelle transport. We previously showed that the G59S missense mutation in the DCTN1 CAP-Gly microtubule-binding domain that causes Hereditary Motor Neuropathy type 7B disrupts the initiation of retrograde axonal transport at terminal bouton of the neuromuscular junction using a Drosophila model (Lloyd et al, 2012). Intriguingly, over the last decade, multiple missense mutations in DCTN1 have been implicated in the pathogenesis of multiple additional neurodegenerative diseases, including Amyotrophic Lateral Sclerosis (G38R), Idiopathic Peripheral Neuropathy, and Perry syndrome, a TDP-43 proteinopathy affecting dopaminergic neurons.

Methods: Using Drosophila, we have used CRISPR-Cas9 to knock-in 10 disease-associated missense mutations into the fly DCTN1 locus. The p150Glued locus was excised and replaced with the attP docking site and LoxP. Genomic Glued was cloned into a pGE expression vector. Using Q5 site-directed mutagenesis kit, mutations were cloned into the vector based on variances identified in the literature. These mutations and wild-type vectors were microinjected. The resulting fly lines were crossed to a cre line, and then backcrossed to w1118 strain for 5 generations. Mutations were verified with sequencing.

Results: Lethality assays show that ALS hemizygous flies have a markedly shortened lifespan, while Perry syndrome hemizygous flies had a more mildly shortened lifespan compared to other mutants and controls. We are currently performing axonal transport assays for multiple cargo in these distinct fly models to identify the mechanisms of cell-type specific neurodegeneration.

Conclusions: Understanding how distinct mutations in p150/Glued cause different cellular phenotypes may allow insight into the molecular pathways leading to distinct neurodegenerative diseases.

References

1. Lloyd TE, Machamer J, O'Hara K, et al. The p150(Glued) CAP-Gly domain regulates initiation of retrograde. 2012.

Grant Support: K08NS118123.

Keywords: hereditary motor neuropathy, axonal transport, dynactin.

Poster No: 285 | **Guillain-Barré syndrome associated with COVID-19 in a tertiary neurological center in Peru**

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Introduction: The study aims to describe demographic, clinical, and neurophysiological characteristics of patients with Guillain-Barré Syndrome (GBS) and COVID-19 from a peruvian neurological center.

Methods: We performed a retrospective cohort study including GBS cases with a concomitant COVID-19 diagnosis admitted to a peruvian tertiary neurological center between April 2020 and January 2021. Demographic, clinical, and neurophysiological information were described. The COVID-19 diagnosis was performed following international guidelines.

Results: Fourteen cases were identified (10 males; median age of 44.5), twelve cases were Brighton level 1 (85.7%). The average time of neurological symptoms at admission was of 8.5 days (IQR: 7-15). The prodromal illness was presented between days 2 and 14 before the first neurological symptom (respiratory symptoms: 11 [78.6%]; diarrhea: 4 [28.6%]). Four (28.5%) reported hyposmia and/or hypogeusia. Six (66.6%) had a para-infections manifestation (pneumonia due to SARS-CoV-2). All the participants had quadriparesis, nine (64.3%) had facial weakness, and eight (57.1%) dysphagia. We found high disability (Hughes 4) in almost all participants (92.85%). Only two (14.3%) presented dyspnea; none required mechanical ventilation. Twelve (85.7%) showed albuminocytologic dissociation. In the electromyography, twelve (84.6%) had findings compatible with acute inflammatory demyelinating polyneuropathy, one acute motor axonal neuropathy, and one was normal. The profile is different from the GBS cases of the previous year in our center. All participants received immunoglobulin, eight (58.14%) improved (changes on Hughes scale of 1 to 2 points) after four weeks since the treatment.

Conclusions: We found frequent cranial nerves compromise, higher severity of the disease, and demyelinating affectation in the electromyography in patients with GBS associated with COVID-19. The clinical and neurophysiological profiles are different from our usual GBS casuistic, suggesting a potential causal association between GBS and COVID-19. However, further prospective studies are needed to elucidate this relationship and assess long-term disability and treatment outcomes.

Keywords: Guillain-barre, covid-19, SARS-CoV-2.

Poster No: 286 | **Analysis of yield and utility of whole exome and whole genome sequencing in neuropathies from a specialized adult neurology clinic**

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Introduction: Whole exome sequencing (WES) and whole genome sequencing (WGS) have become increasingly commercially available in the last few years. In a recent cohort of 50 patients with undiagnosed neuropathy, WES yielded a 24% diagnostic (pathogenic or likely pathogenic) result.

