PNS 2024 Annual Meeting

Abstract Supplement

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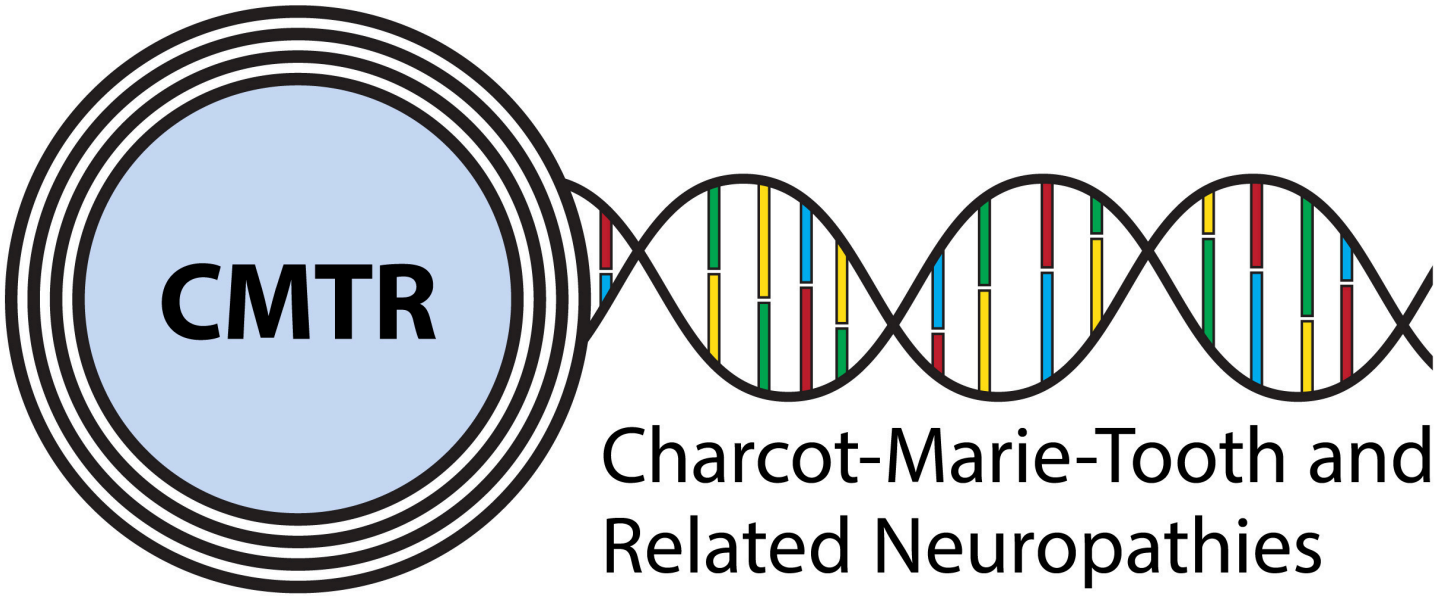
Table of Contents

**P - Poster Only, O - Oral Presentation*



Charcot-Marie-Tooth and Related Neuropathies (CMTR) Abstracts

P 010 - 127

SMALL FIBER TESTS IN THE ASSESSMENT OF NEUROPATHY PROGRESSION IN A DIVERSE COHORT OF ATTRv PATIENTS

Poster No:
P 010

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Introduction:
Hereditary transthyretin (ATTRv) amyloidosis is an autosomal-dominant multi-systemic disorder, where clinical manifestations are related to extracellular deposition of misfolded TTR fibrils. A range of symptoms, including cardiomyopathy, polyneuropathy, with frequent and early small fibre and autonomic dysfunction are the most common manifestations. Given the clinical heterogeneity, there is no definite protocol to assess neuropathy worsening, however adding small fiber tests (SFT) may help better quantify disease progression. We aimed to assess the value of including SFT in the follow-up of a diverse cohort of patients with ATTRv.

Methods:
We prospectively included ATTRv patients who had 2 clinic visits with electrophysiologic assessments and SFT (quantitative sensory tests, laser doppler imaging/LDI, corneal confocal microscopy/CCM).

Results:
Of 11 individuals (5 female, 9 families/ethnical backgrounds, 8 different mutations), 8 had assessments before and after initiating therapy, 1 post-liver transplant and 2 before therapy (pre-symptomatic carriers). Age of onset was 50.1+-9.67 years. PND score was I in eight patients and IIIb in one. Baseline and follow-up studies showed progression of disability (PND I=03patients/PND II=04patients/PND IIIa=01patient, PND IV=01 patient; ONLS 2+-2.36 vs 2.54+-2.54,p=0.006); no worsening of CTS parameters(p=0.36 for amplitudes and 0.88 for conduction velocities) or sural amplitudes (p=0.16); no significant changes in LDI(2.54+-0.63 vs 2.41+-0.95,p=0.6), cooling detection thresholds for upper(28.78+-3.85 vs 29.47+-1.67,p=0.42) or lower limbs(25.92+-7.59 vs 25.78+-6.79,p=0.87) or COMPASS-31 total score (35.71+-26.76 vs 38.87+-24.85,p=0.17). There was a significant reduction in the corneal nerve fiber length/CNFL (6.97+-1.15 vs 5.90+-1.82 mm/mm2,p=0.04), but not in the fiber density (12.31+-3.85 vs 12.4+-7.19 mm/mm2,p=0.94), the number of mature dendritic cells (32.75+-25.21 vs 20.95+-14.32 cells/mm2,p=0.09), or immature dendritic cells (22.5+-15.12 vs 14.5+-10.41cells/mm2,p=0.09).

Conclusions:
In a diverse cohort of ATTRv patients and 2 pre-symptomatic carriers who presented with clinical deterioration, among a range of clinical and electrophysiologic tests, CNFL was the only parameter that showed progression with time.

References:
No

Keywords: Polyneuropathy, Amyloidosis, TTR, Corneal confocal microscopy

Pathologic Classification of a Late Onset Peripheral Neuropathy in the Labrador Retriever

Poster No:
P 012

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Introduction:
Late-onset peripheral neuropathy (LPN) is a life-limiting heritable canine neuropathy common in Labrador Retriever. Disease features include inspiratory stridor due to laryngeal paralysis, esophageal dysmotility and pelvic limb weakness. The age of onset is typically 9-12 years. In the Labrador, LPN appears to be inherited in an autosomal dominant manner. It is currently not known whether LPN is a single disease or, like comparable human conditions, a common clinical presentation resulting from multiple genetic mutations, particularly in different breeds. The objective of this study was to evaluate the neuropathologic features of LPN in pure-bred Labrador Retrievers to quantitatively classify LPN as a myelinopathy or axonopathy and to evaluate disease length dependency. We hypothesized that Labradors clinically diagnosed with LPN would have pathologic features consistent with a length-dependent peripheral axonopathy.

Methods:
We undertook an electrodiagnostic study, peripheral nerve cross-sectional histology, and spinal cord motor neuron staining using a total of 35 dogs.

Results:
We found compound muscle action potential amplitudes were significantly decreased in distal sciatic and ulnar nerves, but motor nerve conduction velocity was not different between groups. Distal limb musculature showed greater changes in LPN affected dogs compared to aged controls with EMG. Median axon diameter was decreased in the LPN group while g-ratio did not differ between groups. No differences were seen between motor neuron density in L5 spinal cord sections.

Conclusions:
These results suggest that LPN in the Labrador Retriever is a length dependent peripheral neuropathy resulting from axonal degeneration.

References:
No

Grant Support:

National Institutes of Health (R03OD026601, K01OD019743), American College of Veterinary Surgeons, Wisconsin Alumni Research Foundation, UW-Madison SVM Companion Animal Fund, UW-Madison Graduate School Fall Competition Grant, Donations from owners and breed clubs from across the USA and Canada

Keywords: Peripheral Neuropathy, Axonopathy, Electrodiagnostics, Neuropathology, Labrador Retriever

Direct reprogramming of canine fibroblasts to induced-motor neurons: A model for age-related canine peripheral neuropathies.

Poster No:
P 013

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Introduction:
Spontaneous, heritable, late-onset peripheral neuropathies are common and life-limiting in the canine pet population. These conditions are strong potential models for similar human conditions, such as Charcot-Marie-Tooth disease. Investigation into these conditions is limited by a lack of a subtype-specific neuronal culture model that accurately recapitulates an aged phenotype in dogs.

Methods:
Direct reprogramming is a method through which a cell's fate can be converted, while maintaining biological age. In this study, we developed a direct reprogramming method that utilizes transcription factors and small molecules to generate induced-motor neurons (iMNs) from canine primary dermal fibroblasts.

Results:
Reprogrammed iMNs from dogs of a variety of ages express early and late protein markers of bona fide motor neurons such as HB9, TUBB3, ChAT, and MAP2. When plated on mouse astrocyte cultures for long-term maintenance, iMNs develop sophisticated neurites that can be used to study features of axonal degeneration in vitro.

Conclusions:
The development of this direct reprogramming model offers new possibilities for studying age-related canine peripheral neuropathies, allowing for a deeper understanding of disease mechanisms and potential therapeutic strategies in these valuable dog models.

References:
No

Grant Support:

This study was funded by UW School of Veterinary Medicine Companion Animal Fund & Wisconsin Alumni Research Foundation.

Keywords: Peripheral Neuropathy, Canine, Direct Reprogramming, Motor neurons

Neurofilament Light Polypeptide (NEFL) Pathogenic Variants are Possibly Associated with Optic Atrophy

Poster No:
P 014

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Introduction:
Charcot–Marie–Tooth disease (CMT) is the most common hereditary peripheral neuropathy. Pathogenic variants in the neurofilament light polypeptide (NEFL) gene are associated with demyelinating (CMT1F), axonal (CMT2E), and intermediate (CMTDIG) neuropathies. Beyond peripheral nerve symptoms, these patients may also present ataxia, hearing loss, pyramidal signs, limb tremor, dysarthria, and nystagmus. Regarding ophthalmological issues, we found only one report of optic nerve hypoplasia and four with delayed visual evoked potential (VEP). In this report, we present three cases of CMT1F with optic atrophy.

Methods:
We report clinical features, nerve conduction studies, exome sequencing, optical coherence tomography (OCT), visual evoked potentials (VEP), brain magnet resonance imaging (MRI), retinography, and biochemical and serological tests of three CMT1F patients.

Results:
Three unrelated Brazilian CMT1F patients (one man) were diagnosed with bilateral optic atrophy by OCT with delayed VEP. The mean age was 32 years and the mean CMT score (CMTNS2) was 25. All of them had diffuse brain atrophy at MRI. A novel class 4 variant was found (c.796G>T) in homozygousity in one patient. The other pathogenic variants had already been published. We ruled out other causes of optic atrophy such as demyelinating diseases, brain tumors, diabetes, radiation, traumatic lesions, toxic (ethambutol, amiodarone, methanol, alcohol), vitamin deficiency, toxoplasmosis, lupus, sarcoidosis, inherited retinal disorders, and glaucoma.

Conclusions:
These results show that NEFL pathogenic variants can be possibly associated with optic atrophy, and it may be a frequent manifestation of NEFL-associated diseases. Therefore, we suggest that CMT1F, CMT2E, and CMTDIG patients should routinely undergo ophthalmological tests to receive proper attention.

References:
Yes

Reference 1: Kim HJ, Kim SB, Kim HS, Kwon HM, Park JH, Lee AJ, Lim SO, Nam SH, Hong YB, Chung KW, Choi BO. Phenotypic heterogeneity in patients with NEFL-related Charcot-Marie-Tooth disease. Mol Genet Genomic Med. 2022 Feb;10(2):e1870. doi: 10.1002/mgg3.1870. Epub 2022 Jan 19. PMID: 35044100; PMCID: PMC8830812.

Reference 2: Horga A, Laurà M, Jaunmuktane Z, Jerath NU, Gonzalez MA, Polke JM, Poh R, Blake JC, Liu YT, Wiethoff S, Bettencourt C, Lunn MP, Manji H, Hanna MG, Houlden H, Brandner S, Züchner S, Shy M, Reilly MM. Genetic and clinical characteristics of NEFL-related Charcot-Marie-Tooth disease. J Neurol Neurosurg Psychiatry. 2017 Jul;88(7):575-585. doi: 10.1136/jnnp-2016-315077. Epub 2017 May 13. PMID: 28501821; PMCID: PMC5580821.

Keywords: CMT1F, NEFL, Optic atrophy

Characterizing The Wasted Mouse As A Motor Neuron Disease Model.

Poster No:
P 015

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Introduction:
Translation defects and tRNA modification in motor neurons contribute greatly to neuromuscular disorders due to defective protein synthesis and cell stress response. The translation elongation factor 1A, eEF1A, has two independently encoded isoforms, eEF1A1 and eEF1A2. The well-conserved developmental switch to eEF1A2 expression in muscles and neurons suggests there may be significant functional differences. In wasted mice (wst/wst), the gene encoding eEF1A2 has a spontaneous 15.8 kb deletion affecting the first exon and all promoter regions. Homozygous mice have neuromuscular abnormalities and survive about 5 weeks. These mice present a valuable opportunity to study early-onset motor neuron disease, given the early onset and aggressive nature of the phenotypic abnormalities. We have confirmed eEF1A2 expression and persistence of eEF1A1 expression in alpha motor neurons beyond post-natal development. The phenotype suggests a critical role of eEF1A2 in motor neurons as the primary defect in the wst/wst mice. We therefore aim to characterize the wst/wst mice in the context of neuron disease.

Methods:
Measurement of clinically relevant outcomes employing electromyography, wire hang test, neuromuscular junction innervation, histology of femoral nerves, spinal cord and brain was carried out on 23day old wst/wst and wildtype littermate controls. Gene expression analysis on the spinal cord of wst/wst and wildtype littermate controls was also carried out.

Results:
Consistent with previous characterizations, the wst/wst mice at about 3 weeks have defects consistent with neuromuscular abnormalities. Data from electromyography, behavioral tests of motor performance, histopathology of nerves and spinal cord, and neuromuscular junction innervation are currently being quantified. We are also analyzing gene expression data to identify dysregulated pathways in the wst/wst mice.

Conclusions:
Results gathered will inform the relevance of the wst/wst mouse as a model for studying early onset motor neuron disease and whether the switch from eEF1A1 to eEF1A2 contributes to the cell-type specificity of neuromuscular disorders.

References:
Yes

Reference 1: Tezuka, H., Inoue, T., Noguti, T., Kada, T. and Shultz, L.D., 1986. Evaluation of the mouse mutant “wasted” as an animal model for ataxia telangiectasia: I. Age-dependet and tissue-specific effects. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 161(1), pp.83-90.

Reference 2: Newbery, H.J., Gillingwater, T.H., Dharmasaroja, P., Peters, J., Wharton, S.B., Thomson, D., Ribchester, R.R. and Abbott, C.M., 2005. Progressive loss of motor neuron function in wasted mice: effects of a spontaneous null mutation in the gene for the eEF1A2 translation factor. Journal of Neuropathology & Experimental Neurology, 64(4), pp.295-303.

Grant Support:

R37NS054154

Keywords: integrated stress response, motor neuron disease, eEF1A, translation, axon

How To Diagnose Amyloidosis Early? The Answer May Be In Your Hands

Poster No:
P 016

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Introduction:
Carpal tunnel syndrome (CTS) is an early manifestation of amyloidosis. Previous evidence indicates that amyloid deposits are present in 10.2% of patients undergoing carpal tunnel release (CTR). We sought to identify the prevalence of amyloidosis in patients undergoing CTR, to outline their neuromuscular and cardiac evaluations, and determine the manifestations of the disease.

Methods:
This was a retrospective cross-sectional study of patients who had CTR and tenosynovial biopsy from January 2021 to September 2022 at our institution.

Results:
Of 183 patients who underwent 194 tenosynovial biopsies, 36 (20%) tested positive for amyloidosis. Twenty-four patients (67%) had genetic testing and 2 were diagnosed with hereditary transthyretin amyloidosis (hATTR). The remaining 22 patients (61%) had wild-type transthyretin amyloidosis (wtATTR). Nineteen patients (53%) had electrodiagnostic studies, of which 9 (25%) demonstrated a large fiber polyneuropathy (LFPN). Two patients (6%) had skin biopsies and 1 (3%) demonstrated a small fiber neuropathy (SFN). Twenty-nine patients (81%) had technetium pyrophosphate scintigraphy, of which 1 (3%) showed grade 1 cardiac amyloidosis. Both patients with hATTR had polyneuropathy (1 LFPN and 1 SFN) and 1 had cardiac amyloidosis. Eighteen patients (50%) were started on green tea extract and 1 (3%) was started on patisiran for amyloid polyneuropathy.

Conclusions:
In our cohort of patients who underwent CTR, 20% had amyloidosis. The majority had wtATTR, no polyneuropathy and no cardiac amyloidosis. However, those who had hATTR also had polyneuropathy or cardiomyopathy. These findings support that CTS is an early manifestation of amyloidosis. We strongly recommend obtaining tenosynovial biopsies in patients undergoing CTR for early detection of amyloidosis.

References:
No

Grant Support:

No grant support.

Keywords: Amyloidosis, Hereditary transthyretin amyloidosis, Carpal tunnel syndrome, Carpal tunnel release, Tenosynovial biopsy

Dysregulation of Cholesterol synthesis in Charcot Marie Tooth disease

Poster No:
P 017

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Introduction:
Charcot Marie Tooth (CMT) is the most common hereditary peripheral neuropathy of which the demyelinating form CMT1A is the most prevalent subtype. CMT1A patients have a demyelinating neuropathy with clinical heterogeneity. CMT1A is caused by a duplication on chromosome 17 that harbours the PMP22 gene, mutations in the PMP22 gene can cause a similar phenotype. Previous studies have shown that PMP22 can bind cholesterol and interacts with amongst others ABCA1, a transporter of cholesterol and phospholipids. Overexpression of PMP22 is shown to affect intracellular cholesterol ester trafficking and causes lipid retention in lipid droplets.

Methods:
We performed longitudinal gene expression and lipidomics analysis of sciatic nerves of CMT1A models.

Results:
PMP22 over expressing models showed a downregulation of mRNAs encoding enzymes involved in cholesterol synthesis. In a mouse model with mild CMT due to intermediate levels of PMP22 overexpression (C3 mouse) in time, a partial compensation of cholesterol synthesis associated with mild functional recovery. This partial recovery is not seen in the severe C22 mouse. The lipidome shows a reduction of the total lipids measured in all models, while they all have a relative increase of triglyceride.

Conclusions:
We propose that the down regulation of lipid synthesis is preventing remyelination, thus aggravating disease. Whereas normal nerves will remyelinate after damage, CMT1A nerves are hampered in this process. Our analysis shows potential mechanisms underlying the shutdown of cholesterol synthesis and will enables development of a potential therapeutic strategy for CMT1A.

References:
No

Keywords: CMT1A, PMP22, Myelin, Cholesterol, Lipidomics

Impaired ATP Release Through Cx32 Hemichannels Carrying The R220X Mutation Linked To Severe CMT1X.

Poster No:
P 018

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Introduction:
Mutations of the *GJB1* gene encoding connexin 32 (Cx32) are linked to the X-linked form of Charcot–Marie–Tooth disease (CMT1X)[1]. Since the molecular function of Cx32 in the peripheral nervous system has not yet been understood, a direct path from genetic diagnosis to personalized treatment is missing. In myelinating Schwann cells, an ATP-mediated paracrine Ca^{2+} signalling was found critical for the myelination process[2]. Cx32 hemichannels (HCs) expressed at these cells may support the Ca^{2+} signalling propagation by releasing ATP in response to sub-micromolar cytosolic Ca^{2+} ($[Ca^{2+}]_{c)}$ elevations[3]. Previous *in vitro* work from our lab[4] uncovered that the R220X mutation of Cx32 (causing a severe CMT1X) impairs the HC opening triggered by $[Ca^{2+}]_c$ increase, despite retaining functional gap junctions (GJs). Nevertheless, it remained undisclosed whether this HC dysfunction impairs ATP release upon physiological conditions.

Methods:
To study the release of ATP through wild type (WT) and mutant Cx32 HCs *in vitro*, HeLa and Schwannoma cell lines were stably transduced by a lentiviral vector system. Experiments were performed at the populational level by a luciferase/luciferin assay or at the single-cell level by a genetically encoded extracellular ATP sensor. Simultaneous Ca^{2+}/ATP imaging was also performed while eliciting a $[Ca^{2+}]_c$ increase by several stimuli, including ionomycin, histamine or inositol trisphosphate (IP_3) photo-uncaging.

Results:
Our results confirmed an ATP release impairment by Cx32-R220X HCs in both cellular models. The defect was linked to a pathological dysregulation of the HC gating mechanism dependent on $[Ca^{2+}]_c$.

Conclusions:
A new paradigm for the molecular pathogenesis of CMT1X has recently been suggested to be no longer related to Cx32 GJs, but rather to unpaired channels (HCs)[3,4]. Our findings support the hypothesis that an altered ATP release through Cx32-R220X HCs is linked to the sequence of molecular and cellular events that lead to the pathological phenotype in CMT1X patients.

References:
Yes

Reference 1: Kleopa, K.A., C.K. Abrams, and S.S. Scherer, How do mutations in GJB1 cause X-linked Charcot-Marie-Tooth disease? Brain Res, 2012. 1487: p. 198-205.

Reference 2: Ino, D., et al., Neuronal Regulation of Schwann Cell Mitochondrial Ca(2+) Signaling during Myelination. Cell Rep, 2015. 12(12): p. 1951-9.

Reference 3: Bortolozzi, M., What's the Function of Connexin 32 in the Peripheral Nervous System? Front Mol Neurosci, 2018. 11: p. 227.

Reference 4: Carrer, A., et al., Cx32 hemichannel opening by cytosolic Ca2+ is inhibited by the R220X mutation that causes Charcot-Marie-Tooth disease. Hum Mol Genet, 2018. 27(1): p. 80-94.

Keywords: CMT1X, Cx32, Schwann cells, Myelination, hemichannels

Phenotype-genotype correlation in X-linked Charcot-Marie-Tooth disease: a French cohort study

Poster No:
P 019

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Introduction:
X-linked Charcot-Marie-Tooth disease type 1 (CMTX) currently lacks a curative treatment, but promising preclinical trials suggest that clinical trials might emerge in the coming years. It is established that tested groups should be matched based on age and sex, as the phenotype depends on these factors. However, data regarding phenotype-genotype correlations are currently limited. Our aim is to better describe these correlations to anticipate the formation of comparable patient groups.

Methods:
We evaluated 276 patients from 12 French reference centers, collecting genetic, clinical, and nerve conduction data. Severity was assessed using the CMTES score. Patients were categorized based on the interpretation of their genetic variants following the international guidelines set forth by the American College of Medical Genetics (ACMG).

Results:
We described phenotype-genotype correlations in 276 CMTX patients from 160 families carrying 87 different variants. Patients with variants in transmembrane domains were significantly more severe, with a CMTES score of 10.7 compared to 7.3 for patients with variants in intracellular domains and 8.8 in extracellular domains. They also had an earlier disease onset (13 years vs. 22 and 20 years), slower nerve conduction velocities, and greater motor amplitude loss. VUS variants did not differ from pathogenic and likely pathogenic variants.

Conclusions:
This study confirms the existence of a correlation between the mutated protein domain and the phenotype. Hence, it will be crucial in future trials to consider patients' genotypes.

References:
No

Keywords: charcot-marie-tooth, clinical trial, CMTX, hereditary peripheral neuropathy, connexine 32

Development Of An iPSC-based Model For The Study Of Peripheral Neuropathies

Poster No:
P 020

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Introduction:
The advent of human induced pluripotent stem cell (hiPSC)-derived neurons has ushered in a new era of neuroscience, offering unprecedented opportunities to unravel the complexities of neurological disorders like Charcot-Marie-Tooth disease (CMT). Characterized by progressive degeneration of motor and sensory nerves, this incurable peripheral neuropathy severely disrupts normal life activities and presents a significant challenge to individuals and their families. In our laboratory, we are committed to deciphering the molecular and cellular mechanisms underlying CMT caused by mutations in connexin 32 (Cx32) channels [1].

Methods:
Taking advantage of hiPSC technology, we developed a simplified *in vitro* myelinating co-culture system that yields both motor neurons and Schwann cells. These iPSCs were previously reprogrammed from healthy donor human skin fibroblasts and expanded in our laboratory under feeder-free conditions. Subsequently, differentiation towards motor neuron, neural crest and Schwann cell phenotypes was successfully carried out by modifying and merging previously reported protocols into one.

Results:
Verification of successful hiPSC differentiation into motorneurons and Schwann cells was achieved through RT-PCR, immunofluorescence, and patch-clamp assays. The differentiated cells exhibited robust expression of lineage-specific markers, displayed electrophysiological properties consistent with their respective cell types, and formed intricate networks of intercellular interactions, corroborating the successful differentiation process. Further optimization of the co-culture conditions facilitated the initiation of axonal myelination evident by the observed elongation of Schwann cells along neurites, a hallmark of the myelinating Schwann cell function.

Conclusions:
By providing the possibility to study the interactions between motor neurons and Schwann cells in a dish, this co-culture model can be an important tool to advance research and personalized medicine of CMT and other peripheral nerve disorders.

References:
Yes

Reference 1: 1. "Structures of wild-type and selected CMT1X mutant connexin 32 gap junction channels and hemichannels. Qi*, Lavriha*, Bayraktar* et al., Science Advances, 9, eadh4890 (2023).

*Equally contributed.

Keywords: Induced Pluripotent Stem Cells, Charcot-Marie-Tooth disease, co-culture system

Variable Phenotype in Females with Heterozygous GJB1 Mutation

Poster No:
P 021

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Introduction:
Charcot-Marie-Tooth-x (CMT-x) is the second most common CMT type due to heterozygous GJB1 mutations. The mutation causes a demyelinating process with secondary axonal involvement due to loss of function of gap junction protein named connexin 32. Although male patients have a moderately severe phenotype, females may present with a variable phenotype. This variable phenotype has been suggested to occur as a result of X inactivation but no difference in X inactivation pattern has been shown in serum samples of female CMT-X patients compared to controls. Here, we report the clinical and laboratory findings of three female patients with different GJB1 mutations.

Methods:
The clinical and electrophysiological findings of three CMT-X female patients were reviewed. Besides, two patients undergone sural nerve biopsy before the genetic diagnosis. The samples were evaluated for morphological findings as well as X inactivation pattern.

Results:
The median age of disease onset was 36 years-old (28-52). All had sensory symptoms and motor weakness more prominent in distal lower limb. Nerve conduction studies were compatible with demyelinating neuropathy with secondary axonal degeneration. Besides, two patients had motor conduction blocks at tibial and peroneal nerve that were considered as secondary immune neuropathy. These patients had moderate motor improvement after immunotherapies. Heterozygous 379A>C mutation was detected in two patients. The other patient has heterozygous 581 T>C which has not been previously reported. This mutation is located on a functional domain of the protein and considered as likely pathogenic. Lastly, nerve biopsies of two patients with 379A>C mutation showed loss of large myelinated fiber with axonal regeneration.

Conclusions:
Females with heterozygous GJB1 mutation have variable phenotype. Although difference in X inactivation pattern has not been shown in serum samples of these patients, X inactivation pattern in Schwann cells may explain the variable phenotype in females with CMT1X.

References:
No

Grant Support:

The study is supported by Hacettepe University Research Project Department.

Keywords: Charcot-Marie-Tooth-x (CMT-x), demyelinating neuropathy, GJB1

Safety, complications and outcomes of anaesthesia in Charcot-Marie-Tooth disease.

Poster No:
P 022

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Introduction:
Anaesthetic management for CMT patients is still controversial. We evaluated the safety/complications/outcomes of general/spinal/local anaesthesia in a large cohort of CMT patients.

Methods:
We administered to patients of the Italian CMT Registry(1) (and age-/gender-matched controls recruited among unaffected relatives/friends) an online ad hoc questionnaire collecting information about type of surgery/anaesthesia (general/local/spinal) and early/delayed complications related to anaesthetics' use.

Results:
245 CMT patients and 60 controls answered. Overall, 185 (76%) patients and 39 (65%) controls underwent a total of 447 (297 general, 68 spinal, and 82 local) and 80 (58 general, 12 spinal, and 10 local) anaesthetic procedures, respectively. Regarding general anaesthesia, delayed awakening (9% vs 3%) occurred with similar rates in patients and controls. However, frequency of prolonged paralysis after awakening was higher in patients (25% vs 5%, $p<0.001$). In the post-operative period, breathing difficulties (4% vs 2%), need for reintubation (2% vs 0%), intensive care unit admission (2% vs 0%), tremor (1% vs 0%), lung/urinary infections (3% vs 2%), nausea/vomit (1% vs 0%) were not more frequent in patients than controls. Concerning spinal anaesthesia, patients reported complications in 15% of cases: urinary retention in 9% (lasting >8h in 6%), nausea/vomit in 4%, lumbar pain in 1%, and lower limbs paraesthesias in 1%. All complications recovered. Among controls, there were only two complaints (lumbar pain). Prolonged weakness and/or sensory loss (>2h) were more frequently observed in patients than controls (82% vs 42%, $p=0.018$). Local anaesthesia complications occurred in 5% (pain 4%, tremor 1%) of patients, all after distal nerve block, while none was reported by controls.

Conclusions:
This is the largest series on anaesthesia in CMT ever studied. General/spinal/local procedures are generally safe in CMT. Prolonged anaesthetic effect may occur, although both expectation bias and anesthesia procedure selection bias should be ruled out. Funded by GUP13006-Telethon grant.

References:
Yes

Reference 1: (1) Pisciotta C, Bertini A, Tramacere I, et al. Clinical spectrum and frequency of Charcot-Marie-Tooth disease in Italy: Data from the National CMT Registry. Eur J Neurol. 2023;30:2461-2470.

Grant Support:

Funded by GUP13006-Telethon grant.

Keywords: Charcot-Marie-Tooth, Anesthesia

MYELIN PROTEIN ZERO MUTATIONS: CMT CLUSTERS ACROSS ITALY.

Poster No:
P 023

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Introduction:
To investigate the clinical features of a large cohort of Charcot-Marie-Tooth patients with MPZ (myelin protein zero) mutation, focusing on five main clusters across Italy(1).

Methods:
We retrospectively gathered a minimal dataset of clinical information in a series of patients recruited among Italian CMT Registry centers(1), including mutation type, disease onset/severity (CMTES-CMT Examination Score), motor/sensory symptoms, use of orthotics.

Results:
We collected data from 185 patients: 60 had the p.Ser78Leu variant ("classical" CMT1B; from Eastern Sicily), 41 the p.Pro70Ser (CMT2I; mainly from Lombardy), 38 the p.Thr124Met (CMT2J; from Veneto), 25 the p.Ser44Phe (CMT2I; from Sardinia), and 21 the p.Asp104ThrfsX13 (mild CMT1B; from Apulia) mutation. Disease severity (CMTES) was highest in p.Thr124Met patients (9.4±6.6), followed by p.Ser44Phe (7.8±5.7), p.Pro70Ser (7.6±4.8), p.Ser78Leu (6.1±3.5), and p.Asp104ThrfsX13 (1.2±1.5). Disease onset occurred later in the p.Pro70Ser cohort (56.4±5.8) as compared to p.Thr124Met (45.2±9.4) and p.Ser44Phe (41.4±10.9) patients. However, disease progression, calculated through cross-sectional (rs, Spearman's rank correlation) and longitudinal analysis, was faster in the p.Pro70Ser cohort ($rs=0.81$, $p<0.001$; $\Delta CMTES/year=0.8\pm1.0$) followed by p.Ser44Phe ($rs=0.72$, $p=0.003$; $\Delta CMTES/year=0.7\pm0.4$), p.Thr124Met ($rs=0.43$, $p=0.024$; $\Delta CMTES/year=0.4\pm0.5$), and p.Ser78Leu ($rs=0.57$, $p<0.001$; $\Delta CMTES/year=0.2\pm0.4$) patients. Disease progression was negligible in p.Asp104ThrfsX13 ($rs=0.21$, $p=0.438$; $\Delta CMTES/year=0.1\pm0.4$) patients, who, however, frequently (78%, $p<0.001$) complained of neuropathic pain. In the other four clusters, walking difficulties were reported by 69-84% of patients, orthotic aid use ranged between 40-62% (24-52% for AFOs), while walking supports devices were used by 16-28% of subjects, with higher frequency in those carrying the p.Ser44Phe (26%) and p.Pro70Ser (28%) mutations. Hearing loss and pupillary abnormalities were almost exclusive of the p.Thr124Met mutation (47% and 74%, respectively).

Conclusions:
This is the largest MPZ cohort ever collected, reporting the heterogeneous features of the five clusters across Italy. Such variability, reflecting different pathomechanisms, suggests the importance of single mutation-based clinical prospective studies on MPZ-related neuropathies.

References:
Yes

Reference 1: (1) Pisciotta C, Bertini A, Tramacere I, et al. Clinical spectrum and frequency of Charcot-Marie-Tooth disease in Italy: Data from the National CMT Registry. Eur J Neurol. 2023;30:2461-2470.

Keywords: Charcot-Marie-Tooth, Myelin protein zero

Pharmacological modulation of myelin synthesis and cytoskeletal remodeling as a therapeutic strategy for CMT4B neuropathies with aberrant myelin

Poster No:
P 024

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Introduction:
Charcot-Marie-Tooth (CMT) type 4B1 and B2 are due to mutations in the MTMR2 and MTMR13 (Myotubularin-related 2 and 13) genes, respectively, and are characterized by early onset demyelinating neuropathy with myelin outfoldings and disabling progression. MTMR2 is a phosphatase, acting on the PtdIns(3,5)P2 phosphoinositide, whereas MTMR13 is catalytically inactive. Mtmr2 KO mice recapitulate CMT4B1, whereas both Mtmr13 KO nerves and cells showed reduced levels of MTMR2, suggesting that decreased MTMR2 activity may represent a common feature for CMT4B. No therapy is available for this or other forms of CMT. We recently proposed a novel mechanism by which the Rab35 GTPase activates MTMR2 and MTMR13 to negatively regulate PtdIns(3,5)P2. In Rab35 and Mtmr2 KO mutants, elevated PtdIns(3,5)P2 overactivates both mTORC1-dependent myelin synthesis and RhoA/myosin II-dependent cytoskeletal dynamics resulting in aberrant myelin. This project aims at assessing whether these pathways act in parallel or rather mTORC1 controls RhoA.