Methods: This is a retrospective review of all WGS and WES results sent to Centogene (Commercial genetic laboratory in Rostock, Germany) from the Neurology department of a large University Teaching Hospital (which includes a specialized Neuropathy clinic). Electronic patient records were also reviewed to identify the phenotype and provide clinical correlation. The date range for this study is Feb 2018-Sept 2020.

Results: A total of 73 WES and 12 WGS results were analyzed, coming from a total of 81 kindred. Demographics were 61% (52/85) male. Mean age at testing of 46 (range: 18-86). The primary referral phenotypes were: 28.2% Neuropathy, 31.8% Ataxia, 15.3% Intellectual disability/Seizures, Myopathy 14.1%. Focusing on the Neuropathy cases, 33 tests were sent with neuropathy as part of the phenotype which included 29 WES and 4 WGS. Using the American College of Medical Genetics (ACMG) classification by Centogene 18.2% (6/33) were class 1 (pathogenic), 6% (2/33) were class 2 (likely pathogenic) and 18.2% (6/33) were class 3 (Variant of Uncertain Significance or VUS). On clinical correlation, these were reclassified as 3.3% pathogenic, 18.2% likely pathogenic, 21.2% VUS. The pathogenic variant was DNMT1, causing autosomal dominant hereditary sensory neuropathy type IE. Likely pathologic variants include a SYT2 mutation and a HADHA compound heterozygote.

Conclusions: WES and WGS revealed a yield of 22.3% in our population of identifying a pathologic or likely pathologic variant after correlating to clinical phenotype and was 21.2% in our Neuropathy population which is comparable to the literature.

References

1. Hartley T, et al. Whole-exome sequencing is a valuable diagnostic tool for inherited peripheral neuropathies: outcomes from a cohort of 50 families. Clin Genet. 2018;93(2):301-309.

Keywords: Inherited Neuropathies, Whole Exome Sequencing, Whole Genome Sequencing.

Poster No: 287 | **Case of vasculitic neuropathy and myelopathy**

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Introduction: Eosinophilic granulomatous polyangiitis (EGPA) is a rare form of antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis. Vasculitic peripheral neuropathy could be the sole or the first and most prominent manifestation of systemic vasculitis.

Methods: We report an interesting case of eosinophilic vasculitic neuropathy and myelopathy.

Results: A 61-year-old female presented with 4-month history of burning pain in hands and feet, proximal and distal weakness, associated with 20-pound unintentional weight loss. Symptom onset coincided with initiation of amlodipine concurrent with statin use for 3 years. She was initially diagnosed as statin-induced myopathy, however CK was normal. Neurological exam revealed significant pain restricting movements and symmetric mild proximal and moderate to severe distal weakness in all limbs, normal deep tendon reflexes at ankles and rest of the reflexes were brisk, and distal symmetric sensory gradient in the legs and arms, with decreased vibratory sensations and proprioception. Cervical spine MRI revealed severe cervical spondylotic myelopathy at C6-C7. Laboratory workup showed eosinophilia, elevated inflammatory markers, positive rheumatoid factor, P-ANCA and myeloperoxidase antibody. Nerve biopsy confirmed the diagnosis of EGPA with eosinophilic perivascular inflammation in epineural vessels with destruction of internal elastic lamina. The patient responded to intravenous methylprednisolone and on protracted oral prednisone taper. Vasculitic neuropathy could present as length-dependent polyneuropathy rather than mononeuritis multiplex. Peripheral neuropathy is commonly seen up to 80% of cases with EGPA, and muscle involvement is rare with only 8 reported cases with eosinophilic necrotizing myositis.

Conclusions: This case illustrates vasculitic neuropathy from EGPA with severe cervical spondylotic myelopathy. The timing of amlodipine initiation was likely coincidental with the onset of EGPA.

Keywords: Vasculitic, Neuropathy, Eosinophillia.

Poster No: 288 | Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disease associated with immune infiltration into peripheral nerves

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Introduction: Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disease associated with immune infiltration into peripheral nerves. Non-Obese Diabetic mice with a G228W Autoimmune Regulator (AIRE) mutation (NOD.AIRE GW/+) manifest spontaneous autoimmune peripheral polyneuropathy (SAPP) that mimics multiple features of CIDP. These mice are useful to understand disease pathogenesis.

Methods: To study SAPP, single-cell RNA sequencing (scRNAseq) is a powerful tool to characterize the cellular landscapes and transcriptomic profiles of immune cells in neuropathic nerves. In this study, we performed scRNAseq on sciatic nerves from neuropathic NOD.AIRE GW/+ mice.

Results: Here, we report the presence of heterogenous populations of immune cells including multiple T cell, DC, NKT and macrophage subsets. Through Gene Set Enrichment Analysis (GSEA) and analysis of hallmark gene signatures from MSigDB, we observed an upregulation of IFNg and TNFa signaling pathways in the NOD.AIRE GW/+ macrophage subset. Compared to "injury macrophages" that infiltrate sciatic nerves after crush, autoimmune NOD.AIRE GW/+ macrophages also upregulate multiple proinflammatory pathways that include the TNFa signaling pathway.

Conclusions: Together, our results demonstrate a potentially pathogenic role for TNFa signaling in autoimmune peripheral neuropathy and a diversity of macrophage populations present in SAPP nerves.

References

1. Su MA, Davini D, Cheng P, et al. Defective autoimmune regulator-dependent central tolerance to myelin protein zero is linked to autoimmune peripheral neuropathy. J Immunol. 2012;18.
2. Subramanian A, Tamayo P, Mootha, et al. Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles. Proc Natl Acad. 2005.
3. Liberzon A, Subramanian, A, Pinchback R, Thorvaldsdóttir H, Tamayo P, Mesirov JP. Molecular signatures database (MSigDB) 3.0. Bioinformatics. 2011;27(12):1739-1740. doi: 10.1093/bioinformatics/btr260
4. DeTomaso D, Jones MG, Subramaniam M, et al. Functional interpretation of single cell similarity maps. Nat Commun. 10, 4376 (2019). doi: 10.1038/s41467-019-12 235-0

Keywords: CIDP, GBS, Neuropathy, scRNAseq, autoimmunity.

Poster No: 289 | Dectin-1 in peripheral nerve injury and regeneration (Late Breaking Abstract)

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Introduction: Dectin-1, a pattern recognition receptor, has been shown to play a role in nerve regeneration in the central nervous system. Stimulating Dectin-1 promoted axon regeneration 14 days after optic nerve crush [1], but increased nerve injury three days after spinal cord injury [2]. We hypothesized that stimulating Dectin-1 may be pro-degenerative at the early phase of peripheral nerve injury, but pro-regenerative at the later phase.

Methods: We performed sciatic nerve crush injury along with an intraneural injection of Dectin-1 agonist, antagonist, or vehicle. We then examined nerve regeneration and degeneration by immunofluorescence

and semithin morphometry analysis of the sciatic nerve at 3, 7, and 14 days after surgery.

Results: Our study showed the presence of Dectin-1 positive macrophages after nerve injury, raising the possibility that Dectin-1 may exert its effect through macrophages. We also demonstrated that inhibiting Dectin-1 resulted in retained myelinated nerve profiles at three and seven days after surgery, and a trend of decreased myelin ovoid density at seven days after surgery. These findings suggested that the Dectin-1 antagonist inhibited nerve degeneration-related processes at the early stage of nerve injury, such as breakdown of injured myelinated nerve fibers and formation of myelin ovoid. In the Dectin-1 antagonist treated group, there was a delayed onset of hypoesthesia at 14 days after surgery, indicating impaired functional recovery.

Conclusions: This report showed that at the early stage of nerve injury, Dectin-1 aided nerve degeneration and debris removal. Moreover, at the later stage of nerve injury, Dectin-1 may promote functional recovery and nerve regeneration.

References

1. Baldwin KT, Carbajal KS, Segal BM, Giger RJ. Neuroinflammation triggered by β-glucan/dectin-1 signaling enables CNS axon regeneration. Proc Natl Acad Sci USA. 2015;112(8):2581-25.

2. Gensel JC, Wang Y, Guan Z, et al. Toll-like receptors and Dectin-1, a C-type lectin receptor, trigger divergent functions in CNS macrophages. J. Neurosci. 2015;35(27).

Poster No: 290 | Guillain-Barré syndrome presenting with bilateral facial nerve palsy following Pfizer-BioNTech COVID-19 vaccination (late breaking abstract)

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Introduction: The Food and Drug Administration (FDA) has authorized the emergency use of the Pfizer-BioNTech COVID-19 vaccine to prevent COVID-19 in individuals 16 years of age and older under an Emergency Use Authorization (EUA). There have been rare case reports of Guillain-Barré Syndrome in both Moderna and Pfizer vaccination trials.

Methods: Chart review and literature search were conducted.