Methods:
Primary Schwann cell/DRG neuron co-cultures. Preclinical trials using the Mtmr2 KO mouse, a model of CMT4B1. Transcriptomics and proteomics analyses

Results:
Rapamycin, a known mTORC1 inhibitor, ameliorates aberrant myelin and reduces RhoA activation in Mtmr2 KO co-cultures. Moreover, Rapamycin and Blebbistatin, a myosin II inhibitor, similarly reduce aberrant myelin in vitro either alone or in combination. These data suggest that mTORC1 regulates RhoA in this system, similarly to other cell types. We then treated Mtmr2 KO mice using Rapamycin. Surprisingly, we found that the number of fibers carrying aberrant myelin in the nerve of Rapa-treated mice was increased. Of note Rapamycin has been used in other models with similar morphology and amelioration of the phenotype was observed. Transcriptomics and proteomics analyses are ongoing to further explore this finding.

Conclusions:
Rapamycin must not be used as a therapeutic strategy for CMT4B1 and likely also for CMT4B2. Our preliminary results indicate that mTORC1 controls RhoA in the nerve.

References:
No

Keywords: Charcot-Marie-Tooth, Schwann cell, Myelin, Myotubularin, Phosphatase

Urine Sorbitol Testing as a Screening Approach for SORD-Neuropathy

Poster No:
P 025

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Introduction:
Sorbitol dehydrogenase (SORD) deficiency recently emerged as one of the most common causes of autosomal recessive hereditary axonal neuropathy. However, detection of patients with SORD deficiency is difficult, as genetic testing is complicated by the presence of a pseudogene (SORD2P), resulting in decreased coverage of homologous regions of the gene by commercially available genetic assays. Studies have demonstrated significantly elevated serum and intracellular sorbitol levels in affected patients, with serum or plasma based sorbitol analysis previously used to screen patients with suspected SORD-related neuropathy. However, commercial availability of serum/plasma sorbitol testing is limited, making this screening test difficult to obtain in a timely fashion. To date, assessment of sorbitol levels in other human tissues has not been published.

Methods:
Urine polyols testing was performed for patients with suspected SORD-related neuropathy.

Results:
Nine patients had markedly elevated urine sorbitol levels (median: 835 mmol/mol creatinine, range 568-1998; controls < 7.2, maximum value = 248). Eight out of 9 of these patients have molecular confirmation of a diagnosis of SORD-related neuropathy. One of the 9 patients was found to harbor one pathogenic allele, with the second pathogenic variant yet unidentified. Normal urine sorbitol levels are reported in two SORD carriers. No false positive samples have been documented, and alternate diagnoses have been identified in a subset of patients initially considered to have possible SORD-related neuropathy who had normal urine sorbitol levels.

Conclusions:
This data suggests that urine polyols analysis is a promising screening test to identify patients with SORD deficiency. This testing is readily available, random urine samples are easy to obtain, and the process avoids the need for blood collection, making this a simple and accessible screening measure for patients of all ages. Additional studies are ongoing to further assess the sensitivity and specificity of urine polyols testing in relation to SORD neuropathy.

References:
No

Keywords: SORD, Sorbitol, Biomarkers, Polyols

Expanding spectrum of Charcot Marie Tooth Disease type 2U: Novel Variants of the MARS gene.

Poster No:
P 026

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Introduction:
Charcot Marie Tooth type 2U is an autosomal dominant disease which is clinically characterized by distal sensory axonal neuropathy which often presents in late adulthood. Few case reports have mentioned early onset of disease in some patients. Disease progression is slow, characterized by muscle atrophy and weakness in the lower extremities. Various genes have been reported to be associated with CMT type 2U. Results of our genetic testing in a familial case further expands the clinical and genetic spectrum of the MARS gene.

Methods:
We present two cases of a slowly progressive predominantly sensory peripheral neuropathy, confirmed with electrodiagnostic testing as sensory axonal peripheral neuropathies. Genetic testing confirmed a MARS gene mutation consistent with CMT type 2U. Patients are father and daughter.

Results:
We have reported two patients diagnosed Charcot Marie Tooth diease type 2U who present as autosomal dominant sensory axonal neuropathy. Both had C2333G>A variants of the MARS gene, which has been reported as a variant of unspecified significance

Conclusions:
To the best of our understanding, this specific variant of the MARS gene has not been reported to be pathogenic in resulting in CMT 2U. Both of these patients have their initial symptoms in the fifth decade of life with predominant involvement of the distal sensory nerves which eventually progressed into all four extremities. Knowing these unique findings further expand the spectrum of CMT type 2U associated with c2333G>A variants of MARS, a true pathogenic variant.

References:
No

Grant Support:

none

Keywords: CMT 2U, Genetics, MARS gene

Electrophysiological Findings in a Sample of Genetically Confirmed Brazilian Citizens with CANVAS

Poster No:
P 027

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Introduction:
Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) is a late-onset, slowly progressive neurological disorder. Usually caused by a biallelic intronic AAGGG repeat expansion in the RFC1 gene. Recently, other motifs have been identified as the genetic cause of CANVAS, expanding its genotypic spectrum. Meanwhile, electrophysiological findings are still to be detailed as patients receive their diagnosis.

Methods:
To evaluate nerve conduction studies and electromyography findings of CANVAS patients from a single Brazilian center. For the genetic diagnosis, flanking polymerase chain reaction (PCR) and repeat-primed PCRs (RP-PCR) for the pathogenic allele expansion configuration 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 nineteen patients of the sample group (18%). Subsequently, fitteen of these patients were submitted to electrophysiological studies. One patient had a normal electrophysiological study and clinically presented with cerebellar ataxia alone. Six patients (40%) had motor involvement associated with neuropathy. Notably, eight patients (53%) had sensory involvement and primarily axonal deterioration. Additionally, 6 patients were submitted to the blink test and 3 (50%) had the R2 reflex impaired. Median nerve and superficial peroneal nerve sensory action potential (SAP) were absent in 40% and 60% of patients, respectively. When detected, median nerve SAP mean amplitude and conduction velocity were 4,3 mV and 52 m/s, respectively; whereas, at the superficial peroneal nerve they were 4,6 mV and 45,3 m/s, respectively. Only three patients had normal amplitude for the superficial peroneal nerve. Regarding autonomic evaluation, four patients were evaluated and one of them showed diminished response to electric stimulus. Moreover, eight patients had cerebellar atrophy on MRI.

Conclusions:
This study shows that in CANVAS there is an axonal involvement of the sensory fibers. The involvement of the blink reflex in the presence of reasonable preserved upper limb sensory nerves suggest a sensory neuronopathy.

References:
No

Keywords: Electrophysiology, CANVAS, Neuronopathy, EMG

Genetic Landscape of Charcot-Marie-Tooth Disease in Türkiye: Distinct Distribution, Rare Phenotypes, and Novel Variants

Poster No:
P 028

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Introduction:
Charcot-Marie-Tooth (CMT) disease is the most common inherited neuropathy. Owing to the advances in molecular genetics, the genetic landscape of CMT has evolved in recent years; however, data from under-represented populations in genetic studies remain limited.

Methods:
In this study, we describe the genetic and clinical features of patients with CMT at our department. Pathogenic variants were identified utilizing MLPA (multiplex ligation-dependent probe amplification), Sanger sequencing, and exome sequencing.

Results:
Overall, 310 patients from 264 families with definitive genetic diagnosis were included in this study. The most frequent subtype was CMT1 (135 families), followed by CMT4 (45 families), CMT-I (31 families), CMT2 (27 families), and AR-CMT2 (26 families). The most frequently mutated genes were PMP22, GJB1, MFN2, SH3TC2 and GDAP1, respectively. Interestingly, only eight families were identified with MPZ variants. Among 76 families with recessive subtypes, causative variants were identified in 20 different genes. We identified pathogenic or likely pathogenic variants in genes unusual for a predominantly CMT phenotype, including FXN, SPG7, and ATM. The mean age of onset was 13.68 ± 12.32 years (range 1-57), and 151 patients were female (48.7%). Patients with autosomal recessive CMT forms, have an early disease onset (mean: 6.28 ± 6.01, range 1-29 years). Symptoms related to lower limb weakness or skeletal deformities were the most common presenting complaint, followed by delayed motor milestones. Among patients with delayed motor milestones, 23 had an autosomal recessive CMT subtype. Atypical clinical features, such as cranial nerve involvement, were more frequent in recessive forms.

Conclusions:
Our study described the genetic distribution of CMT in a referral center in Türkiye by including the largest number of genetically solved cases to date. Furthermore, we expanded the genetic and phenotypic spectrum by identifying novel variants and describing new clinical features.

References:
No

Keywords: CMT, Hereditary neuropathies, Polyneuropathy, Turkey, Variant

Motor Unit Remodelling As An Early Biomarker Of Disease Involvement In Hereditary Transthyretin Amyloidosis

Poster No:
P 029

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Introduction:
MScan-motor unit number estimation (MScan-MUNE) was evaluated to estimate axonal loss, as a potential biomarker of transition to symptomatic disease in hereditary transthyretin amyloid polyneuropathy (ATTRv-PN).

Methods:
Ulnar MScan-MUNE was undertaken in 19 prospectively recruited patients carrying ATTR variants, and parameters were compared between patients with large fibre neuropathy (LF+), those without (LF-), and healthy controls. Relationships to clinical severity scores were determined and cut-off values calculated.

Results:
A consistent trajectory of change was observed with MScan-MUNE and the number of large units decreasing, and mean unit amplitude increasing with increasing disease severity. Compared to healthy controls, LF+ patients had fewer motor units (LF+: 51.8 ± 35.8 vs HC+: 102.8 ± 42.2, p=0.003) and large units (LF+: 11.3 (9.4-15.6) vs HC: 25.4 (18.3-33.8), p=0.007). Greater mean unit amplitude was found in LF- and LF+ groups when compared to their respective HC groups (LF-: 117.0 ± 24.4 vs HC-: 84.2 ±30.0 = $p<0.05$; LF+: 146.8 ± 65.5 vs HC+: 99.7 ± 37.4, p=0.005), despite similar distal CMAP amplitudes across all groups (LF-: 9.4 vs HC: 10.7mV, p = 1; LF+: 7.65 vs HC+: 9.71mV, p=0.42). MScan-MUNE and the number of large units were able to predict disease severity scores, with a reduction in each of these associated with worsening disease severity on PND, NIS-LL, INCAT, CMTNS and mBMI (all $p<0.05$). A cut-off value of 76 motor units was able to distinguish PND 0 from PND 1 or above (AUC 0.80, 95% CI 0.54-1.00) with a sensitivity of 100% and specificity of 78.6%.

Conclusions:
ATTRv-PN is associated with progressive axonal loss, measured by MScan-MUNE, that correlates with disease severity. Motor unit loss occurs early in ATTRv-PN, masked by re-innervation, which preserves CMAP amplitudes. MScan-MUNE may be a promising targeted biomarker of transition to symptomatic disease in ATTRv-PN.

References:
No

Keywords: ATTR, Biomarker, Hereditary transthyretin amyloidosis, Motor unit number estimation, MScan-Fit

The Spectrum Of Neuropathy In Hereditary Transthyretin Amyloidosis (ATTRv) In Australia

Poster No:
P 030

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Introduction:
Hereditary Transthyretin amyloidosis (ATTRv) is characterised by relentlessly progressive small fibre, autonomic and large fibre neuropathy and cardiac failure. ATTRv is caused by dominantly inherited transthyretin gene variants which drives transthyretin misfolding and amyloid deposition. Little is known about ATTRv in Australia. We describe the clinical and genetic spectrum of ATTRv neuropathy in Australia in 2024.

Methods:
A retrospective analysis of ATTRv patients attending Australian Amyloidosis Network clinics between 2007–2024 was performed. TTR variants, clinical features and treatments were evaluated.

Results:
161 individuals were identified (62% NSW/ACT, 20% QLD, 12% VIC/TAS, 4% WA, 2% SA). Average age was 59.4 years (range 21.5–91.4). 53% were male. 37% were presymptomatic (average age 52.7 years, range 21.5–71.0). 24 genetic variants were identified, including Thr60Ala (31%), Val30Met (23%), Val122Ile (12%), Ala97Ser (6%), Glu89Gln (5%), with the remaining 22.6% comprising 19 mutations (n=1-4 in each). The diagnosis was made by genetic testing in 70.3%, Biopsy in 16.8% and cardiac amyloid bone scan in 12.9%. The diagnosis rate has increased from 2 p.a in 2011–13 to 5 p.a in 2015–17, and 12 p.a in 2020–22. The average time to diagnosis was 3.8 years (range 1–15). 13 asymptomatic individuals developed symptomatic disease over an average 2.3 years (range 0–8). 40% had neuropathic-predominant disease, 32% cardiac, 25% mixed cardiac and neuropathic, and 3% had other organ-predominant disease. Of the 130 living individuals 45% had a PND score of 0, 22% PND1,10% PND2, and 9% PND3a or above. Similarly, 53% of individuals had a FAP0, 31% FAP1, 15% FAP2 and 1% FAP3. Of individuals with PND0–2, only 22% were on highly efficacious treatments, all via clinical trial or compassionate access schemes.

Conclusions:
Our study is the first to demonstrate the spectrum of ATTRv in Australia. Affordable TTR genotyping and access to highly efficacious novel therapies remain substantial unmet needs in this population.

References:
No

Keywords: ATTR, Hereditary transthyretin Amyloidosis, Gene Variants

Pathway Analysis of Inherited Neuropathies Identifies Putative Common Mechanisms of Neuropathy and Therapeutic Targets

Poster No:
P 031

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Introduction:
Inherited neuropathies are a heterogenous group of disorders with variable penetrance and pleiotropy. Over 100 genes have been identified among several subtypes of inherited neuropathies, including Charcot-Marie-Tooth (CMT), Hereditary Sensory and Autonomic Neuropathy (HSAN), Distal Hereditary Motor Neuropathy (dHMN), and various metabolic and mitochondrial disorders. A variety of classification schemes of inherited neuropathies have been proposed, most recently with emphasis on the identified genotype for a given phenotype, but such schemes may cloud common pathways or mechanisms for such disorders. Signaling pathway analysis of genes associated with inherited neuropathies provides a mechanism by which common pathophysiologic mechanisms can be identified. Such commonalities may not only offer a more physiologic schema of organization, but also predict possible novel genotypes as well as shared therapeutic targets.

Methods:
Eighty-eight unique genes associated with CMT, HSAN, dHMN, and mitochondrial disorders were analyzed for common pathways by protein-protein interactions (PPI) as well as ontologic clusters by Metascape pathway software. Analysis was performed separately on axonal (67 genotypes), demyelinating (18 genotypes), and intermediate (11 genotypes) neuropathies, as well as the combined gene set.

Results:
In the axonal only analysis, PPI analysis demonstrated high dynein binding connectivity as well as nodes including NTRK1 and GARS1. The top transcription factor target was MEF2. The demyelinating only set identified two PPI clusters with MTMR2 and EGR2 central nodes as well as top transcription factor target of HFH4. The combined analysis of all genes demonstrated multiple high connectivity PPI nodes of VCP, NTRK1, HK1, and DYNC1H1 with ZIC1 as the top transcription factor target. An ontologic network of this more complex dataset demonstrated multiple sub-clusters including tRNA metabolism, development, mitochondrial dynamics, and cytoskeletal maintenance.

Conclusions:
Pathway analysis identifies novel clusters of inherited neuropathy genotypes. The structure of the identified nodes, common pathways, and predicted phenotypes will also be presented.

References:
No

Keywords: CMT, HSAN, Inherited neuropathy, Pathway analysis, Bioinformatics

Partial Motor Conduction Block in Inherited Neuropathies

Poster No:
P 032

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Introduction:
Partial motor conduction block (PMCB) is defined as significant decline of compound muscle action potential amplitude (CMAP) amplitude between distal and proximal stimulations of a peripheral nerve. Conduction block represents failure of nerve impulse to propagate in some (partial) or all (complete) of the structurally intact motor axons. While commonly seen in acquired demyelinating neuropathies, CB is not considered a feature of inherited demyelinating neuropathies. We report four patients with genetically confirmed Charcot-Marie-Tooth disease (CMT) who showed conduction block in their nerve conduction study (NCS).

Methods:
A retrospective chart review was done to identify CMT patients who showed PMCB on their NCS. PMCB was defined by the presence of ≥30 percent reduction in proximally stimulated negative peak CMAP amplitude compared to distal negative peak CMAP amplitude (EFNS/PNS CIDP diagnostic criteria Eur J Neurol. 2021; 3556–3583). Sites of entrapment were excluded.

Results:
Four patients with genetically confirmed CMT were found to have PMCB. Two patients (26M and 54M) had CMT1A, one (20F) had CMT1B, and one (50M) had CMTX. All presented with typical clinical features of CMT including slowly progressive length-dependent sensory and motor deficits. CMT Neuropathy Scores ranged from 7-20 (Mean 12.75). PMCB was demonstrated in the forearm (wrist-elbow) segment of median nerve in all patients; upper arm (elbow-axilla) segment of median nerve in 1 patient; forearm (wrist-elbow) segment of ulnar nerves in 2 patients; and upper arm (above elbow- axilla) segment of ulnar nerve in 1 patient. NCS also demonstrated diffuse uniform slowing in the range of 10-20 m/s in patients with CMT1A and 1B, versus 30-40 m/s in 1 patient with CMTX.

Conclusions:
Nerve conduction study in inherited demyelinating neuropathies can show PMCB, mimicking NCS features of acquired demyelinating polyneuropathies.

References:
No

Keywords: CMT, Conduction Block, Demyelination

Development And Phenotypic Characterization Of A CRISPR/Cas9 Model Of Riboflavin Transporter Deficiency In Zebrafish

Poster No:
P 033

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Introduction:
Riboflavin transporter deficiency (RTD) is a rare disease caused by mutations in SLC52A2 and SLC52A3 which functionally impair riboflavin transporter proteins 2 and 3, respectively, leading to metabolic dysregulation and subsequent sensorimotor neurodegeneration. Patients present with muscle weakness, hearing impairments, and respiratory difficulty. Riboflavin supplementation has improved symptoms in over 70% of cases, with remaining patients either stabilizing or further deteriorating due to rapid excretion of riboflavin. In this study, we developed zebrafish RTD models for use in therapeutic screening of riboflavin and/or probenecid - an inhibitor of OAT-3-mediated riboflavin excretion.

Methods:
We generated morpholino-mediated slc52a3 knockdown zebrafish and CRISPR/Cas9-mediated slc52a3-targeted crispants. Various behavioural and morphological characteristics were assessed, including motor axon length, locomotor ability, and hearing ability. To assess phenotype specificity, slc52a3 morpholino was co-injected with either human SLC52A3 mRNA or p53 morpholino. Riboflavin and/or probenecid treatment was then tested on slc52a3 morphants.

Results:
The slc52a3 morphant model displayed RTD-like characteristics including shortened motor axons, impaired hearing, and reduced locomotor ability. The slc52a3 morphant phenotype was independent of p53 activation - a potential off-target effect following morpholino microinjection - and co-injection of slc52a3 morpholino with human SLC52A3 mRNA rescued the slc52a3 morphant phenotype, reinforcing phenotypic specificity and highlighting the clinical relevance of this study. The slc52a3-targeted F0 crispant phenotype partially overlapped with slc52a3 morphants. Riboflavin-treated slc52a3 morphants exhibited partial phenotypic improvement, while riboflavin and probenecid co-treatment did not provide additional benefit.

Conclusions:
F0 slc52a3-targeted crispants and slc52a3 morphant zebrafish exhibited partially-overlapping RTD-like phenotypes. Riboflavin-treated slc52a3 morphants showed partial phenotypic amelioration, reflective of the clinical impact of riboflavin treatment in RTD patients. Development of CRISPR/Cas9 knockouts and further therapeutic screening of riboflavin, probenecid, and other therapeutics using both the morphant model and the CRISPR/Cas9 knockout line will help to advance the search for novel RTD treatment strategies.

References:
No

Keywords: Zebrafish, CRISPR/Cas9, Morpholino, Probenecid, Neurodegeneration

Lower extremity MR images in Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay patients with SACS mutations: Korean CMT cohort

Poster No:
P 034

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Introduction:
Mutations in the SACS gene are associated with peripheral neuropathy, cerebellar ataxia, and spasticity, which manifest in the form of CMT 5 or Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) disease. The aim of this study is to investigate phenotypic heterogeneities and characteristics of CMT patients with SACS mutations in Korean population.

Methods:
This study screened SACS mutations in Korean CMT patients (1,363 families) by whole exome sequencing and targeted sequencing

Results:
We identified 4 pathogenic mutations in 4 families (4 male, 2 female) as the underlying cause of the CMT5. All six had mild distal dominant weakness but severe gait disturbance and 4 of the confirmed cases had upper motor sign. Three patients with brain MRI showed cerebellar atrophy, and four patients with hearing loss had abnormal BAEP findings. Lower limb MRI showed no lesion or mild fatty change. Nerve conduction study showed axonal neuropathy pattern.

Conclusions:
In conclusion, we report on the genetic variants and clinical findings in four families with SASC gene mutations in Korea. We found minimal changes on limb MRI compared to gait disorder, suggesting that the disorder is distinct from other hereditary neuropathy disorders.

References:
No

Keywords: ARSACS, CMT, Lower extremity MRI, SACS gene

Development of a functional outcome measure for patients with Riboflavin Transporter Deficiency

Poster No:
P 035

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Introduction:
Riboflavin transporter deficiency (RTD) is a progressive inherited neuropathy of childhood onset, characterised clinically by pontobulbar palsy, sensory ataxia, sensorineural deafness, muscle weakness, optic atrophy, and respiratory failure. A robust and responsive functional outcome measure is essential for future clinical trials of disease-modifying therapies. The CMTPedS is a well-validated outcome measure for CMT and might have utility for measuring disease progression in individuals with RTD. However, the CMTPedS requires modifications to account for phenotypic differences between children with CMT and RTD. The aim of this study was to develop a functional outcome measure based on the CMTPedS for specific use in individuals with RTD.

Methods:
A literature review for functional outcome measures generated an item pool, and five potential items (30-second sit to stand, shoulder internal rotation strength, shoulder external rotation strength, elbow flexion strength, and feet apart on a line eyes open) were pilot tested in a cohort of five individuals with RTD. The results of this pilot testing, alongside analysis of existing CMTPedS item scores in the RTD cohort, informed the modification of the CMTPedS.

Results:
The final version of the RTDPedS has the following modifications. 'Shoulder internal rotation' and the '30-second sit to stand test' were added as proximal measures of strength and function. The composite balance item comprising nine tasks in the CMTPedS showed a ceiling effect and was replaced with the single 'Feet apart on a line eyes open' balance item. Pinprick sensation was removed due to a floor effect.

Conclusions:
The RTDPedS is a standardised functional outcome measure that assesses strength, upper and lower limb function, balance, and mobility. The RTDPedS grades level of disability in affected individuals to healthy age and sex-matched controls and can be scored online at ClinicalOutcomeMeasures.org. It also provides a standardised approach to tracking disease progression and treatment response over time.

References:
No

Keywords: Riboflavin transporter deficiency, functional outcome measure

ClinicalOutcomeMeasures.org: Implementing a training and quality assurance program for CMT trial endpoints

Poster No:
P 036

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Introduction:
Members of the Inherited Neuropathy Consortium have developed reliable, sensitive and responsive clinical outcome assessments (COAs) for patients with Charcot-Marie-Tooth disease (CMT) across the lifespan e.g., CMTPedS, CMT-FOM and CMTInfS. In an effort to standardize training and quality assurance for use of these COAs as clinical trial endpoints, the aim of this study was to develop and implement a comprehensive training and quality assurance program to ensure accurate multicenter data collection.

Methods:
The ClinicalOutcomeMeasures.org training and quality assurance program was created following eight rounds of review by seven CMT experts. Then training resources were co-designed with 60 key stakeholders including CMT experts, clinical evaluators, pharmaceutical representatives, and patients through a collaborative, multi-method approach involving surveys and focus groups/interviews. Professional videos and still images of each item of each COA were captured. An online portal hosting all training and quality assurance resources was activated and usage statistics monitored.

Results:
To date, 930 users from 35 countries are registered on ClinicalOutcomeMeasures.org. A 3-phase training and quality assurance program was developed and implemented i.e., Phase 1: 'Self-directed e-learning' through review of equipment and training resource manuals; Phase 2: 'Training' via online basic and advanced level courses and quizzes as well as in-person training followed by reliability assessments; Phase 3: 'Monitoring' involves refresher/annual training courses. 75 clinical evaluators have completed the recently launched training and quality assurance program.

Conclusions:
ClinicalOutcomeMeasures.org is a web-based resource housing key clinical trial endpoints for monitoring response to therapy. This new training and quality assurance program promotes accurate and reliable data collection to overcome unnecessary delays in the translation of rational therapies for individuals with CMT across the lifespan.

References:
No

Grant Support:

2021 Muscular Dystrophy Association Ideas Grant; Inherited Neuropathy Consortium Pilot Grant

Keywords: Charcot-Marie-Tooth disease, Clinical Outcome Assessments, Training and Quality Assurance

Peripheral myelin disorders and the mechanisms of hidden hearing loss

Poster No:
P 037

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Introduction:
Hidden hearing loss (HHL) is a recently described auditory neuropathy believed to contribute to deficits in speech discrimination and intelligibility, and in hearing in noisy environments, in people with normal audiological tests. In animal models, HHL presents as normal auditory thresholds but reduced sound-evoked potentials (ABR peak 1 amplitudes). The animal studies showed that age-related and noise-induced loss of synapses between the inner hair cells (IHCs) and spiral ganglion neurons (SGNs) correlate with HHL. Thus, IHC synaptopathy is currently seen as the only cause of HHL.

Methods:
Since myelin impairments cause many other peripheral neuropathies, we tested whether myelin disorders can also cause HHL using three mouse models.

Results:
First, Schwann cell ablation was induced by genetic means, causing a near total loss of auditory nerve myelin within one week followed by complete remyelination by four months. This demyelination does not alter auditory thresholds yet induces permanent reduction in sound-evoked potential amplitudes and longer latencies. Importantly, transient demyelination does not change IHC-SGN synapse density but causes a permanent disorganization of cochlear heminodes. Moreover, HHL caused by transient demyelination and noise are additive, indicating that HHL can be caused by at least two distinct mechanisms. Similar pathologies, i.e., HHL and disorganized heminodes, were found in a mouse model of Charcot Marie Tooth disease type 1A (CMT1A) and a mouse line that has peripheral nerve hypomyelination due to loss of ErbB receptor signaling in myelinating Schwann cells.

Conclusions:
Together, our results show that peripheral myelinopathies can cause an HHL that is very similar to that seen with synaptopathy except that it also affects ABR peak 1 latencies. It also suggests that the heminodes play a critical role in the generation of the auditory nerve compound action potential, possibly acting as the action potential initiation site; and that patients with peripheral myelin disorder might also suffer from HHL.

References:
No

Grant Support:

This work was supported in part by R01DC018500 and by a grant from Decibel Therapeutics (GC)

Keywords: Hearing loss, auditory, heminode, Schwann cell, neuroapthy

In-Vivo Reflectance Confocal Microscopy of Meissner Corpuscles in CMT1A: longitudinal data from the ACT-CMT study

Poster No:
P 038

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Introduction:
Accelerate Clinical Trials in Charcot-Marie-Tooth Disease (ACT-CMT) is an NIH-supported, multi-center clinical trial readiness study that aims to validate clinical outcomes and biomarkers for CMT1A. In-vivo reflectance confocal microscopy (RCM) of Meissner corpuscle (MC) density is one of the candidate monitoring biomarkers for sensory nerve involvement.

Methods:
Participants with CMT1A and healthy controls aged 18 to 75 were enrolled across multiple sites. Ongoing serial assessments over three years include in-vivo RCM of MC densities and areas and monofilament tactile thresholds at the distal palmar surface of digit V (DV) and the thenar eminence (TE). Other clinical severity measures include the CMT Functional Outcome Measure, CMT Neuropathy Score and Exam Score, CMT Health Index, MRI of intramuscular fat fraction, and electrophysiology.

Results:
MC measurements and tactile thresholds were quantified in 123 participants with CMT1A and 23 controls. Age and gender distributions were balanced across groups. In CMT, MC densities were measurable in all participants and associated with tactile thresholds and clinical severity measures. Repeated measures analyses using baseline, 6-, and 12-month data revealed lower MC densities at DV ($p = 0.005$) but not at TE ($p = 0.06$), larger mean MC areas at DV ($p < 0.001$) and TE ($p = 0.003$), and higher (worse) tactile thresholds at DV ($p = 0.003$) and TE ($p < 0.001$) in CMT compared to controls. MC densities and areas and tactile thresholds did not change over 12 months in CMT or controls. Twenty-four month data will be analyzed and presented.

Conclusions:
In-vivo RCM of MC density and mean area are non-invasive objective measures of sensory nerve involvement in CMT1A. MC densities are associated with clinical severity measures, not limited by floor effects seen with electrophysiology measures, and stable over 12 months. Ongoing longitudinal assessments will further characterize these measures' roles as biomarkers in CMT1A.

References:
No

Grant Support:

NINDS U01NS109403

Keywords: Charcot-Marie-Tooth, biomarker, Meissner corpuscle, reflectance confocal microscopy

Evaluating AI performances in VarPB for genetic diagnoses in CMT and beyond

Poster No:
P 039

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Introduction:
While over 100 genes have been implicated in inherited neuropathies, still nearly half patients remain undiagnosed. The same is true for many other monogenic diseases. Recently, the AlphaMissense and PrimateAI-3D unsupervised AI tools demonstrated impressive performance at predicting functional missense variant effects. However, in medical genetics practice, a highly relevant use case is the ability to prioritize a single medically pathogenic change in a pool of ~10,000 coding variants per genome. Here we introduce the Variant Prioritization Benchmark (VarPB) to objectively compare 52 variant pathogenicity prediction tools in this medical genetics task.

Methods:
The VarPB task is to rank all variants in an individual by likelihood of causing disease, when one high-confidence pathogenic missense variant from ClinVar is artificially spiked-into each genome. Analysis of 3.4 million spike-in events are measured by the normalized areas under the curve of the rank position of the true pathogenic variant relative to all scored variants within each individual. It uses 100x WGS from over 100 individuals.

Results:
Maverick achieves the best overall performance among the tested tools. Supervised learning approaches show a clear advantage over unsupervised methods in this task. We observe low correlation between VarPB and MAVE performance suggesting that VarPB indeed represents a useful additional dimension for pathogenicity prediction tool evaluation. We also observe only a moderate correlation between VarPB performance and the classification of balanced sets of known benign versus pathogenic variants in ClinVar, emphasizing the difficulty of working with a large excess of benign variation in medical genetics.

Conclusions:
Predicting functional effects of protein-altering mutations must not be confounded with medically relevant pathogenicity in disease-associated genes. Tools that demonstrate excellent performance at identifying functional mutation effects may not necessarily be the best choice for identifying the disease-causing variant within an individual with CMT or other inherited disease.

References:
No

Keywords: Artificial Intelligence, Peripheral Neuropathy, Diagnosis, CMT, Pathogenicity

Adult-onset Hyperhomocysteinemia With Demyelinating Neuropathy, Combined Cord Degeneration And Optic neuropathy, A Treatable Conundrum

Poster No:
P 040

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Introduction:
Neurometabolic disorders typically manifest in childhood, making them more familiar to pediatricians. Nevertheless, it is crucial for adult neurologists to remain vigilant in considering these disorders, since they can be treatable.

Methods:
Participants received standard clinical care in a neuromuscular reference center and provided written informed consent for genetic analyses. Each of the 2 unrelated probands underwent either targeted whole exome sequencing (WES)-based gene-panel analysis or trio whole exome analysis. Acquired cobalamine metabolism disorders such as due to nitrous oxide abuse and atrophic gastritis were ruled out.

Results:
Two probands presented with long-standing psychiatric medical history followed by progressive gait abnormalities, fine motor skills loss, vision impairment and in one proband hearing loss. Neurological examination 2 to 3 years after disease onset revealed severe sensory ataxia including pseudoathetosis, areflexia and bradyphrenia. Neurophysiological tests indicated a mixed sensorimotor neuropathy with demyelinating features. Magnetic resonance imaging revealed dorsal column T2/FLAIR hyperintensities in both probands. Blood analysis revealed hyperhomocysteinemia, cobalamine and folate deficiency in both patients. In retrospect, several family members of both probands showed evidence of hyperhomocysteinemia or chronic cobalamine deficiency. Despite no established genetic diagnosis, suppletion with hydroxycobalamine, levofolic and betaine stabilized one proband, while the other showed signs of improvement.

Conclusions:
The presence of combined cord degeneration, peripheral neuropathy, and optic neuropathy warrants a diagnostic investigation for cobalamin-related neurometabolic disorders. In cases where an etiological diagnosis remains elusive, prompt initiation of treatment is necessary.

References:
No

Grant Support:

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Keywords: hyperhomocysteinemia, peripheral neuropathy, combined cord degeneration, treatable

What Is The Best Electrophysiological Biomarker For Monitoring Asymptomatic Transthyretin Mutation Carriers?

Poster No:
P 041

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Introduction:
The follow-up protocol for asymptomatic transthyretin (TTR) gene mutation carriers is not entirely standardized. The aim of this study was to identify the electrophysiological data most sensitive to changes over time in asymptomatic carriers.

Methods:
Electrophysiologic examination encompassed nerve conduction study on median, ulnar, tibial, fibular and sural nerves, motor unit count index (MUNIX), electrochemical skin conductance measured by Sudoscan®, sympathetic skin response and heart rate variability on deep breathing (HRV). Measurements at first and second examinations were compared using the non-parametric Wilcoxon test for paired data.