Results: The patient of interest is a 32-year-old male with a history of mild asthma who received the first dose of the Pfizer-BioNTech vaccine in March 2021. In the first few hours, he noticed muscle soreness, leg heaviness, and fatigue. Three days later, he developed a right facial droop. He presented to the emergency department on post-vaccination day 7, where he was diagnosed with Bell's palsy and given oral steroids. Several hours later, he noticed a new left facial droop with paresthesias in his bilateral hands and feet. He was admitted to the hospital where his SARS-Cov-2 PCR testing was negative. His neurologic examination demonstrated bilateral severe facial nerve palsy and lower extremity areflexia with intact limb strength and sensation. MRI of the brain was unremarkable. Cerebrospinal fluid analysis demonstrated elevated protein of 116 mg/dL and no white blood cells, consistent with a diagnosis of Guillain Barré Syndrome. Electromyography (EMG) demonstrated bilateral facial nerve palsies with both demyelinating and axonal features, with normal nerve conduction velocities. He was treated with a five-day course of intravenous immunoglobulin (IVIG) resulting in mild improvement of his facial weakness.

Conclusions: This variant of GBS occurring within one week of Pfizer-BioNTech vaccination suggests that this may be a rare complication of the vaccine. IVIG is the treatment of choice. Further observational studies are needed to better understand the association between vaccination and the GBS variant. Nevertheless, the benefits of the vaccine far outweigh its potential risks.

Poster No: 291 | Prodromal sensory neuropathy in Pink1-SNCA double mutant Parkinson mice (late breaking abstract)

Lucie Valek[1], Bao Tran[1], Annett Wilken-Schmitz[1], Sandra Trautmann[1], Juliana Heidler[2], Tobias Schmid[3], Bernhard Brüne[3], Dominique Thomas[1], Thomas Deller[4], Gerd Geisslinger[1], Georg Auburger[5], Irmgard Tegeder[1]

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Introduction: Parkinson's Disease (PD) is frequently associated with a prodromal sensory neuropathy manifesting with sensory loss and chronic pain. We have recently shown that PD-associated sensory neuropathy in patients is associated with high levels of glucosylceramides. Here, we assessed the underlying pathology and mechanisms in Pink1−/-SNCA-A53T double mutant mice.

Methods: We studied nociceptive and olfactory behaviors and the neuropathology of dorsal root ganglia (DRG) including ultrastructure, mitochondrial respiration, transcriptomes, outgrowth and calcium currents of primary neurons, and tissue ceramides and sphingolipids before the onset of a PD-like disease that spontaneously develops in Pink1−/-SNCA-A53T double mutant mice >15 months of age.

Results: Similar to PD patients, Pink1−/-SNCA-A53T mice developed a progressive prodromal sensory neuropathy a loss of thermal sensitivity starting as early as four months of age. In analogy to human plasma, lipid analyses revealed an accumulation of glucosylceramides (GlcCer) in the DRGs and sciatic nerves, which was associated with pathologic mitochondria, impairment of mitochondrial respiration and deregulations of transient receptor potential, TRPV and TRPA channels at mRNA, protein and functional levels in the DRGs. Direct exposure of DRG neurons with GlcCer caused transient hyperexcitability, followed by a premature decline of the viability of sensory neurons cultures upon repeated GlcCer application.

Conclusions: The results suggest that pathological GlcCer contribute to prodromal sensory disease in PD mice via mitochondrial damage and calcium channel hyperexcitability. GlcCer-associated sensory neuron pathology might be amenable to GlcCer lowering therapeutic strategies.

Poster No: 292 | **Guillain-Barré syndrome associated with COVID-19 (late breaking abstract)**

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Introduction: Guillain-Barré syndrome (GBS) is the most frequent cause for acute palsy after the eradication of poliomyelitis. The disease is autoimmune in nature and etiological agents most frequently are *Campylobacter jejuni*, Cytomegalovirus, Epstein-Barr virus, HIV and Zika virus. The aim of our presentation is to analyze all cases GBS that have been described during the COVID 19 pandemic.

Methods: We performed a systematic review of all case descriptions of GBS associated with COVID-19 that were published from between December first up to April 15th. 88 cases of GBS related to COVID 19 have been issued by specialized literature. We describe the countries of origin, the clinical picture, the findings of the electroneuromyography (ENMG), the spinal fluid, the treatment and the outcome.