Results:
A total of 23 asymptomatic carriers were included with a median age of 49 years (interquartile 37-58). The V30M mutation was the most frequent (10/23). Portuguese origin was reported in 2 asymptomatic carriers. The median time between two examinations was 3 years (2-4). There was no significant difference between the two measurements for MUNIX, cutaneous sympathetic reflex, sudoscanner and HRV. The only parameters that exhibited significant modifications were the motor distal latency of the median nerve (+0.07 ms/year) and the CMAP duration of the ulnar (+0.10 ms/y) and fibular (+0.12 ms/y) nerves. The ulnar nerve CMAP duration was the most sensitive biomarker to change when performed within the 10 years preceding or following the age of the youngest amyloid polyneuropathy in the family, with a standardized response mean of 0.91.

Conclusions:
Nerve conduction parameters undergo variations even in the asymptomatic phase of familial amyloid polyneuropathy. Ulnar CMAP duration appears to be a promising electrophysiological biomarker for the monitoring of asymptomatic TTR mutation carriers.

References:
No

Grant Support:

no

Keywords: Familial amyloid neuropathy, asymptomatic carrier, biomarker, electrophysiology

Human Dental Pulp Stem Cells as a Patient-in-a-Dish Model for Charcot-Marie-Tooth Disease Type 1A

Poster No:
P 042

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Introduction:
Charcot-Marie-Tooth disease type 1A (CMT1A) is the most prevalent demyelinating peripheral neuropathy worldwide. CMT1A is caused by the duplication of the peripheral myelin protein 22 (PMP22) gene, predominantly affecting Schwann cells. Many CMT1A candidate drugs have failed trials due to a lack of clinically relevant in vitro models. Remarkably, human Dental Pulp Stem Cells (DPSC), a subset of mesenchymal stem cells, share their embryonic lineage with Schwann cells: the neural crest. Our research group has pioneered a differentiation protocol to generate DPSC-derived Schwann cells (DPSC-SC). Hence, we aim to develop a novel CMT1A patient-in-a-dish model by overexpressing PMP22 in DPSC-SC.

Methods:
Ten healthy DPSC donor lines were isolated from third molars using the explant method. Following differentiation towards DPSC-SC, Schwann cell phenotype was determined using qPCR and immunocytochemistry. Additionally, DPSC-SC myelination capacity was further evaluated in a 3D hydrogel co-culture model with rat dorsal root ganglion neurons. Finally, lentiviral transduction and CRISPR-Cas9 were used to overexpress PMP22.

Results:
Ten donor DPSC-SC lines displayed relatively stable gene and protein expression of P75NTR, S100B, SOX10, and laminin, validating the consistency of the differentiation. Our data revealed variable expression patterns of myelin-related genes (MPZ, PLP1, KROX20, OCT6, SOX2, C-JUN, and NCAM). However, DPSC-SC successfully myelinated rat neurons in a 3D hydrogel model, highlighting the importance of neuronal interactions. Moreover, we overexpressed PMP22 in DPSC and DPSC-SC using lentiviral transduction and successfully integrated one additional copy of PMP22 in DPSC using CRISPR-Cas9.

Conclusions:
We successfully differentiated ten donor DPSC lines towards a Schwann cell phenotype that were able to myelinate rat neurons in a hydrogel model. Moreover, we successfully overexpressed PMP22 in DPSC-SC and DPSC using lentiviral transduction and CRISPR-Cas9, respectively. These PMP22-overexpressing DPSC-SC offer a novel toolbox for studying CMT1A and PMP22-related mechanisms with high clinical relevance.

References:
No

Grant Support:

This research was funded by the CMTA-STAR program and FWO Flanders.

Keywords: Charcot-Marie-Tooth disease type 1A, Schwann cells, Human Dental Pulp Stem Cells, Peripheral Myelin Protein 22, In vitro models

Body Fat Percentage is associated with disability severity in children with Charcot-Marie-Tooth disease

Poster No:
P 043

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Introduction:
Children with Charcot-Marie-Tooth disease (CMT) experience progressive and lifelong disability. Being severely underweight or overweight according to the Body Mass Index (BMI) has been shown to compound the rate of disability. Since BMI cannot differentiate between fat and fat-free-mass, we sought to explore the impact of body composition measured by bioelectrical impedance analysis (BIA) and disability assessed with the CMT Pediatric Scale (CMTPedS) in a paediatric CMT cohort.

Methods:
Body Fat Percentage and Fat Mass Index was captured in children with CMT, with predominant subtypes including CMT1A, 1B, 2S, 4C aged 4-18 years (63.8% male) using BIA (Tanita MC-780MA) and disability was assessed using the CMTPedS at baseline, (n=107), and at 1 year follow up (n=51). BMI was classified into five categories according to the International Obesity Task Force.

Results:
BMI classification of 107 children, mean age 11.6 years (SD 4.0), assessed at baseline was 2.8% severely underweight, 14.7% underweight, 58.7% healthy weight, 15.6% overweight and 8.3% obese. At baseline, mean body fat percentage was 25.8% (SD 9.4), FMI was 5.35kg/m2 (SD 0.3), and disability according to the CMTPedS was 16.4 points (SD 9.4). Body Fat Percentage correlated with disability ($r=0.514$, $p<0.001$) as did Fat Mass Index ($r=0.948$, $p<0.001$). Fat Mass Index correlated with disability ($r=0.456$, $p<0.001$). At follow-up, Body Fat Percentage increased to 27.2% (SD 11.1), Fat Mass Index increased to 5.9 kg/m2 (SD 4.6) and CMTPedS to 18.0 points (SD 9.4). Rate of change of Body Fat Percentage and Fat Mass Index was related to change in CMTPedS.

Conclusions:
Higher Body Fat Percentage and Fat Mass Index was associated with more severe disability progression in children with CMT. Evaluating body composition might explain some of the heterogeneity in disease severity of paediatric CMT, and potentially identify dietary and lifestyle therapies.

References:
No

Keywords: Charcot-Marie-Tooth Disease, Pediatrics, Body Composition, Inherited Neuropathies

Charcot-Marie-Tooth Subtype Biomarkers and Outcome Measures in Subjects with CMT1B, CMT2A, CMT2F and CMT1X

Poster No:
P 044

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Introduction:
Natural history studies of CMT1B, CMT2A, CMT1X and CMT2F (the four genes) utilizing the CMT Neuropathy Exam Scores (CMTNS/CMTES), recent clinical outcome assessments (COA) such as CMT Functional Outcome Measure (CMT-FOM) and CMT Health Index (CMT-HI) are being collected at five international sites. These measures are being collected in combination with magnetic resonance imaging (MRI of calf and thigh), plasma and skin biopsy sample. The data collected (mentioned above) can be used to learn about the four disorders, to help develop therapies and to achieve 'clinical trial readiness' over time periods that are reasonable for industry partners.

Methods:
The objective is to prospectively measure the natural history of patients with CMT1B, CMT2A, CMT1X and CMT2F correlating subject's clinical outcome assessments, MRI imaging and plasma and skin samples over a 12-month period. Each subject will complete two visits baseline and a 12-month follow-up visit. Clinical information from each visit is electronically submitted and maintained in a database housed at the Rare Disease Clinical Research Network (RDCRN) at the Data Management and Coordinating Center at Cincinnati Children's Hospital.

Results:
Overall, 179 patients have been enrolled across the study's five participating sites. This can be broken down into 40 CMT2A, 68 CMT1B, 59 CMT1X and 12 CMT2F. Across the study sites, 179 baseline and 120 follow-up visits have been completed.

Conclusions:
Study recruitment for all sites is ongoing and will continue to facilitate clinical trial readiness for CMT1B, CMT2A, and CMT1X and CMT2F. With 179 subjects currently enrolled, all sites continue to work towards the goal of 60 subjects in total (15 subjects per gene).

References:
No

Grant Support:

Funding for this research is provided by the CMTA.

Keywords: CMT, Charcot-Marie-Tooth, Neuropathy

Plasma and Skin Biomarkers for Charcot-Marie Tooth Disease

Poster No:
P 045

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Introduction:
While several candidate biomarkers have been developed for CMT1A, it is important to establish if similar biomarkers apply to other common forms of Charcot Marie Tooth (CMT) disease, including CMT1B, CMT1X, and CMT2A. Pilot studies showed elevated levels of muscle-associated microRNA's in plasma from CMT1X, 1B, and 2A. In addition, we have developed a platform to detect Schwann cell-derived transcripts in skin of individuals with CMT1A, but it is not clear if this technology could be used for other types of CMT.

Methods:
We have collected plasma and skin samples from larger cohorts of individuals with genetically confirmed cases of CMT1B, CMT1X, CMT2A, and CMT2F and are evaluating plasma samples using microRNA profiling. We also have screened for Schwann cell-enriched transcripts using Nanostring analysis of skin biopsies with a custom gene set based on bioinformatic analysis of peripheral nerve data sets from CMT mouse models. Biomarker levels are correlated with other patient data to test if biomarkers levels correlate with disease severity.

Results:
Screening of plasma miRNA from pilot cohorts revealed that muscle-derived microRNA's (myomirs) are elevated in CMT1B, 1X, and 2A compared to controls. The myomiRs likely reflect the progressive muscular atrophy. In addition, we have further developed a Nanostring transcript detection assay to apply to larger cohorts of CMT1B and CMT1X, and several candidate biomarkers have emerged from the analysis of the larger cohorts of these forms of CMT.

Conclusions:
Biomarkers for CMT may be subtype-specific based on the unique pathogenesis of each CMT subtype, but others may reflect common processes involved in CMT progression, and our data sets allow comparative analysis across major CMT subtypes. The elevation of muscle-derived myomiR's likely reflects ongoing muscular atrophy in individuals with CMT, and it is possible that this could provide a complementary biomarker in clinical trial design for CMT.

References:
No

Grant Support:

NIH R21TR003034 and Charcot-Marie-Tooth Association

Keywords: CMT, Charcot-Marie-Tooth, Neuropathy

Loss of HINT1 Function Impairs Actin Cytoskeleton Dynamics

Poster No:
P 046

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Introduction:
Loss of functional histidine triad nucleotide binding protein 1 (HINT1) causes autosomal recessive axonal neuropathy associated with neuromyotonia (NMAN). Patients suffer from motor-greater-than-sensory polyneuropathy with age of onset within the first decade of life. Currently, 28 NMAN-causing variants have been described resulting in loss of HINT1 function, e.g. by impairing conformational stability and leading to protein degradation (p.Arg37Pro), or abolishing enzymatic activity without affecting protein stability (p.His112Asn). HINT1 is a ubiquitously-expressed purine phosphoramidase involved in intracellular signaling and transcriptional regulation. However, its role in peripheral nerves remains unknown. Previously, we created a *HINT1* knockout (KO) HeLa cell line using CRISPR/Cas9 technology and studied their transcriptome profile. Gene ontology and pathway analyses identified affected pathways related to actin cytoskeleton remodeling. This cellular process has never been associated with HINT1 function and we aimed to validate our findings and explore their relevance in the context of NMAN.

Methods:
We generated HeLa cell lines stably expressing comparable levels of wild-type, p.Arg37Pro, or p.His112Asn alleles in a *HINT1*-KO background. To investigate actin cytoskeleton dynamics, we studied cell migration using an in-vitro scratch assay and performed kymographic analysis of protrusion dynamics of the cell membrane at the leading edge of the scratch.

Results:
Our preliminary findings demonstrated slower migration during wound closure of *HINT1*-KO versus naïve HeLa cells within 24 hours post-scratch. There was a higher rate of dynamic protrusions (e.g., lamellipodia) at the cell membrane during wound closure in *HINT1*-KO and HINT1^{CMT} cells versus naïve HeLa. Cells expressing two different HINT1^{CMT} alleles showed impaired migration comparable to *HINT1*-KO cells. Importantly, reintroduction of wild-type HINT1 in the *HINT1*-KO cells rescued the protrusion rate impairment.

Conclusions:
Our findings identify actin cytoskeleton remodeling as a pathway affected by loss of HINT1 enzymatic function, providing a foundation to further study HINT1's role in actin dynamics as a potential pathomechanism of NMAN.

References:
No

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AFM-Telethon, France, 2021 – 2024, Research Project Grant

Keywords: Charcot-Marie-Tooth disease, HINT1, Actin cytoskeleton, Mammalian cells, Disease mechanism

Towards a New Humanized Mouse Model for the Study of Peripheral Neuropathies

Poster No:
P 047

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Introduction:
Schwann cells provides support and insulation to ensure proper function of the peripheral nerves. Dysfunction of the myelinating Schwann cell is a key element in many forms of peripheral neuropathy. Nevertheless, attempts to understand and find new therapeutics for human neuropathies are hampered by a lack of adequate models of these conditions and by the inherent differences between mouse and human Schwann cells. To fill this void, we are developing a general new humanized mouse that will enable studying human myelinating Schwann cells in vivo, regardless of the genetic background of the patient.

Methods:
We have shown previously that genetic ablation of Schwann cells, using the ROSA26-eGFP-DTA line, results Schwann cell loss and acute demyelination. Using the inducible PO-CreERt line, that upon Tamoxifen injection mediates recombination solely in myelinating Schwann cells, we are now ablating the myelinating Schwann cells and replace them with human Schwann cells, derived from human inducible pluripotent stem cells.

Results:
Electrophysiological, transcriptomic, immunohistochemical (IHC) and morphological studies to characterize the fate of the engrafted human cells in vivo, and to characterize the nature and integrity of this model, are ongoing.

Conclusions:
Our universal model will allow the study of human Schwann cells with any specific mutation and genetic background, circumventing the laborious generation of mouse models specific for each human mutation.

References:
No

Grant Support:

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Keywords: Schwann cells, glia, Humanized Mouse Model, Neuropathy, Myelin

Family with Two Forms of Inherited Neuropathy Caused by Parental Mosaicism of LITAF and de novo Duplication of PMP22

Poster No:
P 048

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Introduction:
Inherited Neuropathies are a highly heterogeneous group of disorders that are collectively common across the population. There is broad spectrum of symptom severity and age of onset. This can make genetic diagnosis complex, especially in families with variable symptom presentation. We describe a sibship with variable symptom presentation diagnosed with two genetic types of inherited neuropathy.

Methods:
Neurological evaluations were performed on patients seen in a large Neuromuscular Clinic for the purpose of diagnosis and management. Genetic testing using phenotype-driven panels were performed.

Results:
Proband presented at 3 years with hip dysplasia and delayed milestones. Electrophysiology of left peroneal, tibial, and median showed velocities of 8-10m/s. Due to no known family history, a recessive CMT panel was performed. A synonymous heterozygous variant of unknown significance (VUS) in SH3TC2 (c.1587T>G) was identified. Del/dup testing of PMP22 followed revealing a diagnosis of CMT1A. Parents were negative for PMP22dup, therefore likely de novo. The proband's younger sibling presented with symptoms in elementary school. No delay in milestones, walked at 12mo. Electrophysiology showed velocities of 15-30m/s and he had milder symptoms compared to proband. Testing for PMP22 del/dup was negative. Hereditary neuropathy panel was performed and identified pathogenic variant in LITAF (c.334G>A; p.G112S) causing CMT1C and a VUS in DNMT1 gene (c.1829A>G; p.Q610R). Family was tested and proband had the LITAF variant, parents were both negative for the LITAF variant.

Conclusions:
This family represents parental mosaicism of LITAF with de novo PMP22 duplication. The proband has combined CMT1A/CMT1C and exhibits a more severe phenotype. This may indicate that genetic testing in multiple family members should be considered if there are differences in phenotype across family members. Identifying multiple forms of CMT in the same family can have significant implications on clinical predictions and family planning/recurrence risk. As broader based testing expanded, more of these genetically complex families may be identified.

References:
No

Keywords: Inherited Neuropathy, Genetic Testing, CMT

Clinical and genetic spectrum of patients with BAG3-related neuromuscular disorders in Europe

Poster No:
P 049

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Introduction:
Autosomal dominant or de novo variants in the BAG3 gene cause a constellation of neuromuscular disorders (NMD) encompassing Charcot-Marie-Tooth (CMT) and myofibrillar myopathy (MFM). As a severe and ultra-rare disease series of patients are lacking. Our aim was to characterize the clinical and genetic spectrum of a European cohort of BAG3-NMD patients and to investigate genotype-phenotype associations.

Methods:
Multicenter, retrospective study collecting clinical, genetic, electroneuromyography (ENMG), muscle imaging and biopsy data of patients with genetically confirmed BAG3-NMD.

Results:
A call was circulated by the ERN-NMD to pediatric and adult neuromuscular reference centers in 2023 and by December, responses from centers in 16 countries in Europe were received: 29 patients with a genetic diagnosis of BAG3-NMD were identified and 28 patients from 18 different families were finally included (67.9% males). Fourteen patients carried the classic p.Pro209Leu variant: onset of symptoms was in childhood, with either axonal (n=7) or intermediate (n=5) sensorimotor neuropathy, or myopathy (n=2). In five patients, cardiomyopathy (CM) preceded or was contemporary to the onset of neuromuscular manifestations. 78.6% of patients developed orthopedic alterations, 64.3% cardiac insufficiency (four patients requiring heart transplantation), 64.3% needed noninvasive ventilation, 35.7% were wheelchair-bound and 28.6% died prematurely (sudden death or heart failure). Patients carrying other BAG3 variants where: one patient with myopathy and axonal sensorimotor neuropathy (p.Pro209Gln), one with intermediate CMT (p.Gln522*), two with CMT2 and one with myopathy from one family (p.Pro115Ser), one with CM and motor neuropathy (p.Arg309Ter), and eight with pure motor neuropathy from one Spanish family (p.Val505GlyfsTer6).

Conclusions:
This is the largest yet-reported cohort of patients with BAG3-NMD, confirming the ultra-rare nature and presenting the wide clinical spectrum of the disease. While the p.Pro209Leu variant causes a severe neuromuscular, orthopedic and cardiorespiratory disease, other BAG3 variants cause milder clinical presentations with isolated axonal neuropathy. Nevertheless, cardiac, respiratory, and orthopedic manifestations should closely followed and managed.

References:
Yes

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Keywords: CMT, Natural History, Genetics, Autophagy, Neuromyopathy

One-year Longitudinal Assessment of CMT1A Patients Using Quantitative MRI

Poster No:
P 050

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Introduction:
Intramuscular fat fraction (FF) assessed using quantitative MRI (qMRI) has emerged as one of the few responsive outcome measures in CMT1A suitable for future clinical trials. This study aimed to identify the most relevant qMRI biomarkers for tracking longitudinal changes in CMT1A over a year and to assess correlations between MRI metrics and clinical parameters.

Methods:
qMRI was performed in 22 CMT1A patients at two time points, a year apart and various metrics were extracted from 3D volumes of interest at thigh and leg levels. A semi-automated segmentation technique was used, enabling the analysis of central slices as well as a larger 3D muscle volume. Metrics included: proton density (PD), magnetization transfer ratio (MTR) and intramuscular fat fraction (FF). Disease severity was gauged using CMTNSv2, CMTES, ONLS scores, and MRC muscle strength.

Results:
FF significantly rose in the 3D-volume at both leg (+1.36±1.87%, p=0.045) and thigh (+1.04±2.19%, p=0.041) levels. The 3D analyses unveiled a length-dependent gradient in FF, ranging from 22.61±10.17% to 26.17±10.79% at the leg level. There was noticeable variance in longitudinal changes between muscles: +3.17±6.86% in the tibialis anterior compared to +0.37±4.97% in the gastrocnemius medialis. MTR at thigh level showed significant decline between the two time-points: -2.75±6.58 (p=0.049), while no significant differences were noted for the 3D muscle volume and PD. Potent correlations were identified between FF and primary clinical measures: CMTNSv2 (rho=0.656; p=0.001) and MRC in the lower limbs (rho=-0.877; p<0.001).

Conclusions:
Our results support that qMRI is a promising tool to follow longitudinal changes in CMT1A patients, FF being the paramount MRI metric. It's crucial to scrutinize the post-imaging data extraction methods considering that annual changes are minimal (around +1.5%). Given the varied FF distribution, the existence of a length-dependent gradient, and the differential fatty involution across muscles, 3D volume analysis appeared more suitable than single slice analysis.

References:
No

Keywords: MRI, CMT1A, QUANTITATIVE, BIOMARKERS, LONGITUDINAL

A comprehensive evaluation on a Brazilian non-5q spinal muscular atrophy cohort: cluster phenotyping and genomic correlation.

Poster No:
P 051

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Introduction:
Spinal muscular atrophy (SMA) is mainly linked to biallelic loss-of-function variants in the SMN1 gene (5q13). With the advance in next-generation sequencing (NGS), several genes outside of chromosome 5 have been recognized. This subgroup, known as non-5q SMA, harbors a wide phenotypic variability and, albeit a growing list of potentially causative genes, there is a low diagnostic yield amongst them.

Methods:
We sought to describe the clinical and genotypic spectrum of non 5q SMA patients from a Brazilian cohort and evaluate NGS performance in different subgroups categorized through deep phenotyping. Cases from a neuromuscular clinic were reviewed. Patients with non-length dependent neurogenic weakness were included and categorized as having a simple phenotype (isolated lower motor neuron weakness) or a complex phenotype (cranial nerve impairment, non-neurological or neurological involvement). Molecular analysis included single gene test (VWA1, AR, VAPB) and WES/WGS in whom initial analysis was negative.

Results:
Ninety patients from seventy-three families were identified, predominantly sporadic cases (75%). Mostly, symptoms began from 0 to 5 years (52%), although a significant proportion of patients had a late-onset disease onset (25,5%). Fifty-one probands (70%) were tested, most of them with WES (90%) and a few with bespoken single gene test (10%). Twenty-one patients (43%) had a positive result and eighteen different genes have been identified: AR, AARS1, COL6A2, COL6A3, TK2, SIGMAR1, VRK1, BICD2, DYNC1H1, FBX038, HEXA, VAPB, TBCK, FUS, SLC52A, MME, PRPS1, COQ7. Forty-six patients (63%) had a complex phenotype achieving a higher diagnostic yield (51% x 27%)

Conclusions:
Non-5q SMA is genetically diverse, in tune with this diversity, a complex phenotype is exceedingly common. A clustered molecular approach might aid in the identification of novel genes and prevent missing known genes. We identified surprising results (COL6A3, COL6A2, COQ7, PRPS1) that would go otherwise unnoticed without a clinical guided approach.

References:
No

Keywords: Non-5q SMA, Neurogenetics, Hereditary motor neuropathy

A homozygous NDUFS6 variant associated with neuropathy, optic atrophy and protein changes

Poster No:
P 052

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Introduction:
The NADH dehydrogenase [ubiquinone] iron-sulfur protein 6 (NDUFS6) gene encodes for an accessory subunit of the mitochondrial membrane respiratory chain NADH dehydrogenase (complex I). Bi-allelic NDUFS6 variants have previously been linked to a severe disorder mostly defined as lethal infantile mitochondrial disease (LMID) or Leigh syndrome (LS). Since 2004, 12 patients were described with pathogenic variants NDUFS6 presenting with this severe phenotype, leading to death in early infancy. Mitochondrial diseases often present with fatal infantile phenotypes but over the last years some reports on isolated neuropathic phenotypes, e.g. for SCO2 and MTATP6 were published.

Methods:
To address the pathogenicity of the variant, different studies (mtDNA copy number quantification, serum ELISA and proteomic profiling of leukocytes) were performed. Immunoblot studies showed absence of the NDUFS6 protein in leukocytes of the index and reduction in the heterozygous father. Proteomics showed a decrease of three further mitochondrial NADH dehydrogenase subunit/assembly proteins (NDUFA12, NDUFS4 and NDUFV1). Mitochondrial copy number was unchanged in leukocytes and the mitochondrial biomarker GDF15 is not significantly changed in serum.

Results:
Here, we identified a homozygous variant (c.309+5G>A) in NDUFS6 in a 10-year-old male patient with typical symptoms of an axonal neuropathy (pronounced distal muscle weakness of the lower limbs, foot drop resulting in an abnormal gait) accompanied by loss of small fibers in skin biopsy and further complicated by impaired vision due to optic atrophy and borderline intellectual disability (intelligence quotient 70). Overall, a much milder phenotype compared to those described in literature.

Conclusions:
Hence, our combined clinical and molecular data strengthen the concept of NDUFS6 being causative for a very rare form of axonal neuropathy associated with optic atrophy and borderline intellectual disability, and thus expand (i) the molecular genetic landscape of neuropathies and (ii) the clinical spectrum of NDUFS6-associated phenotypes.

References:
No

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Keywords: Charcot-Marie-Tooth, axonal neuropathy, NDUFS6, white blood cell proteomics

Giant axon neuropathy (GAN): Cross-sectional data on phenotypes, genotypes and biomarkers – the German experience

Poster No:
P 053

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Introduction:
Giant Axon Neuropathy (GAN) is a pediatric, hereditary, neurodegenerative disease characterised by involvement of both, the peripheral and central nervous system. It is caused by biallelic variants in the GAN gene, which encodes gigaxonin. Gigaxonin is crucial for intermediate filament turnover and protein ubiquitination. Loss of gigaxonin leads to protein aggregates in various types of cells, causing microscopically visible swollen (giant) axons. These aggregates originate abnormal cellular function that manifests as a variety of symptoms including nerve degeneration, cognitive issues, muscle weakness, and typical frizzy hair. Less frequently, patients show a milder disease course with isolated symptoms of peripheral neuropathy. Yet, the disease cannot be cured, but a gene therapy approach is currently being investigated in a clinical trial in the USA.

Methods:
So far, there has been no structured survey of GAN patients in German-speaking countries. We therefore conducted an enquiry using the "Survey of rare neurological diseases in childhood and adolescence (ESNEK)" e-mail list of German speaking pediatric neurologists enabling the collection of epidemiological, clinical and genetic information from a total of 15 patients from 10 families living in Germany.

Results:
The patients were on average 11.7 years old at the time of data collection, >50% were of Syrian origin, eight different variants in the GAN gene were found, interestingly all homozygous and one which had not been described in the literature before. 13 patients had a progressive course corresponding to classical GAN.To identify minimal-invasive biomarkers, proteomic profiles on serum and white blood cells derived from four patients were conducted enabling the definition of marker candidates.

Conclusions:
In view of the potential genetic treatment option, these combined data are important for study design in preparation for gene therapy trials in Europe.

References:
No

Keywords: Giant Axon Neuropathy, gigaxonin, gene therapy trials, biomarkers, white blood cells

Neuromuscular Junction Dysfunction In Subset Of Charcot Marie-Tooth And Related Peripheral Neuropathy Mouse Models

Poster No:
P 054

Authors:
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Institutions:
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Introduction:
The neuromuscular junction (NMJ) is the critical synapse for functional muscle contraction. NMJ dysfunction is implicated in multiple neuromuscular diseases (NMDs), including peripheral neuropathies. We investigated multiple mouse models of rare NMDs to assay the NMJ, laying groundwork for future mechanistic and preclinical studies.

Methods:
We used repetitive nerve stimulation (RNS) to measure electromyography decrement and immunofluorescence to assess neuromuscular junction anatomy in proximal and distal muscles. Seven mouse models were evaluated at pre-, post-, or late-onset disease stages. Additionally, electron microscopy (TEM) and muscle histology are in progress in one model.

Results:
The following models exhibited RNS decrement or highly unusual NMJ morphology: Gars (CMT2D), Nefl (CMT2E), and Nadk2 (rare NMD). Other models (Ighmbp2; CMT2S, Pla2g6; INAD, Gjb1; CMT1X, Yars; DI-CMTC) did not display appreciable NMJ defects. Gars mice show RNS decrement, NMJ denervation, and reduced motoneuronal mitochondria numbers at the NMJ, reproducing previous findings and providing a baseline for comparison. RNS data in Nefl mice do not show significant decrement at early- or late-disease stages. However, the presynaptic motoneuron terminals show immense swellings apposed to largely intact postsynaptic sites. This is more pronounced in proximal muscles. Nadk2 mice display RNS decrement shortly after disease onset (5 weeks), however synaptic dysfunction and NMJ denervation appears to improve 1 month later, consistent with an acute phase of denervation. This pattern is variable muscle-to-muscle, and the time course and spectrum of these changes is being evaluated.

Conclusions:
Pre-synaptic release defects at the NMJ were established in Gars mice via two-electrode voltage clamp (TEVC), providing a basis for comparison with the present studies. Further investigation into synaptic dysfunction and the role of mitochondria mediating the phenotypes across all three models is planned.

References:
Yes

Reference 1: Spaulding, E. L., et al. (2016). “Synaptic Deficits at Neuromuscular Junctions in Two Mouse Models of Charcot-Marie-Tooth Type 2d.” J Neurosci 36(11): 3254-3267.

Keywords: NMJ, CMT, Neurophysiology, Models, Mitochondria

Ablation of XBP1 and ATF6 UPR-related pathways interferes with myelination and exacerbates disease severity in mice models of CMT1B

Poster No:
P 055

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Institutions:
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Introduction:
Charcot-Marie-Tooth type 1B is a hereditary neuropathy characterized by mutations in myelin protein zero (MPZ/P0). Studies have shown that many MPZ mutations activate a canonical unfolded protein response due to retention of the mutated protein in the ER, leading to cell stress and impaired myelination. We previously showed that genetic manipulation of PERK-related pathway, one of the three arms of the UPR, significantly ameliorates disease severity in the P0S63del mice, a model of CMT1B. How the other two arms of the UPR, such as those related to XBP1 and ATF6, are also actively involved in disease pathogenesis, is currently unclear.

Methods:
the XBP1 and ATF6 genes were genetically ablated in mice models of CMT1B either conditionally in Schwann cells (XBPKO/P0S63del) or systemically (ATF6KO/P0S63del). CMT1B mice with overexpression of XBP1 were also generated. Locomotor tests, neurophysiology and morphologic studies were performed. Pharmacologic modulation of ATF6 was also assessed in explants of dorsal root ganglia (DRG) of CMT1B mice.

Results:
We observed a worsening of disease phenotype on locomotor and neurophysiological tests in XPBKO- and ATF6KO/P0S63del mice compared to P0S63del mice, more marked in those ablated of XBP1 compared to ATF6. Morphological studies showed thinner myelin sheaths, a higher number of a- or hypo-myelinated fibres and significantly increased g-ratios in sciatic nerves of XPBKO- and ATF6KO/P0S63del compared to P0S63del mice, as observed in both semithin resin and electron microscopy sections. On the other side, overexpression of XBP1s improved neuropathy phenotype at all levels. In DRG cultures explanted from P0S63del mice, use of pharmacologic activators of ATF6 pathway increased internodal length, thus aiding in myelination.

Conclusions:
Besides PERK, genetic and/or pharmacologic modulation of the XBP1- and ATF6-related pathways of the UPR affect neuropathy severity and progression, suggesting that these may be newly attractive targets for therapeutic development.

References:
No

Keywords: CMT, UPR, mice models, XBP1, ATF6

MTMR2-related Disorder in a Brazilian Amazon Indigenous Descent Presenting with Facial Myokymia

Poster No:
P 056

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Introduction:
The Amazon rainforest comprises a huge area with low immigration rate and low population density, with high prevalence of consanguineous marriages. All of this favors the emergence of autosomal recessive diseases, as Charcot-Marie-Tooth. The genetic background of these population is still unknown.

Methods:
The patient was studied following informed consent and approval of our institution. The phenotype was determined by a neuromuscular neurologist and genetic analysis was carried out using a target neuropathy panel.

Results:
A 26-year-old female born from a consanguineous parents presented in her first decade of life with distal weakness, difficulty walking and frequent falls. Her symptoms slowly progressed over the years and her balance and gait worsened at age of 6 and became wheelchair bounded at age of 22. On neurological examination at age of 26 she had tongue weakness and atrophy, as well as involuntary movement on her face. Nerve conduction studies at age of 26 revealed a severe demyelinating neuropathy and electromyography revealed myokymic potentials in facial muscles. Target genetic panel found a homozygous class 4 nonsense variant in the MTMR2 gene (RefSeq NM_016156.5: c.1810C>T ; p.Arg604*).

Conclusions:
Despite being extremely rare, MTMR2-related disorders are more frequent in Middle East population. Interesting, the patient is from a native Amazon family, with an indigenous background. To the best of our knowledge this is the first case of CMT 4B1 described in Latin America. Furthermore, this case adds facial myokymia as a novel clinical manifestation. This study will help to elucidate the phenotypic and genotypic variability of this rare form of CMT, as well as to expand knowledge about CMT in this still unknown population.

References:
Yes

Reference 1: Pareyson, D., Stojkovic, T., Reilly, M. M., Leonard-Louis, S., Laurà, M., Blake, J., et al. (2019). A multicenter retrospective study of charcot-marie-tooth disease type 4B (CMT4B) associated with mutations in myotubularin-related proteins (MTMRs). Ann. Neurol. 86, 55–67. doi: 10.1002/ana.25500

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Keywords: Charcot-Marie-Tooth, MTMR2, Neuropathy, Myokymia

Analysis Of Individuals With Inherited Neuropathy And Heterozygous DHTKD1 Gene Variants In Large Research Cohort

Poster No:
P 057

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Introduction:
The DHTKD1 gene encodes a component of a mitochondrial 2-oxoglutarate-dehydrogenase-complex-like protein, dehydrogenase E1 and transketolase domain containing 1. It is involved in the degradation pathways of amino acids such as lysine and tryptophan. Biallelic pathogenic variants in DHTKD1 cause 2-aminoadipic 2-oxoadipic aciduria. The association of heterozygous variants in DHTKD1 with Charcot-Marie-Tooth type 2Q has been previously reported. Causation has not been well established. Currently, only three families have been reported to have CMT2Q and two have pathogenic variants in a different CMT gene. The first two cases were reported in China and most recently, one was reported in Mexico.

Methods:
The phenotype, genotype, and demographic data of research participates from a large inherited neuropathy consortium with a heterozygous DHTKD1 variant identified on clinical testing was analyzed.

Results:
Out of 7,862 research participants with an inherited peripheral neuropathy, there are 11 individuals in 10 families identified to have 6 unique heterozygous DHTKD1 variants. Eighty-five percent of the research participants identified as White, 3.1% identify as Asian, and 2.7% identify as Hispanic. No variant information was available for one individual. One variant is classified as pathogenic for autosomal recessive disease, 3 variants are classified as of uncertain significance and one variant is likely benign. The family with the likely benign variant identifies as Asian. All other families identify as White. Of the individuals with a VUS, only one did not have another confirmed genetic cause for their CMT. Further phenotypic analysis is ongoing.

Conclusions:
The addition of this data from a large international research cohort of participates with inherited neuropathy will provide important data to consider while curating a gene-disease relationship and assigning a validity classification of DHTKD1 with CMT. Efforts to expand the diversity of research participates is important for understanding the significance of rare gene variants.

References:
Yes

Reference 1: Xu WY, Gu MM, Sun LH, Guo WT, Zhu HB, Ma JF, Yuan WT, Kuang Y, Ji BJ, Wu XL, Chen Y, Zhang HX, Sun FT, Huang W, Huang L, Chen SD, Wang ZG. A nonsense mutation in DHTKD1 causes Charcot-Marie-Tooth disease type 2 in a large Chinese pedigree. Am J Hum Genet. 2012 Dec 7;91(6):1088-94. doi: 10.1016/j.ajhg.2012.09.018. Epub 2012 Nov 8. PMID: 23141294; PMCID: PMC3516600.

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Grant Support:

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Keywords: Charcot-Marie-Tooth Disease, CMT, Gene

Pseudodominant Inheritance Of Biallelic RFC1 Expansions Causing HSN With Cough And Gastroesophageal Reflux

Poster No:
P 058

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Introduction:
Introduction: Recently discovered pathogenic mutations causing recessive peripheral neuropathy have high carrier frequencies in the healthy population (e.g. RFC1 and SORD). These high carrier frequencies give rise to the possibility of pseudodominance, whereby an autosomal recessive condition appears as autosomal dominant due to reproduction between an affected individual and a carrier. Pentanucleotide biallelic expansions in intron 2 of RFC1 are known to cause 'cerebellar ataxia, neuropathy and vestibular areflexia syndrome' (CANVAS), late-onset ataxia, and hereditary sensory neuropathy (HSN). We aimed to assess a previously reported three-generation kindred (HSN32) with 'HSN 1 with cough and gastroesophageal reflux (GER)', (Kok et al., 2003). Affected individuals were reported in all three generations, indicative of autosomal dominant inheritance.

Methods:
Methods: Flanking PCR and repeat-primed PCR (RP-PCR) of RFC1 intron 2 was conducted on the index individual. Segregation analysis using flanking PCR, RP-PCR, and long-read sequencing (LRS) of RFC1 intron 2 was performed on seven additional individuals from HSN32.

Results:
Results: Flanking PCR produced no amplifiable product in the index individual, indicating the presence of biallelic RFC1 expansions. RP-PCR revealed the presence of the canonical pathogenic (AAGGG)exp allele, however the repeat motif of the second allele was not clear. Targeted LRS on the index identified a complex mixed motif in the second allele [(AGGGC)exp/(AAGGC)exp]. Additional flanking PCR, RP-PCR, and LRS revealed that biallelic RFC1 expansions were present in six previously reported affected individuals from HSN32 for whom DNA was available. Further RP-PCR and LRS also confirmed that an affected individual had reproduced with an unaffected carrier resulting in affected offspring in two consecutive generations.

Conclusions:
Conclusions: To our knowledge, this is the first report of pseudodominant inheritance of RFC1-related disease. Apparent autosomal dominant inheritance should not exclude an investigation of biallelic RFC1 expansions due to high carrier frequencies reported in the healthy population (0.7-6.5%).

References:
Yes

Reference 1: Kok C, Kennerson ML, Spring PJ, Ing AJ, Pollard JD, Nicholson GA. A locus for hereditary sensory neuropathy with cough and gastroesophageal reflux on chromosome 3p22-p24. Am J Hum Genet. 2003 Sep;73(3):632-7. doi: 10.1086/377591. Epub 2003 Jul 17. PMID: 12870133; PMCID: PMC1180687.

Grant Support:

Medical Research Future Fund (MRFF) Genomics Health Futures Mission (APP2007681)

Keywords: Hereditary Sensory Neuropathy, RFC1, Pseudodominant, long-read sequencing, expansion

Heterozygous PNPT1 variants in two families with sensory ataxic neuropathy

Poster No:
P 059

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Institutions:
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Introduction:
Inherited neuropathies encompass a range of diseases from those in which the neuropathy is the sole or predominant feature of the disease to those in which the neuropathy occurs as part of a multisystem disease. Patients with sensory ataxic neuropathy (SAN) present with loss of proprioception and vibration sense with relative preservation of muscle strength. Previously reported biallelic variants in polyribonucleotide nucleotidyltransferase-1 (PNPT1) have been associated with variable phenotypes ranging from syndromic hearing loss to multisystem Leigh disease1. More recently heterozygous variants in PNPT1, with incomplete penetrance and variable expressivity, have been associated with cerebellar ataxia and prominent sensory neuropathy2. The clinical presentation is variable including gait disturbance, upper limb incoordination, nystagmus, dysarthria, scoliosis, and sensory neuropathy with decreased reflexes. Other features including cognitive impairment and hearing loss have been described. Barbier et al, 2022, identified two novel heterozygous PNPT1 variants in two families with autosomal dominant sensory and cerebellar ataxia3. Aim: We report 2 families with heterozygous PNPT1 variants with SAN.

Methods:
Whole genome sequencing was performed in 2 families with autosomal dominant SAN.

Results:
Pathogenic heterozygous splice site (c.2014-3C>G) and nonsense (Arg715Ter) variants were detected, and confirmed on sanger sequencing, in family 1 and 2 respectively. All patients in both families presented with an isolated SAN clinically and neurophysiologically. In family 1, two patients developed additional cerebellar and autonomic signs respectively, where as family 2 only have SAN. Neurophysiology showed a sensory neuropathy in all patients and brain imaging was consistent with a cerebellar atrophy in 3 individuals.

Conclusions:
We report 2 heterozygous PNPT1 variants (including 1 novel) in 2 families with a predominant SAN. This highlights the genetic and phenotypical heterogeneity of PNPT1 and identifies PNPT1 as a cause of isolated SAN.

References:
Yes

Reference 1: 1) Alodaib A, Sobreira N, Gold WA et al. Whole-exome sequencing identifies novel variants in PNPT1 causing oxidative phosphorylation defects and severe multisystem disease. Eur J Hum Genet. 2017 Jan;25(1):79-84. doi: 10.1038/ejhg.2016.128. Epub 2016 Oct 19. PMID: 27759031; PMCID: PMC5159763.

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Reference 3: 3) Barbier M, Bahlo M, Pennisi A, Jacoupy M et al; Heterozygous PNPT1 Variants Cause Spinocerebellar Ataxia Type 25. Ann Neurol. 2022 Jul;92(1):122-137. doi: 10.1002/ana.26366. Epub 2022 May 7. PMID: 35411967.

Keywords: PNPT1, Sensory ataxic neuropathy, Heterozygous variant

A Novel Mutation in GJB1 Associated with Clinical Charcot-Marie-Tooth Disease with Asymmetric Demyelination

Poster No:
P 060

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Introduction:
Genetic neuropathies typically present with specific characteristic findings on nerve conduction studies, such as uniform demyelination in Charcot-Marie-Tooth disease, type 1A. We report a novel mutation in GJB1 which showed an asymmetric demyelinating neuropathy on nerve conduction studies.

Methods:
A 30-year-old African American man presented with 15 years of gait impairment and falls. Symptoms began with balance and foot movement difficulties, followed by diminished hand strength and coordination. Examination revealed pes cavus, hammer toes, and ankle contractures, as well as atrophy and weakness of his intrinsic hand muscles, and distal greater than proximal lower extremities. Sensory examination demonstrated decreased sensation to all modalities in a length dependent manner. He was areflexic. His mother and maternal grandfather had similar symptoms, and were wheelchair bound by their fifties. Neither had genetic testing, and both were deceased. Nerve conduction studies showed a length-dependent, sensorimotor, demyelinating greater than axonal neuropathy, with asymmetric median and ulnar sensory responses, and non-uniform conduction velocity slowing. Cerebrospinal fluid studies were notable for a white blood cell count of 2 cells/mm^3, and protein of 20 mg/dL. Serum studies showed a hemoglobin A1c of 5.7%, normal serum protein electrophoresis and immunofixation, vitamin B12 of 432 pg/mL, negative ANA, ESR of 5, and negative ganglioside, HIV, and Lyme antibody titers. A panel of 57 genes related to inherited neuropathies showed a hemizygous variant of unknown significance in GJB1, c.231G→T (p.Trp77Cys, W77C).

Results:
N/A

Conclusions:
Inherited neuropathy usually results in symmetric demyelination on electrodiagnostic testing. The W77C mutation in GJB1 has been described as causing non-functional channels in *Xenopus* oocytes, but has not previously been noted in humans. This case represents an atypical finding of asymmetric demyelination associated with a previously clinically undescribed mutation in GJB1.

References:
Yes

Reference 1: Skerrett IM, Aronowitz J, Shin JH, Cymes G, Kasperek E, Cao FL, Nicholson BJ. Identification of amino acid residues lining the pore of a gap junction channel. J Cell Biol. 2002 Oct 28;159(2):349-60. doi: 10.1083/jcb.200207060. Epub 2002 Oct 28. PMID: 12403817; PMCID: PMC2173043.

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Keywords: Charcot-Marie-Tooth, GJB1, Connexin 32

ATF4 expression drives pathogenic changes in tRNA synthetase-associated forms of Charcot-Marie-Tooth disease

Poster No:
P 061

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Introduction:
Dominant mutations in 6+ tRNA synthetase genes cause Charcot-Marie-Tooth disease. Integrated stress response (ISR) activation is central to the disease mechanism and causes two major cellular consequences – shutdown of cap-dependent translation, and expression of the transcription factor, ATF4. It is unclear what role ATF4 plays in peripheral axon degeneration.

Methods:
Neuromuscular performance, nerve histology, ATF4 target-gene expression, and translation levels are being assessed in mice that express ATF4 specifically in motor neurons and Gars/CMT2D mice with motor neuron-specific ATF4 knockout.

Results:
Mice with WT Gars and motor neuron-specific ATF4 expression have a similar phenotype to Gars/CMT2D mice with decreased body weight, nerve conduction velocity (NCV), nerve size, and latency to fall in an inverted wire hang test. Conversely, motor neuron-specific ATF4 knockout in Gars/CMT2D mice ameliorated neuromuscular deficits such as decreased NCV, decrement in compound muscle action potential (CMAP) amplitude after repetitive nerve stimulation, nerve histology, and wire hang ability. We are currently evaluating gene expression, performing more detailed analysis of nerve histology, and measuring rates of protein synthesis in these mice.

Conclusions:
Our results show that ATF4 expression in motor neurons drives pathogenic changes similar to those seen in mice with tRNA synthetase-associated forms of CMT. Knocking out ATF4 in motor neurons of Gars/CMT2D mice significantly improves nerve physiology, nerve histology, and wire hang performance. is detrimental to neuromuscular function and may be a feasible therapeutic target for CMT2D. These results indicate ATF4 may be a viable therapeutic target for tRNA synthetase-associated forms of CMT.

References:
Yes

Reference 1: Spaulding EL, Hines TJ, Bais P, Tadenev ALD, Schneider R, Jewett D, Pattavina B, Pratt SL, Morelli KH, Hill DP, Gobet C, Pipis M, Reilly MM, Jennings MJ, Horvath R, Bai Y, Shy ME, Alvarez-Castelao B, Schuman EM, Bogdanik LP, Storkebaum E, Burgess RW. (2021). The integrated stress response contributes to tRNA synthetase-associated peripheral neuropathy. Science, 373(6559):1156-1161.

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Keywords: Charcot-Marie-Tooth disease, tRNA synthetase, GARS, integrated stress response, ATF4

Diagnosis Of Small Fiber Neuropathy In Asymptomatic Carriers Of Hereditary Transthyretin Amyloidosis

Poster No:
P 062

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Introduction:
Introduction: Hereditary transthyretin amyloidosis (ATTRv) has a heterogeneous clinical presentation, with symptoms mainly neuropathic, including autonomic, sensory and motor impairment. Furthermore, they may be associated with gastrointestinal, cardiac, renal and ocular impairment. Diagnosis in the early stages is essential to allow adequate treatment and to prevent or delay the progression of the disease.

Methods:
A transversal study was carried out on asymptomatic ATTRv carriers from the Neuromuscular Diseases Outpatient Clinic at Hospital Pedro Ernesto in Rio de Janeiro. They were evaluated clinically and through complementary exams including assessment of large and thin nerve fibers

Results:
4 of 16 individuals (25%) showed changes in at least two complementary exams related to the evaluation of small fiber neuropathy even though they were completely asymptomatic. It was possible to confirm the disease through salivary gland biopsy

Conclusions:
Monitoring pre-symptomatic individuals is essential to detect the disease as early as possible, as it is directly related to more effective therapy

References:
No

Keywords: amyloidosis, transthyretin, early diagnosis

CLCN1 mutation and right foot drop

Poster No:
P 063

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Introduction:
Background: It has been known that CLCN1 mutations can cause myotonia congenita, which typically results in clinical symptoms of muscle stiffness, myotonia, and weakness.

Methods:
Methods: A 58 year old proband had genetic, clinical, radiographic and electrophysiological testing.

Results:
Results: A very healthy 58 year old athletic gentleman presented with painless right foot drop. Electrophysiological testing revealed a right peroneal neuropathy with no myotonia. Genetic testing revealed a pathogenic CLCN1 mutation, c.950G>A, (p.Arg317Gln). Extensive laboratory work up including CK, acetylcholine receptor antibody, voltage gated calcium channel antibody, GM1 antibody, paraneoplastic panel, MRI imaging of the lumbar spine was unrevealing.

Conclusions:
Conclusion: CLCN1 mutations can cause a wide spectrum and severity of presentations. In our subject, an isolated right peroneal neuropathy is a rare presentation of a CLCN1 mutation.

References:
No

Keywords: clcn1 mutation, foot drop, hereditary neuropathy

A Case Report of Progressive Bilateral Foot Drop in a 31-year-old Indian Male

Poster No:
P 064

Authors:
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Introduction:
GNE myopathy is a form of autosomal recessive inclusion body myopathy (IBM) that presents with progressive muscle weakness, leading to bilateral foot drop. This is an ultrarare muscle disease with an overall low prevalence (1:1,000,000), which may lead to under-diagnosis.

Methods:
This is a case report and literature review was conducted.

Results:
We present a case of a 31-year-old male of Indian descent who presented with a few years of frequent falls from bilateral foot drop. An initial workup at an outside clinic demonstrated unrevealing lumbar spine MRI, so he was referred to our neuromuscular clinic for possible neuropathy. Prior to the foot drop, he noticed significant fatigue after minimal exertion, some hand weakness and twitching in both thighs. He denied any family history of neuromuscular disorders. His neurological exam showed diffuse muscle weakness, particularly in the hip adductors and ankle dorsiflexors (R/L: finger abduction 4+/4, thumb abduction 5/4+, hip flexion 5/4, hip adduction 2/2, ankle dorsiflexion 2/2, ankle plantar flexion 4+/4+, hallux extension 1/1, ankle eversion 3/3, and ankle inversion 4/4), with diminished reflexes. His sensory examination was normal. He walked in a normal-based steppage gait. Myasthenia gravis workup was negative; CPK was 600 U/L; and electromyography revealed moderate diffuse myopathy, worse in the lower extremities, but no evidence of large fiber neuropathy. Genetic testing for myopathy revealed a heterozygous GNE mutation c.2179G>A (p.Val727Met), confirming GNE myopathy.

Conclusions:
This case highlights the importance of clinical recognition and epidemiological risk. Literature review showed that as much as 31% of inherited myopathies in India have GNE mutations, with Val727Met being the most common. GNE myopathy often presents with progressive bilateral foot drop with quadriceps sparing, mimicking neuropathy, but distinct from typical myopathy. In cases of profound distal and hip adductor weakness in an Indian population, genetic studies are warranted to evaluate for GNE myopathy even without family history.

References:
No

Keywords: GNE myopathy, Hereditary inclusion body myopathy (HIBM)

Physical Activity And Healthy Living Choices Among Children And Young People With Charcot-Marie-Tooth Disease: Protocol

Poster No:
P 065

Authors:
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Introduction:
Children and young people affected by Charcot-Marie-Tooth (CMT) disease are less physically active than their unaffected peers. In 2022, a clinical practice guideline for the management of paediatric CMT was published with one evidence-based exercise and 10 consensus-based exercise and physical activity recommendations. To develop effective physical activity and exercise management strategies including healthy lifestyle choices it is important to understand from young people and families of children with CMT 1) what they know about the role of physical activity, exercise and healthy lifestyle choices in managing disability related to CMT; 2) what physical activities and exercise they currently participate in; and 3) the barriers and enablers to participation and uptake of physical activity and exercise.

Methods:
A cross-sectional electronic survey of young people (aged 10 to 18 years) and families of children with CMT (up to and including 18 years). Recruitment will be across three major paediatric neuromuscular and peripheral neuropathy centres, neuromuscular and professional networks and through a national patient organization. The survey tool will allow snowballing to maximise recruitment. The survey has been developed by specialist neuromuscular clinicians and a stakeholder group with lived experience.

Results:
The survey will collect information about the child or young person with CMT including age, gender, ethnic background, CMT subtype, surgical history in the past 12 months, postcode, anthropometrics (height, weight, waist circumference), current health status including a Global impression of change, and current functional mobility. Information about activities they participate in, enablers and barriers or limitations to physical activity participation, which health or exercise professionals they consult for physical activity and exercise advice and support, how they monitor physical activity participation, positives and negatives of physical activity participation, funding of physical activity and exercise participation.

Conclusions:
Recruitment will commence in early 2024 and the results will inform a healthy lifestyle management program.

References:
Yes

Reference 1: Kennedy RA, Carroll K, Paterson KL, Ryan MM, Burns J, Rose K, McGinley JL. Physical activity of children and adolescents with Charcot-Marie-Tooth neuropathies: A cross-sectional case-controlled study. PLoS One. 2019 Jun 12;14(6):e0209628. doi: 10.1371/journal.pone.0209628. PMID: 31188833; PMCID: PMC6561632.

Reference 2: Yiu EM, Bray P, Baets J, Baker SK, Barisic N, de Valle K, Estilow T, Farrar MA, Finkel RS, Haberlová J, Kennedy RA, Moroni I, Nicholson GA, Ramchandren S, Reilly MM, Rose K, Shy ME, Siskind CE, Yum SW, Menezes MP, Ryan MM, Burns J. Clinical practice guideline for the management of paediatric Charcot-Marie-Tooth disease. J Neurol Neurosurg Psychiatry. 2022 May;93(5):530-538. doi: 10.1136/jnnp-2021-328483. Epub 2022 Feb 9. PMID: 35140138.

Reference 3: Burns J, Sman AD, Cornett KMD, Wojciechowski E, Walker T, Menezes MP, Mandarakas MR, Rose KJ, Bray P, Sampaio H, Farrar M, Refshauge KM, Raymond J; FAST Study Group. Safety and efficacy of progressive resistance exercise for Charcot-Marie-Tooth disease in children: a randomised, double-blind, sham-controlled trial. Lancet Child Adolesc Health. 2017 Oct;1(2):106-113. doi: 10.1016/S2352-4642(17)30013-5. Epub 2017 Jul 10. PMID: 30169201.

Grant Support:

This project has been funded by grants from the Charcot-Marie-Tooth Association of Australia and the Eirene Lucas Foundation.

Keywords: Physical activity, Charcot-Marie-Tooth disease, Exercise, Paediatric, Participation

Physical Activity And Exercise Guidelines For Paediatric Charcot-Marie-Tooth Disease: What Do Australian Health Professionals Know?

Poster No:
P 066

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Introduction:
Clinical practice guidelines for the management of paediatric Charcot-Marie-Tooth (CMT) disease were published in 2021 comprising a single evidence-based recommendation for progressive resistance training and ten consensus-based recommendations for other exercise and physical activity. We conducted a survey of Australian and New Zealand (NZ) health professionals working in neuromuscular disease to determine 1) awareness of the guidelines; 2) whether treatment recommendations were guideline-based; and 3) barriers and facilitators to uptake of the guidelines.

Methods:
A secure electronic cross-sectional survey based on the practice guideline questions for weakness, contracture management, balance impairment, muscle cramp and musculo-skeletal pain was developed, and a link emailed to Australian and NZ neuromuscular clinics, disability services and health professionals. The study was promoted through neuromuscular and professional networks and allowed for snowballing. Recruitment ran between April and June 2023. Descriptive statistics characterised the respondents and the responses to guideline awareness.

Results:
Sixty-eight health professionals completed the survey; of which twenty-four provided paediatric CMT care and thirteen were aware of the guidelines. Most professionals delivering paediatric CMT care worked in a metropolitan area (21) and in one of three states (19) with a dedicated paediatric neuromuscular clinic. Ten professionals had less than 5 years clinical experience in paediatric CMT. Twenty recommended exercise/physical activity for weakness; 13 recommended hydrotherapy and 12 recommended distal lower limb progressive resistance training. Nineteen recommended stretching for contracture management, fourteen recommending daily stretching. Balance activities (18), stretching for cramp (15) and physical therapy for pain management (19) were also recommended. Barriers to uptake included lack of awareness or access to the guidelines, insufficient training and awareness of appropriate treatment strategies.

Conclusions:
Awareness and implementation of physical activity and exercise clinical guidelines in paediatric CMT is limited. A strategic dissemination plan is required to increase uptake, including training and resource development for health professionals.

References:
Yes

Reference 1: Yiu EM, Bray P, Baets J, Baker SK, Barisic N, de Valle K, Estilow T, Farrar MA, Finkel RS, Haberlová J, Kennedy RA, Moroni I, Nicholson GA, Ramchandren S, Reilly MM, Rose K, Shy ME, Siskind CE, Yum SW, Menezes MP, Ryan MM, Burns J. Clinical practice guideline for the management of paediatric Charcot-Marie-Tooth disease. J Neurol Neurosurg Psychiatry. 2022 May;93(5):530-538. doi: 10.1136/jnnp-2021-328483. Epub 2022 Feb 9. PMID: 35140138.

Reference 2: Burns J, Sman AD, Cornett KMD, Wojciechowski E, Walker T, Menezes MP, Mandarakas MR, Rose KJ, Bray P, Sampaio H, Farrar M, Refshauge KM, Raymond J; FAST Study Group. Safety and efficacy of progressive resistance exercise for Charcot-Marie-Tooth disease in children: a randomised, double-blind, sham-controlled trial. Lancet Child Adolesc Health. 2017 Oct;1(2):106-113. doi: 10.1016/S2352-4642(17)30013-5. Epub 2017 Jul 10. PMID: 30169201.

Grant Support:

Dr Kennedy was supported by a Murdoch Children's Research Institute Clinician Scientist Fellowship.

Keywords: Clinical guidelines, Charcot-Marie-Tooth disease, Physical activity, Exercise, Paediatric

Feasibility And Benefits Of Telemedical Patient Monitoring Through App-based Patient Reported Outcomes

Poster No:
P 068

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Introduction:
Transthyretin amyloidosis (ATTR) can be hereditary or acquired and causes systemic progressive disease including neuropathy, cardiomyopathy, and other organ manifestations depending on the subtype. Variable phenotypes and disease course, as well as the increasing number of therapeutic options rise the importance of close monitoring. However, long distances to specialist centers impose a challenge especially for patients in rural areas, demanding new solutions for patient-centered follow-up. In an optimal scenario, electronic PROMs integrate the positive effects of digital use of patient-centric endpoints with those of the register and complement clinical pathways.

Methods:
In this study, we aim at evaluating feasibility, patient-experience, and outcome using different patient reported outcome measures (PROMs) integrated into the flutter-based "dotbase" App connected with the registry TBase.

Results:
We evaluate patients' experience with digital PROM entry and at-home app use. Data from the app will be integrated into our registry database and assessed for use as medical decision aid. Follow-up data can be efficiently integrated into the database, allowing a more continuous monitoring of patients. Challenges in the use of the app arise due to the age of patients especially in wild type ATTR. On the other hand, asymptomatic carriers of hereditary ATTR may benefit from continuous surveillance of possible symptom onset.

Conclusions:
Digital applications may facilitate clinical monitoring through entry of continuous electronic PROMs and improve time efficiency for patients and physicians. However, different ATTR subtypes and patient age may affect compliance. Further evaluation of this app will give new insights into the use and impact of digital apps in rare disease care.

References:
No

Keywords: Telemedical patient Monitoring, Amyloidosis, Patient reported outcomes, Patient App, ATTR

Expanded Demographics Categories to Capture the True Diversity of an International Registry of Rare Disease Patients

Poster No:
P 069

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Introduction:
The NIH (National Institutes of Health) requires NIH-funded studies to use their standard race and ethnicity categories for demographics data collection. We questioned whether these categories are appropriate for an international population as they were only designed for use within the United States (US).

Methods:
Common categories were identified between the US, United Kingdom, and Italy. The expanded categories were used by the three selected Inherited Neuropathy Consortium (INC) study sites when completing demographics data collection on subjects who were newly enrolling into the INC for three months. We then created a survey in which participants were asked to provide their racial, ethnic, sex and gender identities using the expanded categories. The survey was sent to anyone who had previously agreed to contact for research when they joined the Rare Disease Clinical Research Network's (RDCRN) contact registry.

Results:
For the RDCRN contact registry survey (n=827), using the standard categories, the demographic breakdown was: American Indian or Alaska Native: 10, Asian: 80, Black or African American: 43, Native Hawaiian or Other Pacific Islander: 1, White: 2793, More than 1 race: 90, Prefer not to answer: 34, Missing/Unknown: 95. The ethnicity breakdown was 87.4% Non-Hispanic/Latino, 5.1% Hispanic/Latino, 4.9% Missing data, 2.7% Prefer not to answer. Sex of registrants was reported as follows: Female: 1886, 60%, Male: 1173, 37%, Missing: 76, 3%, Prefer not to answer: 11, 0%. Using the expanded categories, the race and ethnicity of the patients enrolled at all three sites, was: 62% White, 24% Mixed, 7% Asian, 5% Black, 2% Middle Eastern/North America, 0% North Americas, Oceana and Not Reported.

Conclusions:
These categories offer several advantages: they capture an increase in diversity among existing study populations to better determine specific demographics for targeted enrollment efforts.

References:
No

Grant Support:

The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01). The INC also receives funding from the Muscular Dystrophy Association and the Charcot-Marie-Tooth Association.

Keywords: Demographics, Enrollment, Diversity, Clinical Trials, Inclusion

Addressing Diversity, Equity, Inclusion and Access within the Inherited Neuropathy Consortium

Poster No:
P 070

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Introduction:
The Inherited Neuropathy Consortium (INC) Diversity Committee is working to improve delivery of clinical care to the true population of patients with inherited peripheral neuropathies through measures aimed at increasing representation of traditionally excluded populations among subjects enrolled in the INC and in the scientific workforce. Our committee is comprised of nine members including seven members from four INC sites in three countries who represent several disciplines and roles within the consortium and representatives from our patient advocacy groups.

Methods:
Current committee initiatives include (1) Implementing the use of updated and more descriptive race/ethnicity sub-categories that can be used in the United States, the United Kingdom, Italy and Australia; (2) Creating an educational workshop and providing ongoing support to those responsible for collecting demographics data, (2) Developing and validating CMT-specific virtual assessments into Spanish, Italian, Hindi, Malayalam, Farsi and Portuguese; (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 patients who prefer languages other than English; and (5) Development of the INC Diversity Intern position.

Results:
Our committee frequently collaborates with the Rare Disease Clinical Research Network (RDCRN) Diversity committee to share efforts and ideas across all RDCRN consortia. The INC's diversity committee frequently pilots initiatives within our own consortium before sharing across the RDCRN and continues to provide strong representation and leadership across all of the RDCRN's diversity subcommittees.

Conclusions:
Next steps for the INC diversity committee include working to implement the use of our expanded race and ethnicity categories across the entire RDCRN, expanding demographics collection to assess barriers to accessing care such as travel and disability status, and further developing the INC Diversity intern position to provide funding and additional leadership opportunities for the intern.

References:
No

Grant Support:

The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01). The INC also receives funding from the Muscular Dystrophy Association and the Charcot-Marie-Tooth Association.

Keywords: diversity, clinical trials, inclusion, demographics, translation

The Hereditary Sensory Neuropathy Serine Trial (SENSE) Protocol

Poster No:
P 071

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Introduction:
Hereditary Sensory Neuropathy type 1 (HSN1) is a rare autosomal dominant neuropathy characterised by severe sensory and motor involvement. It is caused by variants in the SPTLC1/SPTLC2 genes, leading to a gain of function mechanism in the serine palmitoyl transferase enzyme. This produces neurotoxic deoxysphingolipids, ultimately causing the neuropathy. L-serine has shown promise as a potential treatment, but a previous small study did not meet the primary outcome measure[1,2]. To address this, we developed a quantitative lower limb muscle MRI Fat Fraction protocol, as a highly responsive biomarker for HSN1[3]. The primary goal is to assess the efficacy of L-serine in treating HSN1 and validate the lower limb MRI Muscle Fat Fraction protocol as a primary outcome measure in inherited neuropathy trials.[2]

Methods:
This is a phase II, randomised, double-blind, placebo-controlled trial involving individuals over 18 years with genetically confirmed SPTLC1/2 diagnosis, capable of undergoing MRI without sedation and with Charcot Marie Tooth Examination Score (CMTES) ≤ 26. Exclusion criteria include factors such as recent foot surgery, diabetes, pregnancy/breastfeeding and current use of L-serine. Participants will take 400mg/kg/day of L-serine or dextrose powder (placebo) for 12-months. The primary outcome measure is the difference in lower limb muscle fat fraction over 12-months between L-serine treated and placebo-treated groups using MRI. Secondary/exploratory measures which will be performed at baseline and 12-months later include biomarkers (neurofilament light chain levels, plasma deoxysphingolipid levels), thigh intraepidermal nerve fibre density on skin biopsy, CMTNSv2, CMTNSv2-R, CMTESv2, CMTESv2-R and questionnaire-based assessments (CMT health index quality of life score, Neuropathic Pain Symptom Inventory, Neuropathic pain diagnostic questionnaire, Brief pain inventory and pain diary).

Results:
Recruitment commenced in August 2023 with a target of 50 patients. Currently, 25 patients have completed screening, 15 have been randomised and recruited.

Conclusions:
Results of the SENSE trial will be presented at a future PNS meeting.

References:
Yes

Reference 1: Garofalo, K., Penno, A., Schmidt, B. P., Lee, H. J., Frosch, M. P., von Eckardstein, A., Brown, R. H., Hornemann, T., & Eichler, F. S. (2011). Oral L-serine supplementation reduces production of neurotoxic deoxysphingolipids in mice and humans with hereditary sensory autonomic neuropathy type 1. The Journal of clinical investigation, 121(12), 4735–4745.

Reference 2: Fridman, V., Suriyanarayanan, S., Novak, P., David, W., Macklin, E. A., McKenna-Yasek, D., Walsh, K., Aziz-Bose, R., Oaklander, A. L., Brown, R., Hornemann, T., & Eichler, F. (2019). Randomized trial of l-serine in patients with hereditary sensory and autonomic neuropathy type 1. Neurology, 92(4), e359–e370.

Reference 3: Kugathasan, U., Evans, M. R. B., Morrow, J. M., Sinclair, C. D. J., Thornton, J. S., Yousry, T. A., Hornemann, T., Suriyanarayanan, S., Owusu-Ansah, K., Lauria, G., Lombardi, R., Polke, J. M., Wilson, E., Bennett, D. L. H., Houlden, H.,

Hanna, M. G., Blake, J. C., Laura, M., & Reilly, M. M. (2019). Development of MRC Centre MRI calf muscle fat fraction protocol as a sensitive outcome measure in Hereditary Sensory Neuropathy Type 1. Journal of neurology, neurosurgery, and psychiatry, 90(8), 89

Keywords: HSN1, L-serine

Hereditary Transthyretin Amyloidosis in Argentina: Descriptive Analysis of the Most Common Genetic Variants and Their Phenotypic Expression.

Poster No:
P 072

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Introduction:
To date, there is limited information on the epidemiology of hereditary transthyretin amyloidosis (TTR) in Argentina. Knowing the genotype with its most frequent phenotypic expression in our environment will allow us to develop strategies for early diagnosis and treatment and timely genetic counseling. Objectives: To describe the variants of the TTR gene in our country and by province; to analyze their phenotypes (cardiology, neurological or mixed); explore whether some clinical factors are associated with a particular variant of the TTR gene

Methods:
Retrospective study. Registries of patients with a pathogenic variant of the TTR gene from a diagnostic program database were included between January 2019 to October 2023.

Results:
A total of 143 registries were included. Most of the genetic studies were requested by neurologists (83.2%). The most frequently observed variant was Val50Met (79.7%) followed by Val142Ile (14%). The highest proportion of subjects were from Buenos Aires (53.9%). Eighty-eight of the subjects (61,5%) had at least 1 symptom. The median number of symptoms was 3 IQR 2-5, being higher in males than in females 3 vs. 4.5 ($p = 0.04$). The most frequent symptoms were: Autonomic Neuropathy 59 (67%); small fiber neuropathy 54 (61,3%) followed by motor neuropathy 47 (53%). The Val50Met variant was associated with the absence of heart failure symptoms; 86.7% vs. 53.3% compared to the other variants (OR 5.7 95% CI 2.3-14.1 $p < 0.001$). Finally Val50Met was associated with positive family history 84.9% vs. 6% of negative family history (OR 3.7; 95% CI 1.5-9.2, $p = 0.005$).

Conclusions:
Val50Met was the most frequent variant in our registry, associated with peripheral neuropathy, family history and absence of cardiac symptoms..

References:
No

Keywords: Amyloid, Polyneuropathy, Transthyretin, Neuropathic pain

Neuropathy Associated to Amyloidosis due to Transthyretin Variants and the Importance of a Multidisciplinary Evaluation

Poster No:
P 073

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Introduction:
Amyloidosis associated to transthyretin variants (ATTRv) is a systemic condition with the need of a multidisciplinary evaluation. Our objective as neurologists dedicated to peripheral nerve conditions was to determine and characterize the presence of neuropathy as one of the cardinal signs, but in the other hand to identify different signs that could help in the management of this population.