Results: Most cases are from Italy, Iran, USA, and Spain. The most clinical presentation was sensory-motor, Miller-Fisher syndrome, bilateral facial palsy, and pure motor form. According to the ENMG, 55 were demyelinating, 18 axonal (AMSAN e AMAN), 5 was mixed type, and in 10 patients the ENMG was not performed. The albuminocytological dissociation was detected in 68 cases, in 8 patients the CSF was normal and in 12 cases it was not mentioned. Most cases (65) were treated with Intravenous Immunoglobulin (IVIg), 7 cases with plasma exchange (PE), 3 with corticosteroids, 4 t cases with a combination of either IVIg, PE or corticosteroids. Ten patients did not receive any specific treatment. Thity-five patients had total improvement, 22 showed partial remission, in 17 the was no improvement, 2 worsened, 7 died, and in 5 the outcome was not described.

Conclusions: Several authors believe that the occurrence of GBS in association with COVID-19 is a mere coincidence. We think that meticulous analyses of epidemiological studies are needed to state that COVID 19 established an outbreak of GBS cases.

Poster No: 293 | **In vivo CRISPR/Cas9 editing of the TTR gene by NTLA-2001 in patients with transthyretin amyloidosis (late breaking abstract)**

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Introduction: NTLA-2001 is a gene-editing therapy designed to treat, by a single intravenous infusion, ATTR amyloidosis, a life-threatening disease of misfolded transthyretin protein accumulation in tissues including peripheral nerves.

Methods: NTLA-2001 comprises a lipid nanoparticle (LNP) encapsulating mRNA for SpCas9 protein and guide RNA targeting the TTR gene. After infusion, LNP uptake into hepatocytes results in precise TTR gene knock-out regardless of disease-causing mutation. This first-in-human phase 1 trial (NCT04601051) enrolls adults with confirmed ATTR amyloidosis and symptomatic peripheral neuropathy, who are not receiving TTR-lowering agents. Safety, pharmacokinetics and pharmacodynamics of NTLA-2001 are assessed in a 3 + 3 design.

Results: In cynomolgus monkey (NHP), a single dose at the no-observed-adverse-effects-level reduced serum TTR levels >90%, which reached nadir by 28 days and persisted beyond 1 year. NHP PK and PD data were used to estimate doses to reduce serum TTR in humans. Six patients received one dose of NTLA-2001 by April 13, 2021. Data on the first 4 (3 at 0.1 mg/kg and 1 at 0.3 mg/kg, 2 women, ages 50-63, weight 70-89 kg, 2 with p.T80A and 2 with p.S97Y mutations) are described here. NTLA-2001 was generally well tolerated. One patient had a grade 1 infusion-related reaction. All adverse events were mild. At Day 28, subjects in the 0.1 mg/kg cohort had a mean 51% serum TTR reduction from baseline (95% CI: 33%, 69%), nominal $P = 0.007$. TTR reductions were observed by Day 14 and declined further by Day 28. Full results of changes in serum TTR for the 0.3 mg/kg cohort will be presented. Dose escalation is ongoing.

Conclusions: Intravenous infusion of the gene-editing therapeutic NTLA-2001 results in substantive reduction in serum TTR protein. These results represent the first proof-of-concept for systemic in vivo CRISPR/Cas9 editing as a therapeutic strategy in humans.

Poster No: 294 | **Effect of combined administration of intravenous immunoglobulin (IVIg) and the classical complement inhibitor ANX005 in Guillain-Barré syndrome (GBS) (late breaking abstract)**

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Introduction: This study assessed the impact of IVIg co-administered with ANX005 in GBS patients from Bangladesh and Denmark.

Methods: A Phase 1b open label study of 26-week duration, assessing safety, pharmacokinetics (PK), pharmacodynamics, and outcome in GBS patients receiving a single dose of ANX005 (75 mg/kg) together with IVIg (2 g/kg over 5 days).

Results: Fourteen patients (median age 41 years) with baseline GBS-DS of 3-5 and MRC sum score (MRC) 0-42 were enrolled. Baseline serum neurofilament light chain (sNfL) ranged from 12 to 3445 pg/mL. Co-administration of ANX005 with IVIg was well tolerated and no unexpected adverse events occurred. As anticipated, the PK of the human mAb ANX005 was modestly reduced relative to ANX005 alone, with full C1q target engagement maintained for 1-3 weeks. In this small sample, sNfL and weakness at inclusion determined the patient's individual trajectory to functional recovery, which clustered into two groups: in 8 patients, 3 from Denmark and 5 from Bangladesh, with baseline MRC >20 and / or sNfL ≤652 pg/mL, early (≤3 weeks) functional improvement resulted in GBS-DS of 0 (37.5%), 1 (37.5%), 2 (12.5%) or pending (12.5%) at Week 26. In contrast, 6 Bangladeshi patients with baseline MRC ≤20 and / or sNfL >928 pg/mL, showed delayed (≥4 weeks after admission) improvement and achieved a GBS-DS score of 3 or 4 at study completion. Furthermore, baseline sNfL correlated closely with the patient's ability to improve [Spearman $r = 0.86$, 95% CI (0.58, 0.96)].

Conclusions: ANX005 with IVIg was well tolerated and demonstrated robust target engagement. For the intended use, dose adjustment is not needed. Considering baseline prognostic factors, patients responded similarly to treatment, irrespective of geographic location. A longitudinal proportional odds efficacy analysis that fully captures patient's trajectories over time is proposed for future studies. A Phase 2/3 trial of ANX005 is ongoing in Bangladesh.

Poster No: 295 | Mononeuropathy and mononeuritis multiplex following COVID-19: A single center prospective observational study from south India (late breaking abstract)

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Introduction: COVID -19 is associated with or complicated by various peripheral nervous system disorders. These include: Guillean Barre syndrome, polyneuritis cranialis, Miller Fisher syndrome, mononeuropathy/multifocal neuropathy, myasthenia gravis and myositis. We aimed to characterize the mononeuropathy or multifocal neuropathy associated with COVID-19.

Methods: This is a prospective tertiary care hospital-based study carried out in the outpatient between October 2020 and March 2021 with a minimum follow-up of one month. Study has the approval of Institutional Ethics Committee. Association with COVID-19 was classified as probable and possible based on the WHO COVID-19 provisional case definition. Diagnosis was based on clinical and electrodiagnostic features. The data collected included demographics, severity of COVID-19, comorbidities, time interval between COVID-19 and neurological manifestations, clinical features, need for ventilation, treatment and outcome.

Results: Eight patients of mononeuropathy/multifocal neuropathy were recruited. All were males and mean age 57.25 years (range 30-72). Associated comorbidities included hypertension (6); diabetes (4); hypothyroidism (1) and coronary artery disease (1). Association with COVID-19 was classified as probable (5) and possible (3). Severity of COVID-19 was critical (3) and moderate (5). Critical patients required ventilation. All except two received dexamethasone for COVID-19. Mean interval between the onset of COVID-19 and neuropathy was 12.6 days (range 5-27); Five had mononeuropathy and three had multifocal neuropathy: ulnar (7), lateral femoral cutaneous nerve (4), common peroneal (3), and sural, sciatic and facial nerve one each. Neuropathy was demyelinating (4), axonal (3) and mixed (1). Nerve ultrasound was done in 4 ulnar (3) and common peroneal nerves. It showed ulnar nerve enlargement in the forearm segment with enlarged fascicles and it was normal in patients with common peroneal nerve involvement. All have improved.

Conclusions: Mononeuropathy/Multifocal neuropathy is a post infectious complication of COVID-19 especially in those who suffered moderate to severe disease. Early identification can optimize long-term outcome.

Poster No: 297 | Altered lysosomal abundance and activity in Charcot-Marie-Tooth disease type 1A (late breaking abstract)

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Introduction: Charcot-Marie-Marie Tooth disease type 1A (CMT1A) is the most common demyelinating peripheral nerve disease, caused by a duplication of the PMP22 gene. Although the exact pathomechanism of the disease remains unclear, the formation PMP22 aggregates in CMT1A Schwann cells and dysfunctional proteostasis are proposed to play an important role. Under physiological circumstances, protein aggregates are targeted and cleared via the lysosomal-autophagy pathway. Although this pathway is altered in CMT1A Schwann cells, the exact pathomechanisms are yet to be elucidated. We describe

lysosomal alterations in the C3 model for CMT1A, expressing 3 to 4 times the human PMP22 gene.

Methods: Lysosomal changes were evaluated in primary Schwann cells from C3 and WT mice. Lysosomal protein abundance was evaluated using transmission electron microscopy (TEM) and immunocytochemistry (ICC). Lysosomal and autophagic mRNA levels were evaluated using qPCR. Next, lysosomal enzymes such as cathepsin B (CTB) and cathepsin D (CTD) were monitored using immunocytochemistry and qPCR. Finally, CTB activity was visualized with confocal live-cell imaging using a CTB specific probe.