Methods:
Retrospective study during March 2022 to August 2023 in patients with ATTRv that performed a multidisciplinary evaluation.

Results:
We studied 42 patients, mean age 45 years old, 29 women. The most frequent variant was Val50Met, however 2 patients had double variant Val50Met/Val142Ile. Twenty-one patients had distal painful paresthesias associated to any symptom related to autonomic disfunction. Quantitative sensory symptoms showed A delta and C fibers compromise in 18 of them, SSR was absent in 11 and NCS showed sensory axonal damage in 12 but 5 of them showed mild signs related to bilateral CTS. The majority of our patients had early onset and distal sensory neuropathy involving small fibers in concordance with the variant Val50Met. However, we found 6 patients with left cardiac concentric hypertrophy of and 5 of them showed abnormalities by electrocardiogram. Two patients had high levels of troponins and NT-ProBNP. Cardiac scintigraphy with PDPTc99 was abnormal in 3 patients. Seventeen patients had mild ophthalmologic changes related to amyloid deposits. Urine analysis in 24 hours showed microalbuminuria in 4 patients and low glomerular filtration rate.

Conclusions:
Distal sensory neuropathy involving small fibers was the principal finding in our patients associated in some cases with CTS. However independent of the characterization of the neuropathy we found another systemic complications that helped us to guide the management and treatments.

References:
No

Grant Support:

None

Keywords: amyloidosis, val50met, neuropathy, transthyretin, small fibers

QUANTITATIVE SENSORY TESTING AND SKIN BIOPSY IN A COHORT OF ATTRV PRESYMPTOMATIC CARRIERS: CROSS-SECTIONAL ANALYSIS AND PRELIMINARY LONGITUDINAL DATA

Poster No:
P 074

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Introduction:
Hereditary transthyretin amyloidosis polyneuropathy (ATTRv-PN) pre-symptomatic carriers often show preclinical abnormalities at small fbre related diagnostic tests. However, no biomarker is still available to follow-up pre-symptomatic carriers, thus helping therapeutic decision making. Our study aimed at assessing nerve conduction study (NCS), quantitative sensory testing (QST), and skin biopsy parameters in a cohort of late-onset ATTRv pre-symptomatic carriers, and to evaluate whether they correlated with predicted age of disease onset (PADO).

Methods:
consecutively enrolled late-onset ATTRv pre-symptomatic carriers underwent NCS, QST, and skin biopsy with intraepidermal nerve fbre density (IENFD) evaluation from a distal and a proximal site. PADO and time-toPADO (delta-PADO) were estimated for each carrier, and correlations with diagnostic test measures were analysed. A subset of ATTRv carrier completed a lingitudinal evaluation of at least 1 years.

Results:
Forty ATTRv pres-symptomatic subjects (M/F: 18/22; V30M/non-V30M: 26/14; age 49, IQR 42.5-59) were enrolled. Twenty carriers (50%) had distal IENFD reduction, with a non-length dependent distribution in 73% of cases. Eleven subjects (27.5%) had cold and/or warm detection threshold (CDT and/or WDT) abnormalities at QST. Delta-PADO positively correlated with sural sensory nerve action potential (SNAP) amplitude (r=0.416, p=0.004), and QST parameters like CDT (r=0.337, p=0.0017), WDT (r=-0.293, p=0.047), and mechanical detection threshold (MDT) (r=-0.462, p=0.003). Simple linear regression models showed a linear correlation between delta-PADO and sural SNAP, CDT, and MDT. Six subjects completed a longitudinal anylisis at at least 1 year: 2/6 subjects showed a relevant modifcation at QST/Skin biopsy and were considered afected.

Conclusions:
Our fndings show that IENFD reduction and QST abnormalities may occur early in ATTRv pre-symptomatic carriers, often with a non-length dependent pattern. Sural SAP amplitude and QST parameters correlated with delta-PADO, suggesting that serial combined QST and NCS evaluation could be useful in pre-symptomatic follow-up.

References:
No

Keywords: Amyloidosis, PADO, IENFD, QST

PAK2 is Necessary for Myelination in the Peripheral Nerve System

Poster No:
P 075

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Introduction:
Myelination enables electrical impulses to propagate on axons at the highest speed, encoding essential life functions. The Rho family GTPases, RAC1 and CDC42, have been shown to critically regulate Schwann cell myelination. P21-activated kinase 2 (PAK2) is an effector of RAC1/CDC42, but its specific role in myelination remains undetermined.

Methods:
We produced a Schwann cell-specific knockout mouse of Pak2 (scPak2−/−) to evaluate PAK2's role in myelination.

Results:
Deletion of Pak2 specifically in mouse Schwann cells resulted in severe hypomyelination, slowed nerve conduction velocity, and behavior dysfunctions in the scPak2−/− peripheral nerve. Many Schwann cells in scPak2−/− sciatic nerves were arrested at the stage of axonal sorting. These abnormalities were rescued by reintroducing Pak2, but not the kinase-dead mutation of Pak2, via lentivirus delivery to scPak2−/− Schwann cells in vivo. Moreover, ablation of Pak2 in Schwann cells blocked the promyelinating effect driven by neuregulin-1, prion protein, and inactivated RAC1/CDC42. Conversely, the ablation of Pak2 in neurons exhibited no phenotype. Such PAK2 activity can also be either enhanced or inhibited by different myelin lipids.

Conclusions:
We have identified a novel promyelinating factor, PAK2, that acts as a critical convergence point for multiple promyelinating signaling pathways. The promyelination by PAK2 is Schwann cell-autonomous. Myelin lipids, identified as inhibitors or activators of PAK2, may be utilized to develop therapies for repairing abnormal myelin in peripheral neuropathies.

References:
No

Grant Support:

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Keywords: Peripheral nerve, Pak2 knock-out mouse, Myelination, Myelin lipids, GTPases Rac1/Cdc42

Disruption of lysosomal homeostasis and extracellular cathepsin release by Schwann cells in Charcot-Marie-Tooth disease type 1A

Poster No:
P 077

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Introduction:
Charcot-Marie-Tooth disease type 1 (CMT1) is the most common peripheral neuropathy. CMT1A is the most predominant subtype and is caused by a duplication of the peripheral myelin protein 22 (PMP22), which is mainly expressed by Schwann cells. Although the exact mechanisms by which PMP22 overexpression leads to dysfunctional Schwann cells is still largely unknown, PMP22 has been shown to accumulate and colocalize with lysosomes. Nevertheless, the presence and role of lysosomal dysfunction in CMT1A remains poorly understood. Here we show lysosomal alterations in the C3-PMP22 mouse model for CMT1A, and confirm our results in human CMT1A patient-derived induced pluripotent stem cell-derived Schwann cell precursors (SCP).

Methods:
The lysosomal marker LAMP1, and lysosomal enzymes Cathepsin B (CtB) and Cathepsin D (CtD) were monitored in 4-week old sciatic nerves and primary isolated Schwann cells. These results were further evaluated in CMT1A patient-derived SCP.

Results:
In sciatic nerves, western blot and immunohistochemistry showed significantly increased levels of LAMP1, CtB and CtD in C3-PMP22 vs. WT mice. These findings were confirmed in murine primary Schwann cells and human CMT1A SCP, using immunocytochemistry. Notably, transmission electron microscopy revealed an increased lysosomal amount and permeabilized lysosomes in CMT1A Schwann cells. Subsequently, we assessed the presence and activity of CtB and CtD in conditioned medium, and found an increased extracellular release of lysosomal enzymes in CMT1A Schwann cells. Finally, we demonstrated that cathepsins in the conditioned medium of CMT1A Schwann cells exhibit higher capability in degrading the extracellular matrix (ECM) components than healthy Schwann cells. This was supported by our findings, demonstrating a reduction in ECM protein levels in the nerves of C3-PMP22 mice.

Conclusions:
Our study demonstrated lysosomal upregulation, instability and extracellular release of cathepsins in CMT1A. Furthermore, our findings suggest that extracellular cathepsins could be a potential new target for addressing CMT1A pathology.

References:
No

Grant Support:

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Keywords: Charcot Marie Tooth disease, Schwann cells, lysosomal alterations, cathepsin release, patient-derived iPSC

Improving Models for the Charcot-Marie-Tooth Disease Using CRISPR-Edited Stem Cells derived Schwann cells

Poster No:
P 078

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Introduction:
Charcot-Marie-Tooth disease (CMT) is the most prevalent inherited peripheral neuropathy, associated with over 100 genes. Most of them, such as SH3TC2, the most frequently mutated gene for the demyelinated autosomal recessive CMT form, are expressed predominantly in neuronal cells. Pathophysiology studies and the exploration of novel therapeutic approaches require suitable cellular models, particularly when accessing relevant cells is challenging. In this regard, human induced pluripotent stem cells (hiPSCs) are a powerful tool, but their reprogramming is time-intensive, and generate clones with diverse genetic backgrounds. Recent advancements in CRISPR base-editing now enhance the quick generation of hiPSCs isogenic cellular models for single nucleotide alterations disorders.

Methods:
Our objective was to use the CRISPR-Cas9 base-editing technology to create the first two CMT hiPSC models harboring SH3TC2 alterations. Starting with a healthy individual's hiPSCs-clone, we aimed at creating two independent models, each harboring variations previously identified in patients : c.2860C>T (resulting in p.Arg954*) in the first model and c.211C>T (resulting in p.Gln71*) in the second one. Due to the time and cost associated with growing and engineering hiPSCs, we optimized the CRISPR strategies in cultivable and transfectable HEK-293T cells. Taking the investigation further, as SH3TC2 is predominantly expressed in Schwann cells, we then differentiated both CMT-hiPSCs clones in this cell type.

Results:
This strategy enabled a quick evaluation of different CRISPR base-editing approaches in HEK-293T cells, subsequently applied to hiPSCs. This approach resulted in 90.5% and 93% On-Target activity for c.211C>T; p.Gln71* and c.2860C>T; p.Arg954*, respectively. Differentiated hiPSCs-CMT clones allowed to study SH3TC2 expression disparity between patient models and control ones throughout the differentiation process.

Conclusions:
This study successfully establishes the first two Schwann cell models derived from hiPSCs harboring pathogenic CMT variations in SH3TC2. These cellular models serve as valuable tools for gaining a deeper understanding of the pathophysiology and for exploring novel therapeutic strategies.

References:
No

Keywords: hiPSCs, CRISPR-Cas9, Disease cellular model, Charcot-Marie-Tooth, Schwann cells

Case report: TTR mutation, Chagas disease and HIV: a severe and unusual autonomic sensory motor polyneuropathy with bulbar involvement.

Poster No:
P 079

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Introduction:
A 71-year-old male presented to a neurology consultation with complaints of weakness and paresthesia in his legs.

Methods:
Data record revealed he had been diagnosed with HIV at 37 years old, initiated antiretroviral therapy (ART) at 48 years old, had an undetectable viral load, and had never experienced an opportunistic infection. At age 50, he developed bilateral carpal tunnel syndrome, which was surgically treated. By 59, he received a diagnosis of Chagas disease, which had led to complications such as achalasia and megacolon, both of which required surgical intervention. At 64, he underwent colectomy due to abdominal distension. Persistent diarrhea ensued post-surgery, accompanied by progressive weight loss.

Results:
One year after symptom onset, weighing 62 kg, he started experiencing numbness and burning in his lower limbs. Subsequently, weakness emerged in the lower limbs, leading to numerous falls. Falls persisted, confining him to a wheelchair by 67, weighing only 48 kg. At 69, weakness extended to the upper limbs, accompanied by dysphonia and dysphagia, further reducing his weight to 45 kg. Physical examination revealed global muscle atrophy with generalized muscular hypotonia and weakness, more pronounced distally in the lower limbs. Global areflexia was observed. Additionally, he exhibited distally graded hypoesthesia in tactile, thermal, painful, and vibratory modalities in both upper and lower limbs. Cranial nerve examination revealed bilateral reduction in auditory acuity, bilateral reduction in palatal veil motility, dysphonia, dysarthria, tongue atrophy +/4+, hypogeusia. Nerve conduction studies indicated a distal axonal sensory-motor polyneuropathy. Genetic testing revealed a heterozygous pathogenic mutation in the TTR gene Ile127Val, a rare variant of ATTR amyloidosis that was described to be prevalent with the presence of lower cranial nerve signs.

Conclusions:
This case underscores the complexity of coexisting medical conditions contributing to a rare neurological presentation, emphasizing the importance of recognizing and understanding such variants for accurate diagnosis and tailored management.

References:
No

Keywords: amyloidosis

A novel homozygous mutation in PNKP responsible for an intermediate/axonal Charcot-Marie-Tooth disease

Poster No:
P 080

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Introduction:
PNKP mutations have been described in various diseases including patients with cerebellar atrophy, neuropathy, microcephaly, epilepsy, and intellectual disability; ataxia with oculomotor apraxia. It was later reported in a patient with early-onset axonal sensory-motor neuropathy followed years later by ataxia and cerebellar atrophy without oculomotor apraxia. CMT with conductions blocks or spatial dispersion are associated with several specific genes and may be difficult to differentiate fron acquired neuropathies.

Methods:
We report the case of a brother and sister born in India of consanguineous parents presenting with an axonal CMT associated with demyelinating features.

Results:
The sister began to experience motor difficulties in all four limbs at age of 33, with sensory symptoms 2 years later. The electromyogram (EMG) revealed a severe sensory-motor neuropathy with intermediate velocities and spatial dispersion. The lumbar puncture was normal, and nerve biopsy showed massive axonal loss. Immunoglobulins were ineffective. At the age of 41,she had a distal sensory-motor deficit in all four limbs and diffuse areflexia. Her brother began stumbling around the age of 32. At 39, there was a distal deficit in the lower limbs at 2/5, in the upper limbs at 4/5; all reflexes were abolished. EMG showed a sensory-motor neuropathy with conduction blocks, along with prolonged F-waves. Genome sequencing found a new homozygous variant in the PNKP gene (c.1124G>A p.(Gly375Glu)) which changes the same amino acid as the already described pathogenic mutation p.Gly375Trp.

Conclusions:
We describe a case of pure axonal CMT with elements of demyelination on EMG associated with a novel mutation in PNKP. This further broadens the spectrum of PNKP-related diseases. The electrical presentation of both patients raised suspicion of an acquired demyelinating pathology. The differential diagnosis between CIDP and CMT is a significant challenge both for patients and in terms of public health. It is crucial for neurologists and geneticists to be well-versed in the various genes involved.

References:
Yes

Reference 1: Pedroso JL, Rocha CR, Macedo-Souza LI, De Mario V, Marques W Jr, Barsottini OG, Bulle Oliveira AS, Menck CF, Kok F. Mutation in PNKP presenting initially as axonal Charcot-Marie-Tooth disease. Neurol Genet. 2015 Oct 22;1(4):e30. doi: 10.1212/NXG.0000000000000030. PMID: 27066567; PMCID: PMC4811384.

Reference 2: Hauw F, Fargeot G, Adams D, Attarian S, Cauquil C, Chanson JB, Créange A, Gendre T, Deiva K, Delmont E, Francou B, Genestet S, Kuntzer T, Latour P, Le Masson G, Magy L, Nardin C, Ochsner F, Sole G, Stojkovic T, Maisonobe T, Tard C, Van den Berghe P, Echaniz-Laguna A. Charcot-Marie-Tooth disease misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy: An international multicentric retrospective study. Eur J Neurol. 2021 Sep;28(9):2846-2854. doi: 10.1111/ene.14950. Epub 2021 Jun

Keywords: Charcot Marie Tooth Disease, Electrophysiology, Genome sequencing

Accelerated Directed Differentiation Of Human Induced Pluripotent Stem Cell Derived Schwann Cell Precursors For Modeling Peripheral Neurobiology

Poster No:
P 081

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Introduction:
Schwann cells are vital components of the peripheral nervous system that interact with and myelinate both sensory and motor neurons. Schwann cell dysfunction is implicated in various human diseases, including diabetic peripheral neuropathy, Charcot-Marie-Tooth syndrome, and pain. Despite the significance of these cell types in disease pathology, studying them in a human-relevant context has been challenging due to the absence of well-characterized translational in-vitro models. Here we present an efficient method for generating Schwann cell precursors (SCPs) from hiPSCs, accomplished through directed differentiation under precisely defined media conditions within 9 days. These SCPs will provide a novel translational human model for peripheral neurobiology.

Methods:
SCPs, motor neurons, and sensory neurons were differentiated from the same hiPSC lines. The identity of all three cell types were confirmed by immunocytochemistry, qPCR, and RNA sequencing. Syngeneic SCPs and motor neurons were co-cultured and evaluated for alignment and myelination via immunocytochemistry and transmission electron microscopy. SCPs and sensory neurons were evaluated by the same methods and these experiments were replicated with multiple donor lines.

Results:
Manufactured SCPs expressed the classical markers for the Schwann cell lineage SOX10, S100b, and OCT6 by qPCR and immunocytochemistry. Time course bulk RNA sequencing of matured SCPs demonstrated increasing similarity to primary human Schwann cells. The co-cultures undergo rapid SCP-axon alignment within 48 hours, and myelination was observed via transmission electron microscopy and expression of the myelin-associated proteins–myelin basic protein (MBP) and myelin protein zero (MPZ) as early as 5 weeks in culture.

Conclusions:
In summation, SCPs can be efficiently and rapidly generated from hiPSCs and cultured with neurons to form myelinating models of the peripheral nervous system. These co-culture systems will lay the groundwork for future experimentation modeling neuropathology in a patient-specific manner.

References:
No

Keywords: Schwann Cells, iPSC, CMT, Disease modeling, Co-cultures

TRPV4 neuropathy patient registry identifies core features and patterns of progression to inform clinical trial design

Poster No:
P 082

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Introduction:
Dominant gain-of-function mutations of the calcium-permeable cation channel TRPV4 cause Charcot-Marie-Tooth disease (CMT) type 2C and forms of distal spinal muscular atrophy, which share features of variably severe arm and leg weakness and frequent vocal cord weakness. While animal models demonstrate that small molecule TRPV4 antagonists represent a promising therapeutic strategy, translating these findings for patients requires delineation of the natural history of TRPV4 disease and identification of relevant clinical outcomes measures.

Methods:
To define the clinical spectrum and natural history of TRPV4-related neuromuscular disease, we developed a TRPV4 patient database within the Inherited Neuropathy Consortium patient registry. We identified and analyzed 68 patients with known pathogenic TRPV4 mutations, and 37 of these patients also completed a detailed TRPV4-specific patient questionnaire.

Results:
TRPV4 patients showed a bimodal age of onset, with the largest peak in the first 2 years of life. Genotype-phenotype analysis revealed that specific TRPV4 mutations were more frequently associated with earlier age of onset. TRPV4 patients showed clearly distinct symptoms and clinical findings as compared to CMT1A patients, manifesting more severe weakness of the lower extremities and frequent proximal arm and leg weakness. Sensory symptoms were often absent, but sensory dysfunction was often detected clinically. Vocal cord weakness was common (62%), and bulbar dysfunction was often cited as the most bothersome aspect of the disease (34%). Many patients also reported various skeletal abnormalities, including scoliosis (67%) and arthrogryposis (35%). Strikingly, patients with congenital onset of disease showed less progression of symptoms and less sensory involvement.

Conclusions:
These results highlight distinctive clinical features in TRPV4 patients, including motor-predominant disease, vocal cord weakness, severe ambulatory difficulties, and skeletal involvement. In addition, patients with congenital onset of disease appear to have a distinct phenotype with less disease progression. These collective observations will help guide future clinical trial design for TRPV4 neuromuscular disease.

References:
No

Grant Support:

Muscular Dystrophy Association, Advancing Clinical Trial Readiness in TRPV4 Neuropathy

Keywords: Charcot Marie Tooth disease, TRPV4, Natural history study, Outcome measures

1000 Norms Filipino Cohort: Capturing ethnogeographic variation to score CMT trial endpoints

Poster No:
P 083

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Introduction:
In the landmark 1000 Norms Project, >1 million reference values from 1000 healthy males and females aged 3-101 years were collected to build responsive clinical outcome measures e.g., CMT Pediatric Scale (CMTPedS) and the CMT Functional Outcome Measure (CMT-FOM). The 1000 Norms Project are used worldwide to detect meaningful effect sizes beyond the natural variability of human disease, growth and development. These data and associated z-scores used to calculate disease-specific Scales, shared online via ClinicalOutcomeMeasures.org with >930 clinical evaluators in >35 countries and implemented in multicenter clinical trials and cohort studies across disease groups. The aim of this study is to extend to a Filipino cohort to enrich the population for Southeast Asia normative data and to investigate the impact of ethnogeography on physical function. This is essential given that the original Australian sample has a European bias.

Methods:
Outcome measures from the 1000 Norms Project will be reviewed for inclusion, based on cultural, social, and contextual appropriateness to the Philippines. Applying the inclusion/exclusion criteria of the 1000 Norms Project, 200 healthy males and females aged 8-19 years will be recruited in Manila, Philippines. Prior to data collection, reliability of the local clinical evaluators will be established via online and in-person training by 1000 Norms Project clinical evaluators.

Results:
Outcomes measures may include isometric muscle strength, joint flexibility and functional measures of balance, dexterity, endurance and power. Descriptive statistics will be applied, creating mean values and z scores, stratified by age and gender. Inferential analyses will be generated to determine if age- and sex-matched reference data differ between the two ethnographic datasets.

Conclusions:
This project will report on the influence of ethnogeography on a comprehensive range of outcome measures that represent physical function and will enrich the diversity of the 1000 Norms Project reference values used to score CMT trial endpoints.

References:
No

Keywords: Normative reference data, Outcome measures, Ethnogeographic variation, CMT

A 29 Year Old Ghanaian Male With Possible Charcot-Marie-Tooth: Time To Move On From Educated Diagnostic Guesses?

Poster No:
P 084

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Introduction:
Charcot-Marie-Tooth disease (CMT) is the most common inherited peripheral neuropathy

Methods:
We report a 29-year-old Ghanaian man who had difficulty walking since childhood that has gradually worsened over the past 5 years. His younger brother has similar, albeit milder symptoms. Examination reveals distal-predominant wasting, motor or sensory deficits, diminished reflexes, and foot drop with high steppage gait.

Results:
Nerve conduction study showed severe uniform demyelination with no conduction block. Genetic testing for CMT is unavailable, and testing privately is beyond the means of the patient. The patient has been counseled and managed as a presumptive case of Charcot Marie Tooth 1.

Conclusions:
Although CMT is not an uncommon disorder in Africa, little is known of its prevalence and genetic subtypes in Ghana. In addition, there is a general diagnostic nihilism with regards to genetic disorders among practitioners. Accurate genetic diagnosis is important for optimal management of the patient as well as to stop unnecessary therapeutic trials with medications that have considerable side effects example corticosteroids. There is perhaps a need for international bodies, such as PNS, to creatively address the issue of the unavailability of basic genetic diagnoses in under-resourced regions.

References:
No

Keywords: Charcot-Marie-Tooth, foot drop, Genetic

In quest for molecular players and drug targets for aminoacyl-tRNA synthetase-associated peripheral neuropathies

Poster No:
P 085

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Introduction:
Aminoacyl tRNA synthetases (aaRS) are essential enzymes linking amino acids to their cognate tRNA, a fundamental step in protein biosynthesis. We identified that dominant mutations in tyrosyl tRNA-synthetase (YARS1) cause DI-CMTC and reproduced the hallmarks of the disease in a Drosophila model of $YARS1^{CMT}$. Currently, six additional synthetases were causally involved in other subtypes of peripheral neuropathies, and we developed matching Drosophila models for $GARS1^{CMT}$, $HARS1^{CMT}$, and $AARS1^{CMT}$. Loss of aaRS enzymatic activity is not causing CMT, suggesting a toxic gain of function mechanism; yet, its nature remains elusive. To unravel the $aaRS^{CMT}$ pathomechanisms and simultaneously create therapeutic opportunities for peripheral neuropathies, we performed a large-scale search for druggable genetic modifiers of $YARS1^{CMT}$ toxicity in Drosophila. Moreover, we tested whether the modifiers are common across $aaRS^{CMT}$.

Methods:
We unbiasedly screened 945 fly genes having druggable human orthologs. Both gain and loss of function alleles were assessed for their capacity to enhance the retinal disorganization induced by $YARS1^{CMT}$ overexpression. The initial hits underwent stringent validation, ensuring they do not cause a rough eye phenotype on its own; do not trigger a retinal disorganization in a $YARS1^{WT}$ background; and their modulation effect is reproducible. The remaining hits were tested in flies expressing other $aaRS^{CMT}$.

Results:
114/1880 fly lines tested aggravated the $YARS1^{CMT}$-associated rough eye phenotype. The initial hits entered a robust filtering pipeline and genuine $YARS1^{CMT}$-specific interaction was validated for 61 misregulated genes. Remarkably, 97% of them also exacerbated the rough eye phenotype in $GARS1^{CMT}$ flies. Most of the modifiers encode transmembrane proteins, oxidoreductases, and phosphorylation-regulating enzymes. Further testing of selected hits across four Drosophila $aaRS^{CMT}$ models demonstrated that some are common, while others are attributed to specific aaRS.

Conclusions:
Our results deliver novel knowledge on the molecular mechanisms of aaRS-induced neurodegeneration and a list of proteins amenable to therapeutic targeting.

References:
No

Grant Support:

AFM, MDA, ABMM, FWO

Keywords: Aminoacyl-tRNA synthetase, Charcot-Marie-Toot neuropathy, Drosophila, Disease modelling, Unbiased screen

CMT1A and HNPP Functional Demyelination Pathomechanisms Caused by Node of Ranvier and Schmidt-Lanterman Incisure Defects

Poster No:
P 086

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Introduction:
Increased and decreased dosage of the PMP22 gene cause dysmyelinating peripheral neuropathy. CMT1A (PMP22 duplication) and HNPP (PMP22 deletion) are the most common inherited peripheral neuropathies, yet many gaps remain about their pathophysiology and pathomechanims. Our previous results with CMT1A model mice demonstrate that muscle atrophy occurs in the leg without evidence of secondary axon degeneration suggesting that primary myelin dysfunction may drive CMT1A pathogenesis and motivating investigation of myelin dysfunction.

Methods:
We are using CMT1A and HNPP model mice and confocal immunofluorescence imaging of teased tibial nerve fibers to determine how altered PMP22 expression disrupts myelin integrity and identify CMT1A and HNPP pathomechanisms.

Results:
Given that PMP22 belongs to the Claudin superfamily, we first characterized adhesion junctions. We identified dramatically disorganized adherens junctions (AJs) at Schmidt-Lanterman incisures (SLIs) in CMT1A and HNPP model myelin. AJ distribution at SLIs is more compact/punctate in CMT1A and more spread out in HNPP. The SLI components MAG and Connexin29 are also disorganized in CMT1A but appear more spread out with focal accumulations visible outside of SLIs. Connexin29 also associates with Kv1 channels at Nodes of Ranvier which led us to evaluate Kv1 distribution. There is often less Kv1.2 enrichment at juxtaparanodes in CMT1A and HNPP model myelin and focal accumulations are frequently spread along the internode. The distribution of Caspr at paranodes is also disrupted; the compact plaque is often segmented and inner mesaxons are more spiraled. The Kv1.2 and Caspr defects appear more dramatic in CMT1A as compared to HNPP.

Conclusions:
We identified dramatic defects at SLIs and Nodes of Ranvier that could indirectly and/or directly affect conduction in CMT1A and HNPP resulting in functional demyelination of grossly normal compact myelin. Ongoing studies are aimed at determining how these defects affect nerve conduction and metabolism and how altered PMP22 and adherens junctions cause these defects.

References:
No

Grant Support:

NIH NINDS K22 Career Transition Award (K22NS125057), Johns Hopkins University Merkin Peripheral Neuropathy and Nerve Regeneration Center Grant

Keywords: CMT1A, HNPP, PMP22, Pathomechanism, Myelin

Which Clinical Factors Prompt Genetic Testing in Hereditary Peripheral Neuropathies? Insights from a Brazilian Cohort Analysis

Poster No:
P 087

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Introduction:
No decision-making algorithm is available to determine when genetic testing should be requested to clarify the etiology of peripheral neuropathies in a Brazilian population.

Methods:
Seventy-one patients were tested for hereditary peripheral neuropathies at an outpatient neuromuscular clinic in Brazil.

Results:
We documented the prevalence of these manifestations and descriptive statistics were performed and the chi-square test was done in subgroups . Of 75 tested patients, 32 were positive and 44 were negative. Weakness (42/75, 69%), numbness (50/75, 66%), neuropathic pain (35/75, 46%), and imbalance (33/75, 44%) were the most commonly reported symptoms, with deafness being the least described (3/75, 4%). Among physical exam findings, distal atrophy, pes cavus, and scoliosis were present in 26% (26/75), 23.9% (19/75), and 5.6% (5/75) of patients, respectively. Among positive tests, 50% (16/32) presented more than 3 hereditary neuropathy related symptoms versus 22% (10/44) between negative group (p=0.04). Among patients with pes cavus, 63% (12/19) had a positive test (p=0.03) 12. The median sum score for muscle strength in the cohort was 57 points (range 0 – 70), while the sum score in positive groupe was 53 points. Notably, 40% (30/75) of patients had a positive family history of peripheral neuropathies. The number of symptoms were more relevant than physical examination findings to prompt genetic testing. Pes cavus was the most relevant clinical finding and was found in 55% (5/9) of the PMP22 mutation patients, vesus 30% (7/23) of other mutations (p=0.00).

Conclusions:
This study sheds light on the characteristics that trigger the need for genetic testing in patients suspected of hereditary peripheral neuropathies.

References:
No

Keywords: hereditary neuropathy

Spectrum of Young onset Motor nerve disorders in Indian cohort

Poster No:
P 088

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Introduction:
Young onset motor nerve disorders (age <45 years) present with mixed UMN and LMN features or with UMN or LMN features in isolation. We aim to describe the clinical, EPS, radiological and genetic profile of a clinically suspected cohort of young onset motor nerve disorders in India.

Methods:
All clinically suspected patients with young onset motor nerve disorders were prospectively recruited into the MRC- funded International Centre for Genomic Medicine in Neuromuscular Diseases (ICGNMD) cohort from a tertiary care hospital in North India. Informed consent was obtained from all participants. All patients underwent clinical examination, deep phenotyping, NCS, EMG and MRI (Brain/ Spine). Genetic testing included triplet primed PCR and short PCR for C90rf72 and whole exome sequencing (WES).

Results:
We included 70 patients (M: F- 54:16) with a mean age of disease onset at 27 years. Three patients had a positive family history. Classic phenotype (UMN plus LMN in 3 segments) were observed in 31 (44%) patients. Other clinical phenotypes included flail arm syndrome 22(31%), flail leg syndrome 8 (11%), bulbar onset 8 (11%) and FTD-associated 1 (1%). Cognition was affected in three patients. 51 patients underwent EPS. EMG showed involvement of four segments in 10 (20%), three segments in six (12%), two segments in 13 (25%) and one segment in 13 patients (25%). Management included Riluzole 35 (50%) alone or in combination with Edaravone,17 (24%) took both Edaravone and Riluzole, 17 (24%) took Riluzole alone and 3 (4%) succumbed. WES are available for 19 patients and C9orf72 for 20 patients, reports of the remaining patients are awaited. 2 patients had pathogenic SOD1 mutation, 1 each had a VUS for the ALS2, UNC13A, DCTN1, NEK1 and TRVP4 genes.

Conclusions:
We describe a prospective cohort of young onset motor nerve disorders in patients from India with deep phenotyping and genetic characterisation.

References:
Yes

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Grant Support:

No grant support

Keywords: Motor nerve disorders, deep phenotyping, genetic characterisation

Lower Limb Muscle MRI Responsiveness In CMT1A Across Five Sites In An International Study

Poster No:
P 089

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Introduction:
We have previously demonstrated lower limb intramuscular fat fraction (FF) as a responsive biomarker in Charcot-Marie-Tooth Disease 1A (CMT1A). Given the development of new treatments, it is vital to demonstrate this internationally on different MRI scanners, to demonstrate responsiveness and validity on a larger scale over a longer time period.

Methods:
Between 2019 and 2021, 67 CMT1A patients and 25 controls were recruited for lower limb muscle 3T MRI (T1, T2-STIR and 3-point-Dixon sequences at thigh and calf-level) across 5 international sites as part of the ACT-CMT 5 year natural history study in CMT1A (1): UK (Siemens); US (Siemens and General Electric); Italy (Philips). Data was transmitted electronically to a central site (UK) for technical review. The 3-point-Dixon fat/water separation technique was used to determine thigh and calf-level FF at a single slice using regions of interest with Musclesense, a trained artificial neural network for lower limb segmentation (2).

Results:
Preliminary results on 52 patients and 18 controls demonstrated that baseline calf-level FF increased significantly over 12 and 24 months for CMT1A patients (1.23±2.09%, $p<0.001$ and 2.06±3.05%, $p<0.001$ respectively). Baseline thigh-level FF also increased significantly over the same period (0.48±1.47%, $p=0.034$ and 0.62±1.33%, $p=0.006$). Patients with baseline calf-level FF between 10-70% increased by 3.71±3.65% over 24 months ($p=0.002$, standardised response mean (SRM)=1.02). Control participants demonstrated no significant change in FF at calf or thigh-level.

Conclusions:
This is the first study to demonstrate lower limb intramuscular FF responsiveness in CMT1A in a multi-centre international study over 24 months and provides further evidence for using this as a biomarker in future clinical trials in CMT1A. Intramuscular FF analysis will be completed on the remaining datasets and results will be presented to further validate the protocol and its responsiveness and correlation with clinical outcome measures.

References:
Yes

Reference 1: Eichinger K, Sowden JE, Burns J, et al. Accelerate Clinical Trials in Charcot-Marie-Tooth Disease (ACT-CMT): A Protocol to Address Clinical Trial Readiness in CMT1A. Front Neurol 2022;13:930435.