Results: Our data show an increase in lysosomal abundance in C3 vs WT primary Schwann cell using TEM ($P < 0.05$). This is confirmed with lysosomal ICC stainings showing a significant increase in C3 vs WT cells ($P < 0.01$). Moreover, LAMP1, CTB and CTD mRNA levels were significantly higher in C3 vs WT cells ($P < 0.001$, $P = 0.0001$ and $P < 0.001$, respectively). Furthermore, both CTB ($P < 0.005$) and CTD ($P < 0.01$) were significantly increased in C3 compared to WT cells using ICC. Finally, CTB activity was significantly higher in primary C3 Schwann cells compared to WT cells ($P < 0.0001$).

Conclusions: Altogether, our data implies not only a significant increase in the lysosomal amount but also an altered lysosomal activity. Nevertheless, further research is necessary to explore the consequences of these lysosomal changes in CMT1A.

References

1. Chad Hoyle J, Isfort MC, Roggenbuck J, David Arnold W. The genetics of Charcot-Marie-Tooth disease: Current trends and future implications for diagnosis and management. Appl Clin Genet. 2015;8:235-243. doi:10.2147/TACG.S69969

2. Chittoor VG, Sooyeon L, Rangaraju S, et al. Biochemical characterization of protein quality control mechanisms during disease progression in the C22 mouse model of CMT1A. ASN Neuro. 2013;5 (5):333-346. doi:10.1042/AN20130024

3. Lee S, Bazick H, Chittoor-vinod V, et al. Elevated peripheral myelin Protein 22, reduced mitotic potential, and proteasome impairment in dermal fibroblasts from Charcot-Marie-Tooth disease type 1A Patients. 2018;188(3). doi:10.1016/j.ajpath.2017.10.021

4. Fledrich R, Stassart RM, Sereda MW. Murine therapeutic models for Charcot-Marie-Tooth (CMT) disease. Br Med Bull. 2012;102 (1):89-113. doi:10.1093/bmb/lds010

Poster No: 298 | A novel mouse model of severe peripheral neuropathy: Beclin1 role in schwann cell (late breaking abstract)

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Introduction: Beclin1 (BECN1) plays an important role in membrane trafficking and restructuring, in the regulation of different autophagy steps, as well as in endocytosis, cytokinesis and phagocytosis. BECN1, essential for embryonic development, is also linked to several human pathologies, including cancer and neurodegenerative diseases. However, while assessed in neuronal populations, astrocytes and microglia, its role was far less investigated in myelinating glia.

Methods: Schwann cells (SCs) are responsible for myelin production in the peripheral nervous system and contribute to the pathogenesis of several inflammatory, metabolic and hereditary neuropathies. Recent findings point at an emerging role of autophagy in regulating maturation and homeostasis of SCs. Interestingly, among the numerous mutated genes identified as responsible for Charcot-Marie-Tooth (CMT), several belong to the autophagy-linked "endosomal sorting and cell signaling" function category, albeit being expressed by either axons or SCs, or both. We generated the novel mouse model Becn1-SC/-SC, in which Becn1 4-7 exons are deleted by a Cre recombinase driven by the Mpz promoter, thus triggering tissue-specific ablation of BECN1 in SCs.

Results: Becn1-SC/-SC mice develop a severe peripheral neuropathy, displaying a progressive neuropathic phenotype, with extensive involuntary tremors, marked muscle loss and decreased body weight. Moreover, they progressively lose the ability to walk properly together with reproduction capability, and show a decreased lifespan. In parallel to the confirmed ablation of Beclin1 at the genomic level, microscopy data reveal marked alteration in nerve morphology, with an almost complete absence of myelinated fibers, in homozygous mutant mice, but not in heterozygous ones. The remarkable impairment of myelination in Becn1-SC/-SC mice is confirmed also by the analysis of myelin-related protein levels.

Conclusions: The characterization of this new mouse model sets once more autophagy in the spotlight for therapeutic strategies in peripheral neuropathies and points to BECN1 and its binding partners as novel candidate genes for recessive CMT forms.

Poster No: 299 | Exploring the role of PMP22 in ordered membrane domains of schwann cell differentiated dental stem cells and how it affects cell-matrix interactions (late breaking abstract)

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Introduction: New therapeutic strategies to establish repair of injured peripheral nerves are desperately needed. For this purpose, our group developed Engineered Neural Tissue with Schwann cell differentiated human dental pulp stem cells (SC-hDPSC) embedded in an aligned collagen hydrogel [1, 2]. The use of SC-DPSCs as a cell source for nerve repair has several advantages but there is a need to better understand

how they interact with the extracellular matrix (ECM) and how this affects their myelinating behavior. We aim to investigate the role of peripheral myelin protein 22 (PMP22) in the interaction of SC-hDPSCs with an endoneurial-like ECM.