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Grant Support:

Accelerate Clinical Trials in Charcot-Marie-Tooth disease (ACT-CMT) study (NIH NINDS # 1U01NS109403-01).

Keywords: CMT, Fat fraction, Biomarker

PMP22 and MPZ form a complex, loss of which leads to a phenotype like HNPP

Poster No:
P 090

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Introduction:
PMP22 and MPZ are major myelin proteins in the peripheral nervous system. MPZ is a single pass integral membrane protein with an extracellular immunoglobulin (Ig)-like domain and works as an adhesion protein to hold myelin wraps together across the intraperiod line. Complete of MPZ causes severe demyelinating Charcot-Marie-Tooth (CMT) peripheral neuropathy. PMP22 is an integral membrane tetraspan protein belonging to the Claudin superfamily. Homozygous loss of PMP22 also leads to severe demyelinating neuropathy, and duplication of wildtype PMP22 causes the most common form of CMT, CMT1A. Yet the molecular functions provided by PMP22 and how its alteration causes CMT are unknown. Here we find that these abundant myelin proteins form a strong and specific complex.

Methods:
Microscopy and coimmunoprecipitation experiments with different MPZ and PMP22 mutants were used to map how they interact on structural level. We also interrogated different patient variants of PMP22 to determine whether any were specifically defective in interactions with MPZ.

Results:
Mutagenesis and domain swapping experiments reveal that these proteins interact through interfaces within their transmembrane domains. Further, we present a model for how these proteins interact and the interface through which this interaction occurs. We also find that the PMP22 A67T patient variant that causes an HNPP (Hereditary neuropathy with pressure palsies) phenotype, reflecting a heterozygous loss-of-function, maps to this interface. The PMP22 A67T variant results in the specific loss of MPZ association with PMP22 without affecting the localization to the plasma membrane or interactions with other proteins.

Conclusions:
These data define the molecular basis for the MPZ:PMP22 interaction and indicate that the MPZ:PMP22 complex fulfills an important function in myelinating cells.

References:
No

Keywords: Peripheral Neuropathy, Protein Interaction, hereditary neuropathy associated with liability to pressure palsy

Real-live evaluation of Vutrisiran treatment in a cohort of hereditary transthyretin amyloidosis patients

Poster No:
P 091

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Introduction:
Hereditary transthyretin amyloidosis (ATTRv) is a systemic disorder that can cause neuropathy, cardiomyopathy, and other organ manifestations. In 2022, Vutrisiran, a subcutaneously applied siRNA mediated knock-down of TTR protein production, was approved for treatment of ATTRv-associated neuropathy stage 1 and 2 in Germany. This is study evaluates first real-live data on Vutrisiran treatment outcomes.

Methods:
We prospectively followed up 12 patients with ATTRv treated with Vutrisiran at a single interdisciplinary amyloidosis specialist center since November 2022. We collected longitudinal data using the neuropathy impairment score (NIS), patient reported outcome measures (PROMs) for quality of life and autonomic neuropathy, laboratory biomarkers such as serum neurofilament light chain (NfL) and B-type natriuretic peptite (NTproBNP), as well as cardiac assessments using 99mTc-DPD scintigraphy and echocardiography.

Results:
At the time of treatment initiation, patients were between 35 and 81 years old. 8/12 patients (67%) were switched from other causative treatments. Eight different TTR variants were represented, the most frequent being p.(Val50Met). Most patients (9/12, 75%) presented with a mixed cardiac-neurological phenotype. During the first year of Vutrisiran treatment, neurological evaluation showed an improvement of NIS and a reduction of NfL levels. PROM assessment showed initial fluctuation and subsequent improvement of daily live function. Cardiac assessment showed variable responses but generally stable disease. There was no discontinuation due to adverse events.

Conclusions:
Vutrisiran was safe and easy to use and showed good response in the first year of treatment in our cohort. Best responses were seen in neurological assessments. Possible reasons for variable results in quality of live and cardiac assessments were differences in disease severity at treatment initiation and subjective affection caused by diverse organ manifestations.

References:
No

Grant Support:

Deutsche Gesellschaft für Muskelkranke (DGM) GmbH, BIH clinical fellow

Keywords: transthyretin amyloidosis, vutrisiran, gene therapy, siRNA therapy, clinical outcome

Complex inherited neuropathies – understanding the unsolved

Poster No:
P 092

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Introduction:
Charcot-Marie-Tooth disease (CMT) and related disorders are inherited neuropathies with over 120 known causative genes. However, approximately one in five patients with CMT still lacks a genetic diagnosis. Complex inherited neuropathies are defined syndromically as neuropathy plus involvement of one or more additional organ systems. These patients present a challenge for diagnosis and treatment.

Methods:
Patients were recruited through a single specialist inherited neuropathy centre. Complex inherited neuropathies were defined as above, excluding individuals with variants in established CMT genes where certain non-peripheral nerve involvement is well described as part of the phenotype. They were clinically assessed using detailed medical history, nerve conduction studies, laboratory testing, and in some cases imaging. Genetic testing was performed using single gene tests, gene panels, whole exome (WES) and whole genome sequencing (WGS).

Results:
Out of 1515 patients with CMT, 53 patients (4%) with complex phenotypes were identified. Out of these, 26 (49%) were genetically solved. Where known, the diagnosis was made using single gene tests (9/25), gene panels (9/25), or research WES/WGS (7/25). The most frequent genes identified were ARSACS (5/26), KIF1A (3/26), KIF5A (3/26), FXN (2/26), MT-ATP6 (2/26), as well as single patients with PLP1, SPG11, COA3, DARS2, MPV17, OPA3, RTN2, SETX, ABHD12, GAN, and GNE. Phenotypes of unsolved patients most frequently included upper motor neuron signs (16/27), cerebral white matter disease (7/27), cerebellar signs (6/27), cognitive deficits (4/27), and other cranial nerve pathologies (6/27).

Conclusions:
Complex inherited neuropathies represent a challenge for clinical classification due to overlap with other neurological disease and a modest yield of genetic diagnosis. We present our approach to classification and investigation of the unsolved and complex clinical presentations in CMT.

References:
No

Grant Support:

Deutsche Gesellschaft für Muskelkranke (DGM) GmbH
EJP RD ERN RD Research Mobility Fellowship

Keywords: CMT, complex inherited neuropathy, whole genome sequencing, phenotyping, genetic diagnostics

Whole Exome Sequencing In Inherited Neuropathies From South India

Poster No:
P 093

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Introduction:
Next generation sequencing (NGS) has helped dramatically increase the genetic diagnosis of inherited neuropathies. However, the diagnostic rate remains very heterogeneous worldwide. The MRC-funded International Centre for Genomic Medicine in Neuromuscular Diseases (ICGNMD) is a project aiming to increase global access to genomic medicine. We present today the results of whole exome sequencing (WES) from a single centre in India.

Methods:
Nine patients with a suspected hereditary neuropathy from one centre in South India were included through the ICGNMD project. Clinical data was collected by the local neurologists. All patients underwent WES as part of the study.

Results:
Four patients out of nine were female (44%). The mean age at onset of the neuropathy was 11.6 years old (range 2-26). Five patients had consanguineous parents and none of the 9 patients had reported family history of peripheral nerve disease. We were able to confirm a genetic diagnosis in 3 patients (33%) with pathogenic variants in MFN2, SH3TC2 and SPTLC1. The causative heterozygous variants found in MFN2 and SPTLC1, respectively p.Thr105Met and p.Cys133Tyr, had previously been described in the literature. In the third patient, we discovered a novel homozygous mutation in SH3TC2: p.Glu423Ter. The patient had a history of family consanguinity and presented with typical CMT4C associated distal weakness, scoliosis, pes cavus and hearing impairment. Loss of function variants are known to be pathogenic in this gene. This nonsense variant was not reported in gnomAD4 and in-silico predictors classified it as "very strongly pathogenic". Variants of uncertain significance were identified in 4 of the 6 other patients in the following genes: KIF1A, IGHMBP2, SPG11, GDAP1. More data is needed to investigate these candidates.

Conclusions:
This South Indian cohort study highlights the potential diagnostic yield of WES for inherited neuropathies in under-investigated countries.

References:
Yes

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Keywords: hereditary neuropathy, next-generation sequencing, CMT

C12ORF65/MTRFR Deficiency Is A Good Candidate For Gene Therapy Treatments

Poster No:
P 094

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Introduction:
The nuclear gene C12ORF65/MTRFR encodes mitochondrial translation release factor rescue-1, a vital protein vital for mitochondrial translation that acts as a mitoribosome release factor when translation is terminated. Patients with recessive MTRFR mutations often have optic and peripheral neuropathies characteristic of Behr's syndrome, Leigh syndrome, and Charcot-Marie-Tooth disease (CMT). There is currently no cure and only palliative treatment available for MTRFR-deficiency.

Methods:
A mouse model will facilitate understanding how MTRFR deficiency leads to neurodegeneration. Presently, we are developing a conditional knock-out mouse to study in combination with our existing loss-of-function and transgenic models of MTRFR deficiency. These mice will clarify the genetic mechanism and cell-specificity of this peripheral neuropathy. By crossing the conditional knock-out model with various Cre-strains we will specifically induce MTRFR deficiency in revelent cell types including retinal ganglion cells and peripheral motor neurons.

Results:
A premature truncation in mouse Mtrfr mimicking a patient mutation was made. This resulted in embryonic lethality in homozygotes, but this phenotype was rescued by expression of a wild-type human transgene. One copy of the fully functional wildtype human gene (WT-KI) was sufficient to rescue the embryonic lethality, with no signs of peripheral neuropathy or optic atrophy. Overexpression of the transgene itself (without presence of the premature truncation) does not lead to any harmful side effects or dominant negative effects, the mice are healthy and normal.

Conclusions:
Understanding MTRFR deficiency provides insight into how mitochondrial translation plays a role in neuropathy and neurodegeneration. MTRFR is critical for survival in mice and plays an important role in neuronal health. We are creating a conditional knock-out model to better model this disease. Our results to date indicate that transgenic expression of wild type MTRFR rescues lethality without producing adverse effects from overexpression suggest that MTRFR-deficiency is a good target for gene therapy approaches.

References:
No

Keywords: Mitochondria, Translation, Neurodegeneration, Peripheral Neuropathy, Mouse Models

CMT1J – ITPR3 mutations in peripheral neuropathy, immunodeficiency, and tooth abnormalities

Poster No:
P 096

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Introduction:
Inositol 1,4,5-trisphosphate receptors (IP3Rs) are ER Ca2+-release channels that control a broad set of cellular processes. They are crucial signaling hubs in cells, releasing calcium from the endoplasmic reticulum upon IP3 binding. Recently, we have identified autosomal dominant mutations in the ITPR3 gene, which encodes the IP3R3 protein, as a novel causative factor for CMT, leading to the designation of a new demyelinating CMT type, CMT1J (OMIM #620111). Charcot-Marie-Tooth disease (CMT) is a group of hereditary neuropathies, characterized by progressive distal sensory and motor impairment, which affects 1:2500 individuals.

Methods:
Given the importance of IP3Rs in human diseases, we investigated their role in human induced pluripotent stem cells (hiPSC) by developing single IP3R and triple IP3R knockouts (TKO) and generated three CMT1J-patient specific knockin hiPSC lines.

Results:
Genome edited TKO-hiPSC lacking all three IP3R isoforms, IP3R1, IP3R2, IP3R3, failed to generate Ca2+ signals in response to agonists activating GPCRs, but retained stemness and pluripotency. Steady state metabolite profiling and flux analysis of TKO-hiPSC indicated distinct alterations in tricarboxylic acid cycle metabolites consistent with a deficiency in their pyruvate utilization via pyruvate dehydrogenase, shifting towards pyruvate carboxylase pathway.

Conclusions:
These results demonstrate that IP3Rs are not essential for hiPSC identity and pluripotency but regulate mitochondrial metabolism. Next, we will investigate the CMT1J pathogenesis and IP3R function. Newly created CMT1J-specific iPSC lines will be differentiated into motor neurons and Schwann cells, and will be studied extensively, with unbiased methods such as metabolomics, proteomics, and electrophysiology.

References:
Yes

Reference 1: Rönkkö J, Molchanova S, Revah-Politi A, Pereira EM, Auranen M, Toppila J, Kvist J, Ludwig A, Neumann J, Bultynck G, Humblet-Baron S, Liston A, Paetau A, Rivera C, Harms MB, Tyynismaa H, Ylikallio E. Dominant mutations in ITPR3 cause Charcot-Marie-Tooth disease. Ann Clin Transl Neurol. 2020 Oct;7(10):1962-1972. doi: 10.1002/acn3.51190. Epub 2020 Sep 19. PMID: 32949214; PMCID: PMC7545616.

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Keywords: CMT1J, iPSC, IP3R3, ITPR3

Co-designing a Strategy to Engage People with Neuromuscular Diseases from Racially Minoritized Backgrounds in Research

Poster No:
P 097

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Introduction:
There is evidence of poor representation people from racially minoritized backgrounds and neuromuscular diseases (NMDs) in clinical research. The people best placed to develop the strategies for engagement are people with this lived experience. We used public engagement workshops to co-design a recruitment strategy in partnership with people living with NMDs from racially minoritized backgrounds.

Methods:
We invited people to three workshops using video conferencing. Workshop 1: Exchange of experiences and ideas; Workshop 2: Bringing ideas together as a strategy with action points; Workshop 3: Agreeing the final strategy.

Results:
Strategy plans were agreed in the following areas: 1. Setting up a Patient Public Involvement group for a specific study or programme 2. Access to information on research 3. Accessible and attractive information 4. Cultural sensitivity and diversity in the research team 5. Incentives for participation in research 6. Involving family members in decisions on research 7. Communicating research outcomes

Conclusions:
We plan to launch the strategy to research colleagues to facilitate greater diversity in trial cohorts at our institution.

References:
No

Grant Support:

UCLH Biomedical Research Centre: Patient Public Involvement grant

Keywords: Diversity, Research cohorts, Public engagement

HNF's Global Registry for Inherited Neuropathies (GRIN) Identifies Importance of Recognizing CMT as Pediatric Disease and the Unmet Need for Treatment

Poster No:
P 098

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Introduction:
Potential upcoming CMT Pediatric trials require urgent analysis of GRIN Natural History data, developed by HNF and advisors to capture comprehensive history of CMT patients to identify CMT as a childhood disease. Pediatric patients ages 0-17 diagnosed with CMT are broadly affected with a wide spectrum of symptoms at a statistically significant rate compared to the adult cohort. CMT impacts quality of life starting in childhood.

Methods:
This IRB-approved online survey was conducted globally from 2013Q1 to 2023Q2. Analysis focused on questions related to patient symptoms, including, "When does the patient recall CMT symptoms first started?". A total of 1550 participants responded, selecting from a series of age bands from 0-5 years to 70+ years. Methodology involved tallying responses per age band and subsequently calculating cumulative percentages.

Results:
Pediatric patients ages 0-17 diagnosed with CMT are broadly affected with a wide spectrum of symptoms at a statistically significant rate when compared to the adult cohort. CMT impacts quality of life starting in childhood. 22.3% of CMT patients experienced initial symptoms during early childhood, between ages 0 and 5 years. About half (50.5%) of CMT patients had symptoms onset before the age of 16 years. 55% of symptoms were noticed by family members before official diagnosis.

Conclusions:
The observed prevalence of symptom onset before age of 16 underscores urgent unmet need to treat this progressively debilitating disease upon diagnosis. These findings have important implications for design of clinical trials and identification of meaningful endpoints. It's critical that pediatric physicians encourage enrollment of patients in GRIN.

References:
No

Keywords: Charcot-Marie-Tooth, Pediatric, Natural History, Unmet need, End points

Neuromuscular Ultrasound as a Biomarker to Improve Clinical Trial Readiness in Charcot Marie Tooth Neuropathies

Poster No:
P 099

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Introduction:
With advances in preclinical proof of concept for treatment approaches for Charcot-Marie-Tooth Neuropathies (CMT), there is an urgent need for clinical trial readiness. Most forms of CMT are slowly progressive, therefore validated biomarkers rapidly providing signals of treatment effect are critical. Neuromuscular ultrasound has emerged as a useful tool in neuromuscular practice and may have utility for research application in CMT neuropathies.

Methods:
18 adults with CMT1A, 14 with CMT1B, 10 with CMT2A, 4 with CMT2F, 12 with CMTX1, and 13 control participants were enrolled in the study. Neuromuscular ultrasound measures including tibialis anterior (TA) echo-intensity (EI) and echo-variability (EV) greyscale quantification were gathered, as well as electrophysiologic characteristics and clinical outcome assessments (COAs) including the CMT examination score (CMTES). Duplicate images were independently acquired in 9 participants with CMT to measure reliability. A p-value < 0.05 was considered significant.

Results:
CMT and control participants had mean ages of 49 and 42 respectively ($p=0.13$), and were 53% and 69% female ($p=0.28$). When compared to controls, TA EI was significantly higher in CMT participants (83.0 vs 69.2, $p <0.0001$), and EV was significantly lower (28.9 vs 46.0, $p<0.0001$). In participants with CMT, EI and EV correlate with fibular nerve CMAP amplitude measured at TA ($R=-0.48$, $p=0.0002$; and $R=0.70$ $p<0.0001$), with dorsiflexion strength ($R=-0.30$, $p=0.02$; and $R=0.65$, $p<0.0001$) and CMTES ($R=0.38$, $p=0.004$; and $R=-0.6$, $p<0.0001$). EI and EV from independently acquired images were highly correlated ($R=0.96$, $p<0.001$; and $R=0.91$, $p<0.001$).

Conclusions:
In this exploratory study, individuals with CMT were shown to have increased TA EI and decreased EV compared to controls. TA EI and to a greater extent EV correlated with both electrophysiology and COAs, supporting the potential utility of neuromuscular ultrasound as a CMT biomarker. Longitudinal data acquisition is on-going to evaluate the sensitivity to change over time.

References:
No

Grant Support:

Tyler Rehbein is supported by Neuromuscular Study Group, American Brain Foundation, and American Academy of Neurology Clinical Research Training Scholarship in Neuromuscular disease. David Herrmann is supported by NIH U01 NS109403-05, NIH U54NS065712, and the CMT association (CMTA).

Keywords: Charcot-Marie-Tooth Disease, Ultrasound, Biomarkers, Clinical Trial Readiness

Testing SARM1 Inhibition In Three Mouse Models Of Charcot-Marie-Tooth Disease

Poster No:
P 100

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Introduction:
Charcot-Marie-Tooth (CMT) disease is a genetic peripheral neuropathy characterized by axon degeneration and/or demyelination of the peripheral neurons. The longest axons are the most affected, but it is still unclear why axons eventually degenerate. SARM1 is an NAD+-cleaving enzyme that is a key effector of Wallerian axon degeneration. Previous studies demonstrate that inhibition of SARM1 prevents axon degeneration in injury, glaucoma, and chemotherapy, for instance, but SARM1 inhibition has not been widely tested in genetic forms of neuropathy. To this end, our goal is to identify potential effects of SARM1 inhibition in three mouse models of axonal CMT.

Methods:
We are utilizing three existing mouse models of CMT, each treated to inhibit SARM1 using an AAV construct carrying dominant-negative SARM1. Virus is delivered neonatally by intracerebroventricular injection. The first model is CMT2D/GARS-DETAQ. These mice carry a patient-associated mutation in the glycyl tRNA synthetase (Gars) that results in decreased translation and downstream activation of the integrated stress response and eventual loss of peripheral motor and sensory neurons. Our second model is CMT2E/Nefl-N98S, which disrupts the trafficking of neurofilament light-chain (as well as other neurofilaments) into the axon, leading to axon degeneration. The final model is CMT2S/Ighmbp2-Y918C, which is a recessive mutation in the Ighmbp2 gene that recapitulates the patient-associated Y920C allele, causing loss of motor axons and reduced muscle strength. The mechanism through which this mutation affects peripheral motor neurons is largely unknown. Treated mice and untreated littermate controls will be aged appropriately and several clinically relevant behavioral, physiological, histological, and electrophysiological outcomes will be assessed.

Results:
These experiments are ongoing. Cohorts containing a minimum of 6 mice per sex per treatment group per genotype have been dosed and will be analyzed in early 2024 for CMT2D/Gars and CMT2E/Nefl mice. Treatment is ongoing for CMT2S/Ighmbp2 mice.

Conclusions:
See Results.

References:
No

Keywords: SARM1, Charcot-Marie-Tooth, Mouse genetics

The underrated value of white blood cells to study neuropathic diseases exemplified on CMT4C

Poster No:
P 101

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Introduction:
Biochemical, histological, and ultra-structural studies are standard procedures in the diagnostic work-up of muscle and nerve biopsies of neuromuscular patients and represent important biomedical research approaches. However, the investigation of tissue biopsies also harbours limitations: sampling is invasive, amount of tissue is often limited, and biopsies can only provide a snapshot of the disease at a given timepoint. Previous studies on certain diseases already emphasized the potential of white blood cells (WBC) in the diagnostics and research of neuromuscular diseases including neuropathies.

Methods:
To further elucidate the potential of WBC in the context of neuromuscular diseases, particularly neuropathies we applied mass spectrometry.

Results:
We catalogued 211 neuromuscular relevant proteins expressed in WBC: for hereditary motoneuron disorders (consisting of (distal) spinal muscular atrophy, and hereditary moto-neuropathies), 75.5% of relevant proteins were identified. For hereditary motor sensory neuropathies, 71.4% relevant proteins were identified including SH3TC2. We confirmed SH3TC2 expression in WBC by targeted proteomics using reference peptides. Prompted by the unexpected SH3TC2 abundance in WBC, we next investigated the proteomic signature of WBC derived from four Charcot-Marie-Tooth type 4C patients with confirmed bi-allelic SH3TC2 variants and identified the dysregulation of 667 proteins (365 increased and 302 decreased). In line with the known function of SH3TC2 as a RAB11-modulator, many affected proteins are involved in endosomal functions and vesicular transport machinery hinting toward a particular affection of ESCRT-III (endosomal sorting required for transport complex III) and cargo loading into COPII-coated vesicles as well as of vesicle-mediated protein trafficking to lysosomal compartments and autophagic pathways. Of note, proteomic data also unveil a profound dysregulation of GTPases and Rab GTPase-activating proteins which among others play a role in vesicular trafficking.

Conclusions:
Hence, our combined data highlight the potential to study pathophysiological processes of neuropathies for certain subtypes in a minimal-invasive manner as demonstrated here for CMT4C.

References:
No

Grant Support:

German Society for Muscular Diseases (grant to AR)

Keywords: CMT4C, SH3TC2, Proteomics, White blood cells, Liquid biopsy

Novel genetic and biochemical insights into the spectrum of NEFL-associated phenotypes

Poster No:
P 102

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Introduction:
Neurofilament-accumulation is a hallmark of many neurodegenerative disorders. NEFL encodes for the neurofilament light chain protein. Pathogenic variants cause demyelinating, axonal and intermediate forms of Charcot-Marie-Tooth disease (CMT) which present with a varying degree of severity and somatic mutations have not been described yet. Muscular involvement was also described in CMT2E patients mostly as a secondary effect. Also, there are a few descriptions of a primary muscle vulnerability upon pathogenic NEFL variants.

Methods:
To expand the current knowledge on the genetic landscape and muscle cell vulnerability in NEFL-related neurological diseases, we applied phenotyping, molecular genetic testing, light-, electron- and Coherent Anti-Stokes Raman Scattering-microscopic studies and proteomic profiling in addition to in silico modelling of NEFL-variants.

Results:
We report on a boy with a muscular phenotype (weakness, myalgia and cramps, Z-band alterations and mini-cores in some myofibers) associated with the heterozygous p.(Phe104Val) NEFL-variant, which was previously described in a neuropathy case. Skeletal muscle proteomics findings indicated affection of cytoskeletal proteins. Moreover, we report on two further neuropathic patients (16 years old girl and her father) both carrying the heterozygous p.(Pro8Ser) variant, which has been identified as 15% somatic mosaic in the father. While the daughter presented with altered neurophysiology, neurogenic clump feet and gait disturbances, the father showed clinically only feet deformities. As missense variants affecting proline at amino acid position 8 are leading to neuropathic manifestations of different severities, in silico modelling of these different amino acid substitutions indicated variable pathogenic impact correlating with disease onset.

Conclusions:
Our findings provide new morphological and biochemical insights into the vulnerability of muscle as well as novel genetic findings expanding the current knowledge on NEFL-related neuromuscular phenotypes and their clinical manifestations. Along this line, our data show that even subtle expression of somatic NEFL variants can lead to neuromuscular symptoms.

References:
No

Grant Support:

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Keywords: neurofilament light chain, protein accumulation, muscle proteomics, somatic mutation, CARS microscopy muscle

Screening Of Hereditary Amyloidosis In Non Endemic Areas: One Step Ahead Of Symptoms

Poster No:
P 103

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Introduction:
Amyloidosis is a deadly disorder caused by misfolded fibrillar aggregates in human tissues. In untreated patients life expectancy is reduced to 2 to 10 years after symptoms onset. The most common aggregated proteins are light chains (AL-Amy), old age wild-type transthyretin (WT-Amy) and mutated transthyretin (hATTR-Amy). Clinical manifestations of hATTR-Amy depend on the specific TTR gene mutations, in a continuum evolving from the most cardiological to the most neurological semiological symptoms. Carpal tunnel syndrome is one of the earliest neurological manifestations, but it is the less specific symptom, so much common worldwide, but can become a very sensitive marker, combining electrodiagnostic tests with guided questionnaires in the routinary setting of the neurophysiological laboratory.

Methods:
We developed a questionnaire to be applied by neurophysiology technicians and neurophysiologists in the routinary setting of the neurophysiological laboratory while performing an electrodiagnostic test for carpal tunnel syndrome, to screen for hereditary amyloidosis in non endemic areas. The items investigate signs and symptoms of neuropathy, vertebral stenosis, autonomic neuropathy, cardiac disorders or biceps brachialis tendon fracture. If 2 red flags are present in a patient affected by bilateral carpal syndrome, neurologists can recommend the oral swab for genetic testing (to be done immediately). In the medical report it is advisable to extend differential diagnosis, by suggestion of serum protein electrophoresis for AL-Amy and/or cardiological evaluation.

Results:
We identified 2 WT-Amy and 1 is waiting for genetic confirmation for hATTR, on 170 patients in 6 months. This approach can reduce diagnostication delay and improve prognosis.

Conclusions:
Carpal Tunnel syndrome may be a clinical predictive indicator of interest because increased awareness of CTS as an ATTR-associated manifestation can enable anticipation of 10 years on diagnosis of this fatal disorder. Neurologists should make an effort to be one step ahead of symptoms in clinical practice, even in carpal tunnel syndrome.

References:
Yes

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Keywords: amyloidosis, neurophysiology, carpal tunnel syndrome, screening, non endemic areas

Acquired transthyretin amyloidosis in domino liver transplantation treated with patisiran

Poster No:
P 104

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Introduction:
Hereditary transthyretin amyloidosis (ATTRv amyloidosis; v for variant) is an autosomal dominant disease caused by mutations in the transthyretin (TTR) gene. Recently new therapeutic strategies have dramatically changed the prognosis of ATTRv but the first therapeutic approach was orthotopic liver transplantation (OLT). The livers of ATTRv patients are fully functional except for the production of the mutated TTR protein, so they are often transplanted into patients with terminal liver failure. We report on a patient who underwent OLT and developed a severe acquired-ATTRv, responsive to patisiran.

Methods:
In 2012 a 65-yr-old diabetic man underwent OLT because of hepatocellular carcinoma on hepatitis C-related cirrhosis. Nine years after OLT (June 2021), he complained of paresthesia at fingertips that gradually extended to hands, legs, and feet bilaterally. From January 2022 motor impairment in the hands (inability to tie shoes or button shirts) and unsteadiness in walking appeared. Orthostatic hypotension, erectile dysfunction and weight loss occurred. Neurophysiological studies revealed axonal sensory-motor polyneuropathy and bilateral carpal tunnel syndrome, which were attributed to diabetes. Neurotoxicity of the immunosuppressants taken for OLT was hypothesized, and tacrolimus discontinued with no benefit.

Results:
When we first saw the patient (October 2022) he had diffuse severe strength, hypoesthesia and areflexia. Neuropathy Impairment Score was 79.75. Neurophysiology revealed severe sensory-motor axonal polyneuropathy with diffuse denervation. Nerve ultrasound showed no changes. Molecular analysis of TTR gene resulted negative. Medical records analysis confirmed that the liver donor was a patient with ATTRv, carrying the Glu54Gln mutation. Serum NT-proBNP and troponin I were increased. Electrocardiogram showed right bundle branch block, and echocardiogram biventricular thickening. The patient was diagnosed with acquired-ATTRv. Gene silencing therapy with patisiran was started with progressive improvement in the following 12 months.

Conclusions:
OLT patients should undergo close follow-up and be made aware of possible complications so to prompt early detection of acquired-ATTRv.

References:
No

Keywords: Hereditary transthyretin amyloidosis

Phenotypical variability in family members homozygous for the TTR p.Val142Ile (V122I) variant.

Poster No:
P 105

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Introduction:
The heterozygous TTR p.Val142Ile (V122I) variant is the most common genetic cause of cardiac amyloidosis in Brazil but little is known about the consequences of the homozygous phenotype. This study aimed to describe the phenotype and the outcomes of homozygous patients belonging to the same Brazilian family.

Methods:
Descriptive study of a series of cases carrying homozygous ATTRv V122I amyloidosis.

Results:
We report 5 homozygous members of a family with 18 affected people carrying the V122I mutation (5/18 – 27.8%). The first cases were a 56-year-old woman (Case 1) and a 59-year-old man (Case 2), presenting with progressive dyspnea. Both had a low-voltage electrocardiogram and significant diastolic dysfunction, thickening of the left ventricular wall, diffuse hypokinesia and reduced ejection fraction on echocardiography. Myocardial scintigraphy with pyrophosphate confirmed amyloid deposits in case 2. The cardiac involvement began before the age of 60 and both progressed to death in less than 5 years. Neurologic evaluation was not performed. Case 3 is a 68-year-old woman and case 4 a 69-year-old man both complaining of paresthesia and burning feet for 8 and 3 years respectively. Examination detected a distal length-dependent hypoesthesia. Electroneuromyography showed an axonal sensory polyneuropathy, associated to bilateral carpal tunnel syndrome. Cardiac evaluation was normal in these cases. Case 5 is a 74-year-old woman with distal sensory symptoms and postural hypotension for two years. Neurological examination confirmed the presence of hypoesthesia and distal weakness, postural instability and difficulty walking. ENMG highlighted a severe chronic axonal sensorimotor polyneuropathy, with acute denervation. Echocardiogram showed discrete signs of diastolic dysfunction and thickening of left ventricular wall.

Conclusions:
This rare, homozygous V122I series of cases showed that homozygosity is associated to variable age of onset, clinical presentation and progression.

References:
No

Keywords: amyloidosis, transthyretin

Modeling Charcot-Marie-Tooth Disease: Insights from hiPSC-Derived Motor Neuron Spheroids with GDAP1 Variant

Poster No:
P 106

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Introduction:
Charcot-Marie-Tooth Disease (CMT) is the most common inherited neuropathy characterized by peripheral nerve degeneration, for which therapeutic opportunities are limited. More than 100 altered genes have been identified as responsible for this disease. These genes are predominantly expressed in neuronal cells, which complicates their study. To investigate the physiopathology of the disease and test new therapeutic approaches, it is essential to develop appropriate and physiologically relevant cellular models.

Methods:
Our goal was to develop a novel in vitro model to investigate the physiopathological mechanisms underlying CMT, with a particular focus on the axonal form of CMT caused by a pathogenic variation in GDAP1. To achieve this, we generated motor neuron spheroids from human induced pluripotent stem cells (hiPSCs) derived from a CMT patient carrying the pathogenic variation p.Ser194* in GDAP1. hiPSCs differentiation progression towards a neuronal lineage in spheroids was assessed using qPCR and immunolabeling methods. GDAP1 expression was checked with the same methods, and its contribution to motor neurons' functionality was assessed.

Results:
Through qPCR and immunolabeling techniques, we evaluated the evolution of hiPSCs towards a neuronal fate in spheroids. In addition, we confirmed a significant reduction in the expression of GDAP1 within patient-derived cells, providing a direct link to disease pathology. Our preliminary functional assessments revealed that GDAP1 mutation had a discernible impact within the spheroid model.

Conclusions:
Overall, our study highlights the importance of developing physiologically relevant models for a deeper understanding of CMT and the pursuit of effective treatments. Building on these findings, our future endeavors will aim to further enhance the complexity of our model system by establishing an all-human in vitro neuromuscular junction in a customized microfluidic chip.

References:
No

Keywords: Charcot-Marie-Tooth disease, In vitro models, Motor neuron spheroids, GDAP1 variant

Virtual CMT Infant Toddler Scale (vCMTInfS); A Remote Evaluation of Infants/Toddlers with CMT

Poster No:
P 107

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Introduction:
Many CMT subtypes present in early childhood, an ideal time to intervene therapeutically before demyelination and axonal loss occur. While the CMTInfS scale enables evaluation of such patients in clinic there is a need to evaluate infants/toddlers who are unable to attend clinic. The aim of this study was to evaluate the feasibility of the vCMTInfS.

Methods:
Following informed consent, children under 4 years were evaluated remotely in their home using Zoom. vCMTInfS was performed identically to the CMTInfS. All testing items were sent to the parents/caregivers for the assessment. The remote examiner directed activities comprising the 15 item vCMTInfS with assistance from the parent while scoring the exam items. vCMTInfS scores were calculated using the CMTInfS calculator available at www.clinicaloutcomemeasures.org. A z-score <1 was considered normal, 1-2 mild-moderate and >2 indicated severe impairment.

Results:
Eight children from 18 months to four years of age (two females, six males) with a variety of CMT types (1A, 2A, 1E, 4B3, unknown) were evaluated. Six children scored as age appropriate, 2 were in the moderate and 4 in the severely affected range when including baseline and follow-up tests. Reproducibility of the vCMTInfS was assessed after 1 month in 5 individuals. Fatigue and time of day contributed to inconsistencies in scores but overall the scale was reproduceable. Other factors which could be modified in the future to improve cooperation include turning off examiner video/use of headphones with parent if intimidating for the infant.