Methods: SC-hDPSC were cultured on 2D coated surfaces and a lipid raft labeling technique with cholera toxin b (Ctxb) AF488 was performed. This was combined with immunostainings for PMP22, integrin $\alpha 6$ and $\beta 1$, and visualized using confocal- and super resolution microscopy. In addition, 2D live cell imaging was performed with Ctxb AF488 to study lipid raft dynamics in SC-hDPSC. Finally, SC-hDPSC were cultured in 3D in free floating hydrogels and collagen I contraction was examined macroscopically and microscopically using label-free second harmonic generation microscopy.

Results: We found that PMP22 is expressed in lipid rafts in the plasma membrane of SC-hDPSC. In addition, we demonstrated that these lipid raft domains are highly mobile. Moreover, we observed a strong colocalization between PMP22 and integrin $\beta 1$ and $\alpha 6$ in the membrane of SC-hDPSC. In addition, SC-hDPSC cultured in 3D hydrogels strongly interact with collagen I fibers via these integrins.

Conclusions: In conclusion, we showed that PMP22 is expressed in ordered regions in the SC-hDPSC membrane together with integrins that are important for cell-ECM interactions and that have a regulatory function in Schwann cell myelination. This implicates that PMP22 may play a role in controlling myelination, but this will be explored in future experiments.

References

1. Sanen K, et al. Engineered neural tissue with Schwann cell differentiated human dental pulp stem cells: potential for peripheral nerve repair? J Tissue Eng Regen Med. 2017;11(12):3362-72.

2. Martens W, et al. Human dental pulp stem cells can differentiate into Schwann cells and promote and guide neurite outgrowth in an aligned tissue-engineered collagen construct in vitro. FASEB J. 2014;28(4):1634-43.

Poster No: 301 | **Small nerve fiber involvement in chilblain lupus erythematosus (late breaking abstract)**

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Introduction: The chilblain lupus erythematosus (CHLE) subtype of chronic cutaneous lupus erythematosus is an unusual condition characterized by painful vascular dysfunction and occasional association with systemic lupus erythematosus. This case offers a rare opportunity to study the autonomic features of this disorder.

Methods: A 42-year-old woman of Indian origin presented with worsening symptoms in the hands and feet. She endorsed four years of tenderness, two years of erythema and mottling, and one year of burning pain, all worsened by activity and cold and relieved by elevation and warming. Examination showed allodynia, minor baseline erythema, and scattered purplish papules in the hands and feet. With activity or pressure, there was increasing erythema, edema, and violaceous mottling in the feet and erythema in the hands.

Results: ESR and CRP were mildly elevated and extensive rheumatological labs were unrevealing. NCS were normal including sural sensory responses of 15-20 uV. Epidermal nerve fiber density was normal in the foot, calf, and forearm. Quantitative sudomotor axon reflex test (QSART) was diffusely abnormal with sweat volumes less than fifth percentile. Antibodies for sensory neuropathy, including anti-HDS and -FGFR3, were absent. Skin biopsy of the right toe revealed vacuolar interface dermatitis with superficial and deep periadnexal lymphocytic infiltrate, compatible with CHLE. At the time of writing, pain had improved with gabapentin. Hydroxychloroquine was ineffective, prompting switch to prednisone and initiation of nifedipine, with effects to be determined.

Conclusions: The pathogenesis of the microcirculation dysfunction in sporadic CHLE is unknown. Notably, hereditary CHLE is associated with genes implicated in systemic autoimmunity, apoptotic damage, and endothelial function. In sporadic CHLE, autoimmune small nerve fiber dysfunction could be a primary driver of the condition, or a secondary effect of epithelial changes and/or a generalized autoimmune disorder. Neurologists should consider CHLE in patients with neuropathic pain and cutaneous autonomic vascular symptoms.

References

1. Obermoser G, Sontheimer RD, Zelger B. Overview of common, rare and atypical manifestations of cutaneous lupus erythematosus and histopathological correlates. Lupus. 2010;19(9):1050-70.

2. Hedrich CM, Fiebig B, Hauck FH, et al. Chilblain lupus erythematosus-a review of literature. Clin Rheumatol. 2008;27(8):949-54.

3. Fiehn C. Familial Chilblain Lupus - what can we learn from type I interferonopathies? Curr Rheumatol Rep. 2017;19(10):61.