Conclusions:
These cases demonstrate the feasibility of performing vCMTInfS virtually as if we were performing the evaluation in clinic though steps to maximize cooperation and preparation proved essential. The scale distinguished different levels of severity and can provide baseline data in very young children in a remote setting where children and their families will not need to travel to specialty clinics.

References:
No

Grant Support:

The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01)

Keywords: Outcome, Infant, Virtual, CMT

Investigating Ferroptosis and Altered Antioxidant Signaling in Charcot-Marie-Tooth Disease Type 1A

Poster No:
P 108

Authors:
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Introduction:
Charcot-Marie-Tooth type 1A (CMT1A), the most prevalent inherited peripheral neuropathy, is caused by the overexpression of peripheral myelin protein 22 (PMP22). This overexpression of PMP22 is known to downregulate lipid and cholesterol metabolism and overwhelm the autophagic system in Schwann cells. PMP22 expression in Schwann cells is essential in regulating cholesterol transport and organizing lipid rafts on the cell membrane, which is crucial for the formation and maintenance of functional myelination. Among these alterations, polyunsaturated fatty acids (PUFAs) are enriched in Schwann cell membranes, which we hypothesize to trigger lipid peroxidation and subsequent ferroptosis, a novel form of regulated cell death characterized by iron-dependent lipid peroxidation. The current research explores the pathological mechanisms and characterizes the link between lipid metabolism alterations, dysregulation of antioxidant signaling and ferroptosis in patient-derived cells with PMP22 overexpression.

Methods:
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Results:
Our study employed CMT1A mice and an iPSC-based protocol for differentiating Schwann cells and Schwann cell precursors (SCPs) to elucidate CMT1A pathogenesis. By using these models, we revealed the specific vulnerability of Schwann cells to lipid peroxidation and ferroptosis. iPSC-SCPs from CMT1A patients demonstrate heightened susceptibility to ferroptosis, coupled with the production of lipid peroxidation end products. Moreover, RNA-seq analysis on SCPs unveiled a significant alteration in the antioxidant system, particularly affecting the catalase-glutathione peroxidase pathway, which were confirmed through Western blot and immunocytochemistry analysis.

Conclusions:
These results indicate that PMP22 overexpression impacts antioxidant pathways, compromising the ability of Schwann cells to counteract reactive oxygen species, which may exacerbate oxidative stress and the formation of lipid peroxides. These changes likely contribute to CMT1A pathogenesis by disrupting the initiation of the myelination program, impeding the proper maturation of Schwann cells and inducting ferroptosis.

References:
No

Grant Support:

FWO PhD Fellowship fundamental research (Belgium)

Keywords: CMT1A, Lipid, Schwann cell, Ferroptosis, Antioxidants

Novel drugs alleviate autophagy deficits in mutant HSPB1 and HSPB8-linked peripheral neuropathies through SQSTM1 dynamics

Poster No:
P 109

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Introduction:
The small heat shock proteins HSPB1 and HSPB8 play crucial roles in regulating protein homeostasis, impacting the entire protein lifespan. HSPB1, by directly interacting, controls SQSTM1 phase separation in p62 bodies, while HSPB8 is involved in chaperon-assisted selective autophagy (CASA) that targets misfolded proteins for degradation. Both proteins promote autophagosome formation, but mutations in HSPB1 and HSPB8 lead to dysfunctional autophagy, contributing to hereditary peripheral neuropathies and myopathies.

Methods:
In a drug repurposing screening on mutant HSPB1 and HSPB8 backgrounds, we identified compounds rescuing autophagy deficits in K141N Hspb8 mouse embryonic fibroblasts and HSPB1_P182L or HSPB8_K141N patient iPSC-derived motor neurons. The mechanism by which these drugs prevent toxic gain-of-function activity in HSPBs remains unclear. High-content imaging quantified p62 bodies and preautophagosome structures, assessing drug effects on autophagy induction. We also examined changes in p62 distribution in the presence of the P182L mutant HSPB1 upon drug treatment.

Results:
In Hela cells and patient iPSC-derived motor neurons with the HSPB1 P182L mutation, SQSTM1/p62 accumulates significantly in the cellular insoluble fraction, alongside autophagy receptors SQSTM1/p62 and NDP52. The P182L mutation reduces SQSTM1/p62 mobility in p62 bodies. Newly identified drugs increased p62 body formation and degradation, therefore enhancing neuronal network density and reducing axonal blebbing in HSPB1_P182L and HSPB8_K141N neuronal lines.

Conclusions:
The identification of therapeutic strategies for various peripheral neuropathy subgroups is challenging. We identified compounds that rescue autophagy activity impairments in mutant HSPB1 and HSPB8 cellular models, offering potential interventions for aberrant HSPB functioning in autophagy and enhancing neuronal proteostasis in Charcot-Marie-Tooth patient motor neurons by restoring SQSTM1/p62 dynamics.

References:
Yes

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Keywords: small heat shock proteins, autophagy, SQSTM1/p62, CMT, drug discovery

Foot Ulceration in Patients with Charcot-Marie-Tooth Disease and Related Disorders

Poster No:
P 110

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Introduction:
Foot ulceration is a prevalent complication in patients diagnosed with Charcot-Marie-Tooth (CMT) disease and related disorders predominantly driven by sensory loss and structural foot deformities. The combination of peripheral neuropathy, the resulting muscular imbalance, and altered foot biomechanics contributes to the development of pressure points and skin breakdown, leading to foot ulceration and consequently increased morbidity. Aim: To assess prevalence of foot ulceration in patients with CMT and related disorders attending our center and identify incidence in different genetic subtypes and associated risk factors.

Methods:
We interrogated our clinical data base and clinical records retrospectively for patients attending our inherited neuropathy clinics.

Results:
Out of 1982 patients with CMT and related disorders attending our clinics, 101 (5%) reported having ulcers. Among these, 70 (69%) were male, and 32 (31%) were female; average age was 48 (range 16-75). Impairment, as measured by CMT Examination Score (CMTES), was on average (± SD) 15.45 (± 5.49), (range 3 - 30). Among these patients, 52 (51%) were diagnosed with hereditary sensory neuropathy (HSN), with the majority (38/52) of patients diagnosed with HSN due to SPTLC1 and SPTLC2 variants (73%); whereas 48 (48%) were diagnosed with CMT. Of those, 33/48 (68%) had CMT1A due to the PMP22 duplication. 58% (59/101) of patients reporting ulcers had foot deformities, with pes cavus being most common, accounting for 70% (41/59). Decreased ability to feel was reported by 95% (96/101) of all patients.

Conclusions:
Addressing foot care through preventative measures such as patient education, orthotic interventions, footwear modifications are crucial to mitigate the risk of ulcerations and prevent associated complications. In addition, referral to podiatry services for regular foot care management is a very important part of multidisciplinary approach to CMT and related disorders.

References:
No

Grant Support:

N/A

Keywords: CMT, Foot ulceration

An Afghanistan family with early-onset, progressive motor neuronopathy

Poster No:
P 111

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Institutions:
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Introduction:
Consanguineous marriages are common in Afghanistan, resulting in high prevalence of autosomal recessive disorders.

Methods:
A case report, illustrated with clinical images and cloud-linked videos.

Results:
A 21 year-old-man complains of progressive generalized weakness, dysphagia and dysarthria for 7 years. He has increased tone, pyramidal and extrapyramidal, clonus and diffuse hyper-reflexia. Babinski's reflex is present and he has mild pyramidal-pattern weakness, worse on the right. No objective sensory loss is detected. He has tongue wasting and fasciculations with brisk jaw jerk. His 26 years-old sister has similar but more overt signs, worse on the left. She also has prominent chin fasciculations and a dystonic left toe that manifests fascicular tremor. She is cognitively impaired. Compound muscle action potentials are reduced in lower limbs. Sensory studies are normal. Needle EMG shows chronic neurogenic motor units in bulbar, lumbosacral and cervical myotomes and, only in the sister, action induced fasciculations. MRI brain in the younger sibling shows mild frontal predominant atrophy. We are currently delineating the clinical and electrodiagnostic features of the extended family in Ghazni province of Afghanistan. The patients are of Hazara ethnicity.

Conclusions:
Our patients have an early-onset motor disorder, characterised by a combination of signs associated with primary amyotrophic lateral sclerosis, frontotemporal dementia and corticobasal degeneration. This pattern is classically seen in TDP-43 pathology, due to repeat expansion of the C9orf72 gene. We hope to find the resources to confirm the genetic pathology. Diagnostic nihilism of genetic disorders is common in under-resourced regions. Accurate genetic confirmation permits optimal management and appropriate genetic counselling of patient. It also stops blind therapeutic trials that may be costly and risk adverse effects. International academic bodies, such as PNS, could consider improving access to basic genetic diagnoses in developing countries as their remit.

References:
No

Keywords: PLS, motor neurone disease, FTD, CBD, TDP-43, C9orf72,

Mendelian Inherited Charcot-Marie-Tooth Disease Caused by Digenic Mutations

Poster No:
P 112

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Introduction:
Charcot-Marie-Tooth disease (CMT) is a group of genetically and clinically heterogeneous disorders group which is characterized by distal weakness, muscular atrophy, and loss of sensation. Although CMT is known as a simple Mendelian inherited disease by a monogenic mutation, rare cases with digenic mutations have been reported. The study aims to unravel the implications of simultaneous mutations in two distinct genes within affected individuals.

Methods:
The methodology comprises clinical and electrophysiological examinations, utilizing nerve conduction velocities and various scoring systems. Genetic analysis involved whole exome sequencing and targeted gene panel sequencing, and Sanger sequencing that showing symptoms of peripheral neuropathy for the affected or single mutation-carrying individuals in the selected families. In silico prediction and conservation analyses provided insights into mutation effects.

Results:
This study identified nine CMT families with digenic mutations, involving simultaneous alterations in GDAP1 and MFN2. These families exhibit a striking spectrum of symptoms, even within familial contexts, challenging the conventional understanding of CMT as a straightforward Mendlian disorder. Clinical and electrophysiological analyses within these families also highlight the complexity and variability associated with digenic mutations. Based on one or more in silico analyses, mutations were predicted to be pathogenic.

Conclusions:
The findings emphasizes the importance of considering multiple genetic factors in the diagnosis and classification of CMT, offering valuable insights for future genetics studies and therapeutic interventions targeting this complex neurological disorder.

References:
Yes

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Grant Support:

This research was supported by grants from the National Research Foundation (2021R1A4A2001389).

Keywords: Peripheral neuropathy, Genetic disorder, WES, In silico, Pathogenic

Charcot-Marie-Tooth disease: clinical, electrophysiological and genetic study of 159 Moroccan Families

Poster No:
P 113

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Institutions:
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Introduction:
Charcot–Marie–Tooth (CMT) and related hereditary neuropathies are the commonest group of inherited neuromuscular disorders worldwide. They are characterized by wide genetic and phenotypic heterogeneity.

Methods:
This is a longitudinal descriptive study including 238 patients from 159 Moroccan families collected from our department of Clinical Neurophysiology from January 1997 to 2023. Clinical, electrophysiological, and genetic data were analyzed and compared among genetic subgroups.

Results:
Axonal CMT form was found in 41,7% of our patient with R298C LMNA mutation ranking first before GDAP1 (25,3 vs 19%). The remaining cases was classified as demyelinating (45,5%), intermediate (5,5%) or pure motor form (17,5%). PMP 22 duplication was the most frequent genetic diagnosis (32,9%) followed by GDPA1 and LMNA gene mutation in 29,1% and 25,3% respectively. Mutations in GDPA1 correspond more to homozygous S194X mutation and less frequently to homozygous P78L mutation or to both mutations in composite state. Homozygous P78L mutation was related to the demyelinating form of neuropathy. Mutations in four other genes were identified but they were less frequent. The mode of inheritance was recessive in 42% of the patients and dominant in 28,9%. 26,9% of the patients were isolated cases. Beside the classical CMT phenotype, our patients exhibit some additional and less common clinical and electrophysiological features.

Conclusions:
Herein, this study exemplifies the genetic distribution and the phenotypic particularity of CMT neuropathy in moroccan populations. However, it presents some limitations since molecular diagnosis was accomplished in only 37 of 159 families (23,3%).

References:
No

Keywords: CMT, phenotypes, genetic mutations

Sphingolipid serum analysis assists in the diagnosis of SPTLC2 Causing Hereditary Sensory Autonomic Neuropathy Type 1C

Poster No:
P 114

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Institutions:
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Introduction:
Hereditary sensory and autonomic neuropathy type 1 (HSAN-1) is an axonal predominant peripheral neuropathy generally presenting from the second decade of life, characterised by autonomic involvement, sensory loss, neuropathic pain, limb weakness and occasionally complicated by ulcerations. HSAN-1 develops secondary to mutations in serine-palmitoyltransferase (SPT) a heteromeric protein consisting of three subunits (SPTLC1, 2, and 3). Mutations in the SPTLC1 of the enzyme, are designated as HSAN-1A and SPTLC2 mutations classified as HSAN-1C. SPT is the first enzyme in the de novo sphingolipid biosynthetic pathway and pathogenic mutations in SPTLC1 or SPTLC2 lead to the formation of atypical and neurotoxic 1-deoxysphingolipids. Liquid Chromatography Tandem Mass Spectrometry (LCMS) reveals the presence of elevated plasma levels of 1-deoxysphingolipids in HSAN1 patients.

Methods:
Review of clinical, neurophysiological, genetic and LCMS evaluations in a single patient.

Results:
A 14-year-old female presented for evaluation with a painful sensorimotor neuropathy associated with recurrent limb ulcerations. Onset was at two years of age. Medical history included seizures and non-epileptic behavioural spells. Family history was unavailable given a history of adoption. Examination revealed length dependent weakness of the upper and lower limbs with absent Achilles and reduced quadriceps reflexes. Large and small fibre sensation was absent to the level of the elbows and knees. Extremity nerve conduction responses were absent, and EMG supported an axonal predominant length dependent polyneuropathy. Next generation genetic analysis revealed three variants of uncertain significance (1) SPTLC2 c.1481T>C(p.Val494Ala), (2) GARS c.1760C>T(p.Thr387Met) and (3) MED25 c.247C>G(p.Gln83Glu). Sphingolipid analysis performed by LCMS revealed accumulation of atypical and neurotoxic sphingoid metabolites 1-deoxy-sphinganine and dihydrosphingosine 1-phosphate, and diminished levels of normal metabolites sphingosine and sphinganine.

Conclusions:
LCMS revealed an abnormal sphingolipid profile in keeping with a loss of function of SPT activity, and supports SPTLC2 c.1481T>C(p.Val494Ala) being a novel pathogenic mutation associated with HSAN-1C.

References:
No

Keywords: Hereditary sensory and autonomic neuropathy, sphingolipids, Liquid Chromatography Tandem Mass Spectrometry (LCMS)

Health-Related Quality of Life in Charcot-Marie-Tooth Disease in Japan

Poster No:
P 115

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Institutions:
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Introduction:
This study aimed to assess the health-related quality of life (HRQoL) in Japanese patients with Charcot-Marie-Tooth Disease (CMT).

Methods:
We have run the online Japan CMT patient registry to elucidate the natural history of CMT patients in Japan, which includes the Short-Form 36 (SF-36) questionnaires to assess an HRQoL scale. We analyzed SF-36 scores obtained from Japanese CMT patients from February 2021 to August 2023.

Results:
The answers from 141 CMT patients (81 men and 60 women) were analyzed. The median age of subjects was 55 (interquartile range (IQR) 43.5–64). The median of the Overall Neuropathy Limitation Scale (ONLS) was 2 (IQR 1–3) for the arm grade and 2 (0–4) for the leg grade. CMT genetic subtypes were as follows: PMP22 duplication (28.4%), GJB1 (7.1%), MFN2 (5.7%), MPZ (5.7%), other genes (14.9%), and unknown (38.3%). All CMT patients' mean scores were lower than those of the national average based on Japan's nationwide survey. Specifically, the mean Physical Functioning (PF) score of CMT patients was prominently lower than that of the general population. The SF-36 scores in Japanese CMT patients showed a similar trend to those previously reported in other countries. The subgroup of CMT patients who reported having pain had significantly lower Body Pain (BP), Role Physical (RP), and General Health (GH) than the subgroup without pain. The PF, RP, BP, GH, Social Functioning (SF), and Role Emotional (RE) scores correlated negatively with the arm grade scores of the ONLS, while only PF and RP correlated with the leg grade scores. There was no correlation between each SF-36 score and onset age or disease duration.

Conclusions:
This study is the first to evaluate the HRQoL of CMT patients in Japan. Low physical performance mainly impaired the QoL of the patients. Additionally, upper limb dysfunction and pain can affect the HRQoL of CMT patients.

References:
Yes

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Grant Support:

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Grants-in Aid from the Research Committee of CNS Degenerative Diseases, Research on Policy Planning and Evaluation for Rare and Intractable Diseases, Health, Labour and Welfare Sciences Research Grants, the Ministry of Health, Labour and Welfare, Japan.

Keywords: Charcot-Marie-Tooth Disease, registry study, health-related quality of life, SF-36

Neuromodulation Effects of Targeted Gene Therapy in Hereditary Neuropathies

Poster No:
P 116

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Introduction:
Hereditary neuropathies, including Charcot-Marie-Tooth disease, present significant challenges due to their genetic basis and lack of curative treatments. This study explores the efficacy of a novel gene therapy technique targeting specific mutations associated with hereditary neuropathies

Methods:
Utilizing a CRISPR-Cas9 based gene-editing approach, the study targets mutations in a cohort of induced pluripotent stem cells (iPSCs) derived from patients with confirmed hereditary neuropathies. The edited iPSCs were differentiated into peripheral neurons and assessed for functional and structural improvements. Additionally, a pilot in vivo study was conducted on a small animal model.

Results:
In vitro studies showed successful targeting and editing of pathogenic mutations. Treated neurons demonstrated improved axonal growth, increased myelin thickness, and enhanced electrical conductivity compared to controls. Preliminary in vivo results indicate improved motor function and reduced neuropathic symptoms in treated models, without significant adverse effects.

Conclusions:
The results provide promising evidence that targeted gene therapy could be an effective approach in treating hereditary neuropathies. This study not only showcases the potential of CRISPR-Cas9 in genetic modulation but also opens new avenues for personalized medicine approaches in the treatment of peripheral nervous system disorders.

References:
No

Keywords: CRISPR-Cas9 Gene Therapy, Hereditary Neuropathies Treatment, Peripheral Neuron Regeneration, Personalized Medicine in PNS Disorders

Development Of Standardized Human-derived Myelin Containing Neuromuscular Organoids As A Reference Model For CMT1A

Poster No:
P 117

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Institutions:
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Introduction:
Charcot-Marie-Tooth (CMT) disease is the most common hereditary peripheral neuropathy, affecting about 1 in 2500 people. We have previously established a therapy testing platform, SCREEN4PN, comprising of CMT patient-derived motor neurons generated from induced pluripotent stem cells (iPSCs). Our platform has proven successful in testing various therapeutic compounds. To enhance the translatability of our readout methods, we are currently incorporating neuromuscular organoids derived from CMT1A iPSC lines. Thorough characterization, optimization and standardization of these organoids are essential to develop a reproducible testing platform, partially due to the heterogeneity of the CMT1A disease phenotype.

Methods:
To characterize the organoids, we employ organoids differentiated from control iPSC lines, CMT1A patient iPSC lines and corresponding isogenic controls. Various standardization (e.g., implementation of quality control measures) and optimization (e.g., freezing/vitrification) steps are currently being performed. Furthermore, pathological phenotypes are being characterized by, but not limited to, imaging (immunostaining and transmission electron microscopy) and biochemical (western blotting and qPCR) assays.

Results:
CMT1A neuromuscular organoids allow the investigation of the amelioration of disease-associated myelin defects after supplementation of therapeutic compounds. In 2024, we aim to fully characterize the pathological features in various CMT1A neuromuscular organoids, with a great focus on the maturation level of the Schwann cells. Furthermore, we strive to optimize and standardize our organoid protocol to establish a reproducible validation platform.

Conclusions:
The development of a reference CMT1A organoid model will allow SCREEN4PN to test potential therapeutics in a highly efficient and cost-effective manner. Our standardized protocol will allow us to generate a consistent model, which is pivotal to the assessment of the heterogeneity of CMT1A. The opportunity to investigate neuromuscular organoids which closely mimic the in vivo disease phenotype, will elevate SCREEN4PN to an even higher level.

References:
No

Grant Support:

The American CMT Association
The Industrial Research Fund, University of Antwerp

Keywords: Charcot-Marie-Tooth disease, Neuromuscular Organoids, Standardization, CMT1A Heterogeneity, Therapeutics testing

A Comprehensive Update of the Inherited Neuropathy Consortium (INC) of the Rare Diseases Clinical Research Network

Poster No:
P 118

Authors:
Kailee Ward[1], Nicole Kressin[1], Michael E. Shy[1], Tiffany Grider[1], Amanda Dragon[2], Thomas Woodford[1]

Institutions:
[1]University of Iowa, Iowa City, IA, [2]University of Iowa Carver College of Medicine, Iowa City, IA

Introduction:
The Inherited Neuropathy Consortium (INC) is composed of 20 active sites and 5 sites in start-up that evaluate patients with Charcot-Marie-Tooth disease (CMT) and maintain data pulled from clinical visits in a standardized manner.

Methods:
Clinical information from patient visits is electronically maintained in a database through a centralized data management center. DNA samples from INC sites are tested for identification of potential new forms of CMT and genetic modifiers of CMT1A. Current projects include: Natural History Evaluation of Charcot-Marie-Tooth disease (with particular emphasis on CMT1B, CMT2A, CMT4A, and CMT4C); Genetics of CMT; CMT Peds Scale for Children with CMT; CMT Infant Scale (CMTInfS); Digital Measures of Physical Activity, Gait and Balance in CMT; Development of Virtual CMTInfS; and Development of Virtual Evaluations into Additional Languages.

Results:
These projects have helped create validated outcome measures to use in clinical trials. Additionally, over the past 12 years, the INC has identified over half of all genes currently known to cause CMT. The INC has evaluated 7,856 patients for the Natural History Evaluation of CMT; 2,952 of these patients also participate in the Genetics of CMT; 1,074 participate in the Pediatric study; 69 participate in the Infant study, and 308 participate in the Digital Measures study. All these studies are actively recruiting. The INC also partners with patient advocacy groups (PAGs) to enhance patient knowledge and establish connections between patients, researchers, and physicians. These groups include the Muscular Dystrophy Association, the Charcot Marie Tooth Association, CMTUK, ACMT-Rete, Hereditary Neuropathy Foundation, CMT Research Foundation, and Telethon from Italy.

Conclusions:
Through development of validated outcome measures, curation of an extensive longitudinal CMT database, and investigation into new genetic factors of CMT, the INC has contributed to the current understanding of the causes and outlook of CMT for medical and patient communities alike.

References:
No

Grant Support:

The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01). The INC also receives funding from the Muscular Dystrophy Association and the Charcot-Marie-Tooth Association.

Keywords: CHarcot-Marie-Tooth, CMT, Genetics, Neuropathy

Phenotypic Presentation of Patients with Charcot-Marie-Tooth Disease type 1E Evaluated at the University of Iowa CMT Clinic

Poster No:
P 119

Authors:
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Introduction:
CMT type 1E is caused by variants within the PMP22 gene. Prior reports show that phenotypes vary depending on the particular variant, ranging from mild to severe. This study aims to serve as a baseline for longitudinal data for the natural history analysis of CMT1E.

Methods:
The baseline visits of patients with genetically confirmed CMT1E seen at the University of Iowa CMT Clinic were retrospectively analyzed. The CMT Neuropathy Exam Score (CMTNS/CMTES), CMT Functional Outcome Measure (CMT-FOM), CMT Pediatric Scale (CMTPedS), CMT Health Index (CMT-HI), electrophysiology, and developmental history were evaluated.

Results:
Twenty-one patients with CMT1E were identified from thirteen families. Ten different variants within PMP22 were identified, including 8 missense variants, two exon 4 deletions, and one 4 amino acid deletion. Nine out of ten of the variants were within the transmembrane domain of the protein. All nine of these patients presented with delayed walking during childhood. Four required full-time or intermittent wheelchair use and twelve used ankle-foot-orthotics or shoe braces. The patients ranged in age from 4 to 67 years at the time of evaluation. The CMTNS of 17 patients ranges from 11 to 31 with an average of 18.4. The CMTES of 20 patients ranged from 3 to 24 with an average of 12.25. CMTPedS scores ranged from 13 to 37 with an average of 27.5. Eighteen patients had delayed onset of walking and thirteen had severely slow motor NCV (<15 m/s). Four patients presented with scoliosis, two had hip dysplasia, and one had both.

Conclusions:
Many of the patients examined were found to have severe early onset presentations and variants scattered throughout the transmembrane domain of the PMP22 gene. This will serve as a baseline for understanding the natural history and phenotypic progression of patients with CMT1E.

References:
No

Grant Support:

The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01). The INC also receives funding from the Muscular Dystrophy Association and the Charcot-Marie-Tooth Association.

Keywords: Charcot-Marie-Tooth type 1E, CMT1E, PMP22, Natural History

Unveiling Genetic Complexities: Tandem Repeat Exploration in Known Charcot-Marie-Tooth and Hereditary Spastic Paraplegia Genes in Long-Read Sequencing

Poster No:
P 120

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Introduction:
Tandem repeats are adjacent repetitive nucleotide motifs that have been understudied due to technical limitations. Expansions and alterations in tandem repeats have been shown to cause neurological disorder in over 50 instances. Peripheral neuropathy is a common accompanying manifestation of tandem repeat disorders, such as in the intronic AAGGG expansion in the gene RFC1 causing CANVAS. Only recently, long-read genome sequencing technology has become sufficiently practical to explore tandem repeats genome-wide with high fidelity and at scale.

Methods:
Here, we established the normative variation of 5,107 tandem repeats in 124 genes known to cause Charcot-Marie-Tooth (CMT) and Hereditary Spastic Paraplegia (HSP). The currently largest control dataset with 1,027 lrWGS (PacBio HIFI) was studied.

Results:
Notably, we gathered novel biological evidence, that the population level variation in repeat length, composition, and purity in these genes are likely relevant for health and disease. We present the spectrum of variation at these loci, explain the underlying new software requirements, and present the status of confirmatory studies.

Conclusions:
Specifically, we have identified highly polymorphic repeats that warrant investigation in undiagnosed CMT and HSP patients for genotypes that deviate from our presented distributions.

References:
No

Keywords: Tandem Repeats, Charcot-Marie-Tooth, Long-Read Whole Genome Sequencing, Hereditary Spastic Paraplegia, Bioinformatics

One Year Follow Up On Virtual Charcot-Marie-Tooth Exam Scores (vCMTES) In Spanish-Speaking Countries

Poster No:
P 121

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Introduction:
The virtual Charcot Marie Tooth Exam Score (vCMTES) is a virtually administered, remotely conducted composite score based on the CMT Exam Score (CMTES) that combines questions about a patient's daily function with items on the neurological examination. This outcome measure provides a method of assessing CMT progression for patients who speak non-English languages, such as Spanish. Patients from Spanish-dominant countries including Mexico, Spain, and Columbia have been recruited and assessed for this study.

Methods:
The vCMTES was performed virtually with the examiner using a Zoom or similar format and the language interpreter to translate to/for the patient and examiner, thus generating vCMTES composite scores as a CMT progression outcome measure. vCMTES scores were collected at baseline and one-year follow up timepoints. Individual item scores and total composite scores were analyzed via paired two sample t-tests in Microsoft Excel version 2302 using the Analysis ToolPak Add-in.

Results:
Nine Spanish-speaking patients with genetically defined CMT were examined remotely for a vCMTES baseline visit and subsequent one-year follow up visit. Patient impairment ranged from mild (vCMTES of 2) to severe (vCMTES of 26). Patients with CMT1A, CMT2A, CMT2F, CMT2K, and CMT2M were included. Individual item score and composite score paired t-tests revealed no significant difference between baseline and one-year follow up vCMTES scores for all item scores and total composite scores ($p > 0.05$).

Conclusions:
The Spanish vCMTES has enabled remote evaluation of patients who could not have been evaluated at existing CMT clinics or by English-speaking examiners, thus broadening CMT evaluation accessibility and patient demographic diversity. These results highlight the reproducibility and accuracy of remote virtual foreign-language exams for relatively slow progressing conditions such as CMT over time.

References:
No

Grant Support:

The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01). The INC also receives funding from the Muscular Dystrophy Association and the Charcot-Marie-Tooth Association.

Keywords: Charcot-Marie-Tooth, Outcome Measures, CMT, vCMTES, Spanish

Transitioning From The CMT Pediatric Scale To The CMT Functional Outcome Measure

Poster No:
P 122

Authors:
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Institutions:
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Introduction:
Lifespan studies of disease impact on individuals with Charcot-Marie-Tooth disease (CMT) require assessment of function and disability over time, beginning in childhood through adolescence and transitioning to adulthood. The aim of this study was to explore the relationship between the CMT Pediatric Scale (CMTPedS) and the CMT Functional Outcome Measure (CMT-FOM) both collected in a cohort of adolescents and young adults with CMT.

Methods:
38 patients with CMT (18 CMT1A, 6 CMT1E, 3 CMT4C, 2 CMT2A, 1 CMT1X, 1 CMT4B1, 1CMT4D and 6 Unknown subtypes) aged 16 to 21 years have been recruited for this study to date. Patients were assessed with both the CMTPedS and CMT-FOM at a single study visit by trained evaluators. Total scores were calculated on ClinicalOutcomeMeasures.org and data were analyzed in SPSS version 29 using Spearman's rank correlation coefficients.

Results:
There was a strong correlation between the CMTPedS and the CMT-FOM (Spearman's rho $\rho = 0.906$, $p < 0.001$). The two clinical outcome measures consistently ranked patients as mild, moderate, or severe in 84% of cases. The CMT-FOM scored individuals as more severe than CMTPedS in five individuals and the CMTPedS scored one individual as more severe than the CMT-FOM.

Conclusions:
These data support the transition from the CMTPedS in childhood to the CMT-FOM in adulthood between the ages of 16 to 21 years as per transition timelines from pediatric to adult care at clinical sites. As a continuum of measuring lifelong function and disability in patients with CMT, we plan to develop an algorithm to extrapolate CMT-FOM scores from CMTPedS scores to aid in transition of care and patient expectations of CMT progression over time.

References:
No

Grant Support:

The Inherited Neuropathy Consortium (INC) is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01). The INC also receives funding from the Muscular Dystrophy Association and the Charcot-Marie-Tooth Association. This research was also supported in part by Accelerate Clinical Trials in CMT (ACTCMT) (grant #U01 NS109403).

Keywords: Charcot-Marie-Tooth, Outcome Measures, CMT, CMTPedS, CMT-FOM

Studying axon-dependent myelination using a co-culture system: Exploring amphiregulin's role for nerve development and injury

Poster No:
P 123

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Introduction:
During peripheral nerve development, Schwann cells play a crucial role in myelin sheath formation around axons through precise membrane alignment and myelin protein expression. In response to nerve injury, Schwann cells initiate demyelination, followed by axon degeneration and regeneration. This study investigates myelination and demyelination using an in vitro co-culture system with rodent Schwann cells and dorsal root ganglion neurons.

Methods:
To explore myelination dynamics, we used an in vitro co-culture system, combining rodent Schwann cells and dorsal root ganglion neurons. Myelin formation was labeled using immunofluorescence staining for periaxin and MBP. The study focused on an axon-dependent myelination mechanism, examining the role of Amphiregulin (Areg), an epidermal growth factor receptor (EGFR) ligand. Areg was knocked down in cultured embryonic DRG neurons, and co-cultures with Schwann cells were assessed for in vitro myelination alterations. EGFR function was inhibited using two distinct inhibitors, and recombinant amphiregulin effects on Schwann cell migration were evaluated in mouse nerve explant cultures.

Results:
Experiments revealed significant in vitro myelination impairment upon Areg knockdown in cultured embryonic DRG neurons. Inhibiting EGFR function reduced in vitro myelination levels. Recombinant amphiregulin treatment significantly enhanced Schwann cell migration from mouse nerve explant cultures, supporting Areg's pivotal role in Schwann cells during nerve repair.

Conclusions:
Findings suggest Areg is essential for peripheral myelination and plays a crucial role in nerve injury responses. This study sheds light on potential therapeutic interventions for nerve regeneration and enhances our understanding of the intricate mechanisms underlying myelination in the peripheral nervous system.

References:
No

Grant Support:

This study was supported by National Research Foundation of Korea (NRF) grants funded by MSIT 2022R1C1C2003395.

Keywords: Myelination, Demyelination, Schwann cell, Axon, Amphiregulin

Modelling the Loss of the Mitochondrial Release Factor in Rescue in Human iPSC-Derived i³ Neurons

Poster No:
P 124

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Introduction:
The mitochondrial release factor in rescue (MTRFR/C12orf65), encoded by the nuclear gene *C12orf65*, is a component of the mitoribosome quality control pathway. Mutations in *C12orf65* lead to a neurological phenotype characterized by optic atrophy, spastic paraparesis, and peripheral neuropathy. To date, no in vitro models of the disease have been developed, limiting our understanding of the underlying mechanisms. We generated *C12orf65* knockdown iPSC lines and differentiated them into cortical and motor neurons to investigate the neuronal deficits that may underlie the neuromuscular phenotypes seen in these patients.

Methods:
To generate knockdown iPSC lines we used a CRISPRi lentiviral vector to guide dCas9-KRAB transcriptional repression of the *C12orf65* gene. Then, we performed transcription factor-mediated differentiation of the iPSCs into cortical and motor neurons. Finally, we investigated whether our model was able to recapitulate the defects previously reported on patients' fibroblasts, including the assessment of OXPHOS complexes and mitochondrial translation.

Results:
We successfully generated three *C12orf65* knockdown iPSC lines and differentiated them into neurons. Both cortical and motor neurons showed OXPHOS complex I and complex IV deficiencies when compared to controls, though the motor neurons were more severely affected. Loss of MTRFR also impaired mitochondrial translation, which was significantly decreased even at early timepoints. Additionally, immunofluorescence showed abnormal accumulation of mitochondria in the neurites, indicative of a transport defect.

Conclusions:
Very little is known about the neuronal deficits driving neuromuscular dysfunction in patients with *C12orf65* mutations. Here, we reported the first neuronal model of MTRFR loss and showed that it successfully recapitulated the OXPHOS and translational defects that have been previously described on patients' fibroblasts and muscle biopsies. Having a reliable in vitro model will allow us to delineate *C12orf65*-related neuronal-specific phenotypes and to examine possible therapies for this mitochondrial disease. Next, we will be using this model to trial a recently developed gene therapy.

References:
No

Grant Support:

Hereditary Neuropathy Foundation, Wellcome Trust, Cambridge Trust, MRC UKRI

Keywords: Mitochondrial diseases, Induced pluripotent stem cells (iPSCs), Spastic Paraparesis, Inherited peripheral neuropathy

Genotype and Phenotype Distribution of 818 patients with Inherited Peripheral Neuropathy in China

Poster No:
P 125

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Introduction:
Inherited Peripheral Neuropathies (IPNs) constitute a group of single gene inherited disorders affecting the peripheral nervous system, characterized by significant clinical and genetic heterogeneity. This study aims to present an overview of the genotype and phenotype distribution in 818 Chinese patients with IPNs.

Methods:
A total of 818 patients were enrolled, and comprehensive clinical data were collected. Multiplex ligation-dependent probe amplification for PMP22 duplication/deletion and CMT multi-gene panel sequencing were conducted. Whole exome sequencing was employed for patients without a molecular diagnosis.

Results:
Among the 818 patients, the overall molecular diagnosis rate was 77.4% (633/818). Diagnostic rates for each clinical subtype of CMT were as follows: CMT1 at 80.8% (320/396), CMT2 at 68% (183/269), HNPP at 100% (34/34), dHMN at 66% (29/44), HSN/HSAN at 63.6% (7/11), and for complex IPNs, the rate was 93.8% (60/64). In CMT1 pedigrees,PMP22 duplication accounted for 46% (182/396), GJB1 mutations for 17% (66/396), and MPZ mutations for 6% (23/396). In CMT2 pedigrees,MFN2 mutations accounted for 26% (70/269), GJB1 mutations for 7% (20/269), and MPZ mutations for 4% (10/269). The four most common genotypes constituted 58.6% (371/633) of molecularly diagnosed patients.Among CMT1A patients, clinical symptoms included predominantly lower limb weakness and atrophy, mild sensory involvement, with slow progression. GJB1 mutations were predominantly located in the second transmembrane region and N-terminus, with no mutations found in the C-terminus. MPZ-related CMT patients with Infantile-onset cases were mostly sporadic or de novo mutations, presenting with significantly reduced motor nerve conduction velocity (MNCV). Childhood-onset cases showed reduced MNCV and mild to moderate functional impairment.Adult-onset cases presented with moderate to severe lower limb motor and sensory involvement, resembling a CMT2 phenotype.

Conclusions:
Our findings offer a comprehensive distribution of phenotypic and genotypic characteristics of IPNs within a cohort of patients from China.This provides essential baseline data for future investigations into the natural history and clinical treatment of these disorders.

References:
No

Keywords: Inherited Peripheral Neuropathy, cohort study, genotype-phenotype distribution, phenotype spectra

Genetic and Clinical Features in Eleven Families of Neurogenetic Disorders with Prominent Sensory Involvement

Poster No:
P 126

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Introduction:
Neurogenetic disorders characterized by prominent sensory involvement constitute a highly clinically and genetically heterogeneous group. This study aims to summarize the phenotypic and genotypic features observed in eleven Chinese families with prominent sensory involvement.

Methods:
The clinical data of eleven families exhibiting prominent sensory involvement were collected retrospectively. Genetic analysis was conducted using whole exome sequencing (WES). Repeated primer PCR and Capillary Electrophoresis were applied for WES-negative patients to analyze repeat expansions in RFC1.

Results:
Among the eleven families, seven exhibited early onset (onset age <20 years). Most pedigrees were sporadic (82%), with one pedigree showing autosomal recessive inheritance and one autosomal dominant inheritance. Seven families manifested as pure sensory type, while four presented as complex types, concomitant with motor symptoms, ataxia, and vestibular dysfunction, respectively. Two families with the classic phenotype of HSAN-IV carried pathogenic variants in NTRK1, and a novel variant c.444C>A (p.N148K) in NTRK1 was firstly reported. A novel variant c.182dup (p.H61Qfs*31) in PUM1 was identified in a family that exhibited adult-onset paresthesia combined with mild ataxia. AAGGG repeats expansion in RFC1 was identified in a family with sensory neuropathies, ataxia, and right vestibular hypofunction. Together with families with variants of SPTLC1 and COX20, 63.3% of families acquired a definite genetic diagnosis.

Conclusions:
We report a novel variant in NTRK1 related to HSAN-IV and a novel variant in PUM1 characterized by adult-onset paresthesia with ataxia for the first time. RFC1 dynamic mutation testing should be added into the molecular diagnostic workflow. Multicenter cohort studies are essential to deepen our understanding of this heterogeneous group of diseases.

References:
No

Keywords: Neurogenetic disorders, Sensory involvement, Genetic variants, Clinical features, NTRK1

The Mutational Profile in a Zambian Cohort with Inherited Neuropathies

Poster No:
P 127

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Introduction:
Genetic testing is challenging to access for patients with suspected genetic neuropathies (GN) in sub-Saharan Africa, resulting in sparse data on these disorders. Here we report the first GN cohort from Zambia using next generation sequencing and virtual gene panel analysis.

Methods:
Twelve probands with suspected GN presenting to a tertiary care center in Zambia were enrolled in a prospective study of inherited neuromuscular disorders between October 2020 and September 2022 and underwent whole exome (WES; n=4) or genome sequencing (WGS; n=8) through the International Consortium for Genomic Medicine in Neuromuscular Disorders (ICGNMD). Variants were classified according to American College of Medical Genetics guidelines.

Results:
All probands were of African ancestry and had symptom onset between 1 – 25 years. Five probands had an affected sibling but no other family history of neuropathy or consanguinity. Ten probands had electrophysiologic evidence of an axonal sensorimotor neuropathy, one pure motor polyneuropathy, and one patient had cerebellar ataxia and axonal neuropathy. One patient had severe electrophysiological involvement with absent motor and sensory responses in all 4 limbs. Additional clinical features included speech and hearing impairment (n=1), scoliosis (n=2), and severe clawing of hands and pes cavus (n=6). Of the twelve GN probands, 5 (42%) achieved a genetic diagnosis: 2 with autosomal dominant Charcot-Marie-Tooth (CMT) disease (heterozygous MFN2 p.Arg364Try and p.His361Gln), 1 with autosomal recessive motor neuropathy (compound heterozygous VWA1 p.GlyArgfsTer74, novel p.Glu222GlyfsTer65), 1 with autosomal recessive ataxic neuropathy (homozygous TDP1 p.His493Arg) and 1 with autosomal recessive CMT disease [compound heterozygous NDRG1 splice donor variants in intron 11 (novel) and 12].

Conclusions:
In this cohort using WES/WGS, we solved nearly 50% of cases, similar to diagnostic yields reported in other global cohorts. Genetic testing in populations traditionally underrepresented in genomic databases has the potential to expand our understanding of the genetics of neuropathy.

References:
No

Grant Support:

International Centre for Genomic Medicine in Neuromuscular Diseases (ICGNMD) Consortium

Keywords: Hereditary Neuropathies, Genetic Mutations, Sub-Saharan Africa, Zambia

International Diabetes Neuropathy Consortium

International Diabetes Neuropathy Consortium (IDNC) Abstracts

P 128 - 153

Combined Large Fiber Loss with Small Fiber Damage Build up Pain in Diabetic Neuropathy.

Poster No:
P 128

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Introduction:
Small nerve fiber damage is one of the early and common pathology in diabetic neuropathy, however, it is not clear why only a part of diabetic patients complain pain. To clarify physiological mechanism of pain in painful diabetic neuropathy (PDN), we carried out SUDOSCAN (SS) and nerve conduction study in diabetic patients with PDN and in those with pain-less diabetic neuropathy (PLDN).

Methods:
From 213 patients with diabetes examined by SS, we found 49 subjects with electro-chemical skin conductance (ESC) less than 50μS evaluated by SS, and compared the tibial and sural NCS results between PDN (n=26) and PLDN (n=23) groups. Overall severity of large fiber neuropathy was estimated by NCS severity classification of Baba's DPN criteria: BDC) as follows; BDC-0: No NCS abnormality, BDC-1: Any delay of F-wave latency and/or MCV, SCV, BDC-2: Fall in sural SNAP amplitude<5μV, BDC-3: Fall in tibial CMAP amplitude to between 2-5mV, BDC-4: Fall in tibial CMAP amplitude less than 2mV.

Results:
In PDN and in PLDN groups, results were as follows respectively; ESC(μS): 30.1±14.8 and 31.0±12.8, minimal F-wave latency (UNL100/height): 109.3±7.4 and 102.7±14.6 ($p<0.05$), sural SNAP amplitude (μV): 2.5±2.5 and 6.3 ±3.4 ($p<0.01$), tibial CMAP amplitude (mV): 5.0±3.9 and 6.3±3.4. Mean BDC value of PDN was 2.7±1.3, while PLDN showed mean BDC value of 1.7±1.4 ($p<0.05$).

Conclusions:
ESC represents peripheral C-fiber function, while sural SNAP amplitude and BDC value is determined by large fiber loss. Remarkable fall in sural SNAP and increase in BDC value in the PDN group with similarly low ESC to the PLDN group suggests that the pain inhibition is weakened at the dorsal horn by large fiber loss in PDN with C-fiber damage. In conclusion, large fiber loss may build up foot pain in PDN with small fiber damage.

References:
No

Keywords: diabetic neuropathy, sudoscan, nerve conduction study, small fiber dysfunction, large fiber dysfunction

Bilateral Foot Drop; An Unusual Presentation of Diabetic Neuropathy.

Poster No:
P 129

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Introduction:
Diabetes Mellitus is associated with a few types of peripheral nerve disorders. Motor predominant neuropathy is often seen in the context of acute-subacute lumbosacral plexoradiculopathy, that may be associated with marked fluctuations in blood glucose. We present a case of bilateral foot drop as that prompted evaluation and diagnosis of diabetes mellitus.

Methods:
We describe a 38 year old woman who presented with a 3 year history of parasthesia and gradual loss of sensation in both feet. Symptoms evolved into weakness in the feet, eventually resulting in bilateral foot drop and gait abnormalities. The onset duration was unclear and she did not report severe neuropathic pain in her feet at onset of foot weakness.Examination revealed distal weakness in the legs with hypoesthesia in the stocking distribution, impaired vibration sense and a high steppage gait.

Results:
HBA1C was 8.4%. The nerve conduction showed bilateral peroneal neuropathy with no definite slowing across the fibula neck. ANA was negative, vitamin B12 was normal; and Hep B, C and HIV screen were negative. There were no clinical features of leprosy or other causes of multiple mononeuropathy. She has no family history and neurodiagnostic features of HNPP. Patient is currently on treatment for the diabetes mellitus; has been prescribed foot orthotics and physiotherapy.

Conclusions:
We speculate that recent worsening of her metabolic state could have triggered a forme fruste of diabetic lumbosacral plexoradiculopathy as motor predominant presentation is unusual regarding the variety of polyneuropathy of diabetes mellitus.

References:
No

Keywords: Peripheral, Neuropathy, Axon

Correction Of Glucose Intolerance And Metabolic Syndrome Improves Small Fibre Neuropathy- A Case Report

Poster No:
P 130

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Introduction:
There is growing evidence to suggest that correction of metabolic syndrome by weight reduction and exercise can improve small fibre neuropathy

Methods:
A 45 year old male, complained of painful cold sensation affecting all four limbs and trunk for 1 year worse at night and associated with intermittent sexual dysfunction. He had a past history of binge drinking. Physical examination was remarkable for grade I obesity (body mass index [BMI] 33.5kg/m2) as well protopathic and algesic hypoesthesia in a stocking distrubution. Vibration threshold and monofilament testing were normal. He had no weakness and deep tendon reflexes were intact. Nerve conduction study was normal. Electrochemical skin conductance (ESC) measured by Sudoscan ® (Impeto Medical) was decreased at 56 microsiemens (µS) (normal value > 60µS). Fasting blood sugar was mildy elevated at 1.13g/l; and he had glucose intolerance- blood sugar was 1.90g/l two hours after ingestion of 75g glucose. Serum triglycerides was 0.73g/l and LDL cholesterol(LDLc) 1.80g/l. Glycated hemoglobin (HbA1c) was 4.83%. HIV, Hepatitis B and C ; TSH, vitamin B12, CRP, ESR and serum protein electrophoresis were normal. He was diagnosed with SFN due to glucose intolerance. He was given dietary advise and asked to commence a prudent exercise regime to achieve ideal body weight, his symptoms were managed with pregabalin (225mg /day).

Results:
Seven months later, his BMI was 30kg/m2. Fasting glucose was 1.03g/l and 2-hour glucose tolerance test 1.04g/l. HbA1c was 5%. The patient was symptom free and his feet ESC normalised at 72µS. His pregabalin could be weaned off.

Conclusions:
This case underscores the reversibility of SFN symptoms with aggressive control of the metabolic syndrome associated with obesity. Additionally, it underlines the usefulness of point of care devices for diagnosis and follow-up of SFN where intra-epidermal nerve fiber density and quantitative sensory testing are unavailable.

References:
No

Grant Support:

None

Keywords: Diabetic neuropathy, Small fibre neuropathy, Glucose intolerance, Reversibility of Small neuropathy, Electrochemical skin conductance

The differences in neuronal and vascular function and structure observed among South Asian and European individuals diagnosed with Type 2 diabetes.

Poster No:
P 131

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Introduction:
Objective: Studies indicate a lower occurrence of foot ulceration among South Asian patients in comparison to European individuals diagnosed with type 2 diabetes (T2DM).

Methods:
Methods: We conducted an evaluation of neurological and vascular function along with skin biopsy, employing detailed light and electron microscopy techniques, in a group of European (n = 25) and South Asian (n = 24) patients with T2DM and healthy volunteers (n = 24).

Results:
Results: South Asians had comparable age, HbA1c, cholesterol, HDL, and blood pressure, but a longer duration of diabetes (P = 0.02), a lower BMI (P = 0.01), and triglycerides (P = 0.01) compared to Europeans. T2DM patients from South Asian and European ethnic backgrounds demonstrated significant differences with control subjects but no difference between each other for the neuropathy symptom profile, neuropathy disability score, thermal threshold, heart rate variability response to deep breathing, intraepidermal nerve fibre density, corneal nerve fibre density, corneal branch density, corneal nerve fibre length, and corneal nerve fibre tortuosity. Epidermal thickness was significantly higher in South Asian patients compared to Europeans. The maximal hyperaemic response was significantly lower in Europeans compared to South Asians. There was no other significant difference in vascular density or any other measure of microangiopathy comparing South Asian to European patients with T2DM.

Conclusions:
In summary, differences in BMI, triglyceride levels, maximal hyperaemic response, and epidermal thickness may contribute to the reduced susceptibility to foot ulceration in South Asian patients compared to their European counterparts diagnosed with T2DM.

References:
Yes

Reference 1: On behalf of the DAEMON group (Diabetes in Asians and Europeans: the Manchester study Of Neuropathy).

Grant Support:

Diabetes UK

Keywords: Diabetic neuropathy, foot ulcers

A Novel Quantitative Artificial Intelligence Approach to Measurement of Intra-Epidermal Nerve Fiber Density

Poster No:
P 132

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Introduction:
Analysis of intra-epidermal nerve fiber density (IENFD) is an established technique providing reliable, reproducible and clinically relevant results. However, IENFD analysis is labor intensive and liable to error, particularly when performed by pathologists with inadequate training. Objective: To develop an unbiased, valid measurement of IENFD that leverages existing reading standards, and integrates full digital microscopy with artificial intelligence to provide quantitative IENFD measurement.

Methods:
We examined three 3-millimeter skin biopsies taken from 34 individuals with a range of neuropathy severity. Tissue was processed and immunostained with protein gene product 9.5 using standard immunofluorescent techniques. Each slide was fully digitized (Olympus VS200) using 3-micron Z-stack images. We created a novel artificial intelligence (AI) driven detection algorithm to define the dermal-epidermal interface and trace individual axons. Intersections between axons and the dermal epidermal junction were counted and reported as IENFD in fibers/millimeter. The immunofluorescent slides were read independently by a pathologist (blinded to detection algorithm results) as the gold standard.

Results:
102 biopsies from 34 participants were reviewed. The mean age was 63.4±6.6 years. Concordance between pathologist score of IENFD of glass slides and AI-independent reading was high ($R2=0.984$, $P<0.001$). Diagnostic concordance between pathologist determination of neuropathy (based on age defined norms) and AI independent reading was high (98%: 100/102 skin biopsies in agreement). Two misclassified biopsies had incomplete confocal capture of tissue that resulted in undercounting of IENFD.

Conclusions:
These data support criterion validity for whole slide digitization combined with artificial intelligence assisted detection of the dermal-epidermal junction with tracing of individual axons. Although not yet suitable for independent use, the AI supported IENFD program could function as a 'pre-reader' to improve pathologist efficiency and facilitate the use of this diagnostic tool in neurological care.

References:
No

Grant Support:

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Keywords: Small fiber, IENFD, artificial intelligence, immunofluorescent

Small Fiber Neuropathy in Mouse Models of Neurodegenerative Disease

Poster No:
P 133

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Introduction:
An increasing number of peripheral nerve impairments are associated with a higher risk of dementia, with effect estimates higher among patients with diabetes. Sensory nerve impairments alone were associated with a 1.4 times higher dementia risk (HR 1.43, 95% CI 0.89-2.30). In addition to Alzheimer's disease, peripheral neuropathy has been identified in Atypical Parkinsonian Syndromes such as Progressive Supranuclear Palsy (PSP), but the mechanisms that drive these conditions are not clear.

Methods:
To uncover mechanisms of peripheral nerve damage in both AD and PSP, we are exploring the hypothesis that either amyloid, tau, or a combined accumulation is toxic to peripheral nerves via toll-like receptor signaling pathways. We examined a 5xFAD transgenic mouse model that overexpresses human mutant APP and PS1 to test this hypothesis. The Barnes Maze test assessed cognitive dysfunction in these mice at eight weeks of age. Experiments also examined the density of epidermal axons in the hind paw. Ongoing studies examine pain responsiveness, pro-inflammatory cytokine levels, assessing amyloid and tau expression and deposition, and activation of spinal microglia. To focus on tau pathology, we are exploring a PS19 transgenic mouse model that encodes the disease-associated P301S mutation in tau and includes four microtubule-binding domains and one N-terminal insert (4R/1N). Results will be presented on a time course study to assess cognitive dysfunction, peripheral neuropathy, immune dysregulation, and tau deposition in the periphery of PS19 mice.

Results:
Homozygous 5XFAD mice had significantly reduced spatial memory and learning compared to wildtype (WT) mice (n=4-5). Homozygous 5XFAD mice had significantly reduced intraepidermal nerve fiber (IENF) density compared to WT mice, consistent with a small fiber neuropathy.

Conclusions:
Exploration of these rodent models of dementia allows for investigation of how tau and amyloid are detrimental to peripheral nerves and whether peripheral nerve damage affects cognitive decline.

References:
Yes

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Reference 4: George, J. (2022, March 11). Peripheral nerve problems tied to later dementia. Medical News. https://www.medpagetoday.com/neurology/dementia/97632

Grant Support:

R01NS043314-17, 5P20GM103418.

Keywords: Dementia, Intraepidermal Nerve Fiber Density, Neuropathy, Beta-Amyloid, Tau

A Search for Drugs that Stimulate C-Fiber Regeneration

Poster No:
P 134

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Introduction:
Peripheral diabetic neuropathy (PDN) is a widespread complication in patients with diabetes that leads to pain, burning, or loss of sensation in the distal limbs. A hallmark of small fiber PDN is a loss of intraepidermal nerve fibers (IENF). Currently, therapeutic options for humans with PDN are limited, with improved glycemic control, pain control, and healthy lifestyle serving as the primary foci. No options are available to stimulate small fiber regeneration. However, preclinical studies have identified numerous drugs or treatments that stimulate IENF regeneration in rodents but have not yet translated to clinical trials or use in humans. Here, we leveraged existing information from published articles to identify drugs or approaches that have reported regenerative effects on IENF in rodents.

Methods:
As part of a more extensive scoping review on IENF, we identified a subset of articles that reported increased IENF density in rodent models. Using PubMed, 323 initial articles were narrowed down using specific inclusion criteria. We analyzed 72 articles and categorized the successful drugs into seven groups based on implied mechanisms of action.

Results:
The mechanistic categories include metabolic improvement (38%), antioxidant reduction (23%), hormonal regulation (18%), anti-inflammatory actions (11%), stem cell therapies (6%), electrophysiological improvements (3%), and others with no known or clear mechanisms (1%). The experimental models used to test these drugs include diabetic, chemotherapeutic, and toxic models, suggesting a narrow set of preclinical models to address IENF regeneration. There are additional diseases and conditions in which IENF loss has been reported, including neurodegenerative and autoimmune models, that may provide new perspectives.

Conclusions:
This information is designed to identify critical roadblocks, allow a focus on common or specific mechanisms, and narrow the areas where research should focus to identify new treatments or modify existing drugs to use in humans with DPN or other forms of neuropathy.

References:
No

Grant Support:

R01NS043314-17

5P20GM103418

Keywords: Regeneration, Drug Therapy, Intraepidermal nerve fiber density, Rodent models, C-Fibers

Interleukin-17 in the Pathophysiology of Diabetic Neuropathic Pain

Poster No:
P 135

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Introduction:
Diabetic neuropathic (DN) pain is a debilitating condition which currently has no effective treatment due to the lack of understanding of the underlying mechanisms. Our RNA-seq data revealed interleukin-17 (IL-17) signaling as the top altered pathway in skin from DN mice. IL-17 is a proinflammatory cytokine implicated in autoimmune disorders and neuropathic pain. This study aims to elucidate the role of skin immune cell-derived IL-17 in the pathophysiology of DN pain and to develop therapies targeting the IL-17 signaling pathway.

Methods:
We created DN mouse models by feeding the wild-type (WT) or transgenic mice with only high-fat diet (HFD) or HFD followed by administration of low-dose streptozotocin. The mice were subsequently assessed by behavioral and morphologic analyses. IL-17 levels in tissue were measured by qPCR. IL-17a knockout (KO) mice were used to evaluate the role of IL-17 in DN pain.

Results:
In DN mice, IL-17 expression was found to increase solely in the skin, with no elevation observed elsewhere in the pain neuraxis such as dorsal root ganglia or spinal cord. The two major IL-17 isoforms IL-17A and IL-17F were both substantially upregulated in skin from DN mice. IL-17 is predominantly secreted by T-lymphocytes. In DN mouse skin and patients' skin biopsy, T cell infiltration was observed in regions where sensory nerve endings or nerve bundles reside. Furthermore, IL-17a KO mice demonstrated decreased diabetic mechanical allodynia and no significant loss of epidermal sensory nerve fibers compared to the heterozygous and WT littermate controls.

Conclusions:
Given that IL-17 receptor (IL-17R) is most abundantly expressed in small-diameter nociceptor neurons, our data suggest that DN pain may result from IL-17-induced injury to epidermal nociceptive nerve endings and subsequent IL-17R-dependent sensitization of nociceptor neurons. Further studies are underway to determine the efficacy of IL-17A blockade in relieving DN pain in animal models.

References:
No

Keywords: IL-17, Diabetic neuropathy, Neuropathic pain, Skin

Evaluation of Symptoms in Conjunction with Pre-Diabetes and Metabolic Syndrome in otherwise Idiopathic, Peripheral Polyneuropathy Patients

Poster No:
P 136

Authors:
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Introduction:
Pre-diabetes (PreD), dyslipidemia, obesity, and hypertension collectively represent the metabolic syndrome (MetS), which have been linked to increased risk of peripheral neuropathy (PN). The purpose of this study is to determine if PreD, MetS, and a combination of these features are related to variations in clinical features of idiopathic peripheral neuropathy.

Methods:
The Peripheral Neuropathy Research Registry (PNRR) is a multi-site cohort study that includes patients with symmetrical and distal axonal PN. A total of 553 participants from two sites were included in this data analysis project because these patients had all the required information on record. The cohort was then divided into four categories: (1) Idiopathic (2) Idiopathic with Metabolic Syndrome (3) Idiopathic with Prediabetes (4) Idiopathic with Metabolic Syndrome and Prediabetes.

Results:
Of the 553 patients, 245 (45%) were classified as Idiopathic, 95 (17.2%) as Idiopathic with MetS, 63 (11.4%) as Idiopathic with PreD and 146 (16.4%) as Idiopathic with MetS and PreD. The Idiopathic cohort without MetS or PreD served as a reference group. There were no differences in the demographics besides a higher percentage of males ($p<0.001$), higher mean age ($p<0.009$), and greater time elapsed since onset of symptoms ($p<0.001$) in the Idiopathic with MetS and PreD group compared to Idiopathic group. BMI, triglycerides, HDL and blood glucose levels showed significant differences in accordance with the categorization. The Idiopathic with MetS group had a higher incidence of painful neuropathy compared to the Idiopathic cohort without PreD or MetS.

Conclusions:
Preliminary analysis has shown that presence of metabolic syndrome, but not pre-diabetes alone, was associated with a higher incidence of painful neuropathy. Additional results will be available for the PNS meeting in June 2024.

References:
No

Grant Support:

This research was supported by the Foundation for Peripheral Neuropathy.

Keywords: Metabolic Syndrome, Peripheral Neuropathy, Prediabetes

Longitudinal Assessment Of Chronic Axonal Polyneuropathy In The Rotterdam Study: The First 473 Rescreened Participants

Poster No:
P 137

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Introduction:
Chronic axonal polyneuropathy (CAP) is a common disease with a prevalence of 4-13% in the general population. Incidence of CAP is insufficiently investigated and identification of early symptoms or signs yet present in the subclinical phase are of interest.

Methods:
This study is part of the Rotterdam Study, a population-based cohort study investigating chronic diseases in the population aged 45 and over. Since 2013 a polyneuropathy screening was implemented consisting of a symptom questionnaire, neurological examination and nerve conduction studies. In consensus meetings, all individual participants are categorized as no, possible, probable or definite polyneuropathy. Participants undergo a (re-)screening every 4-7 years. Physicians participating consensus meetings are blinded for the results of previous screenings.

Results:
From June 2013 till August 2023, 4878 participants were screened (294 participants were excluded because of insufficient data) of which 188 (4.1%) had definite polyneuropathy. Of these 4584 participants, rescreening was performed in 473 (10.3%) participants (17 prevalent cases and 20 participants were excluded because of insufficient data). In the resulting 436 rescreened participants, the median age was 75 years (IQR 70-80) and 53.4% (N=233) was female. During the study, 28 participants had developed definite polyneuropathy resulting in a 10.2-years cumulative incidence of 6.4% (95%CI 4.1-8.7%). Interestingly, participants newly diagnosed with definite polyneuropathy more often reported cotton wool feeling and numbness at the first visit than other participants (60.7% vs. 11.8%, and 67.9% vs. 16.9% respectively).

Conclusions:
The estimated 6.4% 10.2-year incidence of CAP emphasizes the importance to search for early features possibly indicating the development of polyneuropathy. We showed that certain symptoms are already more common in the subclinical phase. The potential of these symptoms aiding early detection of CAP need to be investigated. These results are preliminary and based on limited sample size. We expect to rescreen more participants in the upcoming months.

References:
No

Keywords: Chronic axonal Popolyneuropathy, Incidence, Early detection

Corneal Nerve Imaging in Early Diagnosis of Diabetes Sensory and Autonomic Neuropathy

Poster No:
P 138

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Introduction:
Diabetes polyneuropathy (DPN) is common among patients with long-standing, poorly-controlled diabetes mellitus (DM) and may be asymptomatic in up to 50%. Cardiovascular autonomic neuropathy (CAN) may also co-exist with potentially life-threatening complications, highlighting the importance of early detection and risk factor control. Current clinical and electrodiagnostic methods for detection of DPN lack sensitivity or reproducibility. In recent years, corneal nerve imaging has shown good sensitivity in early diagnosis of DPN and CAN. We aim to evaluate the utility of corneal nerve imaging in early diagnosis of DPN and CAN.

Methods:
Patients with poorly-controlled DM (defined as HbA1c 9% or more) were recruited from outpatient clinics at two tertiary centres. Those with pre-existing corneal abnormalities or contraindications to autonomic function testing were excluded. All patients were assessed using MNSI and COMPASS-31 questionnaires (where an abnormal score increases likelihood of DPN and CAN respectively) and underwent a standard battery of assessments: corneal nerve imaging, autonomic function test and continuous glucose monitoring. We compared the demographics, diabetes duration and control, body-mass index (BMI), lipid profiles and corneal nerve fibre density/length (CNFD/CNFL) between those with abnormal and normal MNSI scores and autonomic function.

Results:
We analyzed 40 patients (median age 53 years, 21 males). All except one had poorly-controlled type 2 DM. Those with abnormal MNSI and cardiovagal sudomotor impairment tended to be older and have higher BMI and triglyceride levels. Conversely, DM duration or glycemic control did not differ between groups. This is consistent with growing evidence implicating metabolic syndrome rather than DM duration, severity or glycemia control as risk factors of DPN and CAN. CNFL and CNFD were reduced in both groups with no significant difference.

Conclusions:
Our study is limited by the small cohort. We continue to explore various parameters of corneal innervation as markers of DPN and CAN.

References:
No

Grant Support:

Nil

Keywords: Diabetes neuropathy, Autonomic dysfunction, Cardiovascular autonomic dysfunction, Diabetes mellitus, Corneal nerve imaging

Pre-diabetic small fiber neuropathy as own entity? – Insights in clinical and morphological studies

Poster No:
P 139

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Introduction:
Small fiber neuropathy (SFN) is a sensory neuropathy which is caused by dysfunction of thinly myelinated A-delta and unmyelinated C nerve fibers. The underlying etiologies of SFN are various, diabetes is known as a common one. We aimed to investigate pre-diabetes as a potential inducer of SFN and analyzed clinical characteristics of patients with SFN and pre-diabetes (pSFN) in comparison to patients with idiopathic SFN (iSFN).

Methods:
We characterized 103 patients with SFN recording medical history with focus on pain, neurological examination, and applying the following small fiber tests: quantitative sensory testing (QST) at the dorsum of the foot and face as control area, corneal confocal microscopy (CCM), and skin punch biopsy from the distal leg and the upper thigh. We analyzed glucose metabolism of all SFN patients and defined pre-diabetes due to the criteria of the American Diabetes Association (1).

Results:
76/103 (64%) patients were classified as pSFN and 27/103 (23%) as iSFN. We found no relevant difference in pain characteristics and clinical sensory assessment between patients with pSFN and iSFN. In QST and CCM, pSFN and iSFN patients did not differ in group comparison. However, skin denervation was more frequent in pSFN (63/76, 83% patients) than iSFN (18/27, 65% patients) and also median distal and proximal intraepidermal nerve fiber density was lower in pSFN than in iSFN ($p<0.01$ each).

Conclusions:
The majority of SFN patients in our cohort had pre-diabetes which was previously unknown. In pSFN patients, generalized skin denervation was more frequent although clinical characteristics including pain did not differ from iSFN. These data suggest that mild epidermal denervation may be tolerated before functional impairment. Our findings highlight the need to screen for pre-diabetes in SFN due to its frequency, the lack of obvious clinical sings, and the potential to prevent manifest functional impairment.

References:
Yes

Reference 1: 1. Association AD. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2013;36 Suppl 1(Suppl 1):S67-74.

Keywords: small fiber neuropathy, pre-diabetes

Determining Normal Values of Epidermal Peripheral Nerve Fiber Density in Healthy Individuals in the North Area of China using Skin Biopsy

Poster No:
P 140

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Introduction:
Objective: This cross-sectional study aimed to determine the normal values of epidermal small nerve fiber density in healthy individuals in the North area of China using skin biopsy.

Methods:
Methods: A total of 98 healthy participants were enrolled, categorized into three age groups: 20-40 (male = 14; female = 17), 41-60 (male = 17; female = 18), and 61-80 (male = 16; female = 16) years. All subjects exhibited no symptoms of peripheral neuropathy, normal neurological examination results, and no peripheral neuropathy risk factors. Blood samples were collected for various tests prior to skin biopsy. Skin biopsies were performed at the distal leg using a 3mm diameter skin rotary knife. The samples were fixed, sectioned, and subjected to immunohistochemical staining with the protein gene product (PGP9.5) antibody. The staining process included negative and positive controls, with each sample stained in four sections. Epidermal nerve fiber density was determined using stereological software.

Results:
Results: The 5th percentile of intraepidermal nerve fiber density (IENFD) was found to be 9.68 fibers/mm for males and 10.1 fibers/mm for females in the 20-40 age group, 9.46 fibers/mm for males and 9.76 fibers/mm for females in the 41-60 age group, and 8.87 fibers/mm for males and 9.44 fibers/mm for females in the 61-80 age group.

Conclusions:
Conclusion: This study establishes the reference values for epidermal small nerve fiber density in healthy adults in the North area of China. The results demonstrate that epidermal nerve fiber density decreases with age, and gender differences are present within the same age group. These findings contribute to a better understanding of normal epidermal peripheral nerve density in the Chinese population and have implications for the diagnosis and management of small nerve fiber disorders.

References:
No

Grant Support:

The study was supported by Dalian Municipal Health Commission Bureau level Project

Keywords: Normal Values, Epidermal Peripheral Nerve Fiber Density, North Area of China, Skin Biopsy

Genome-Wide Association Study of Diabetic Neuropathy in UK Biobank

Poster No:
P 142

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Introduction:
Wallerian degeneration is a well-characterised axon death mechanism in disease and injury. Axons die early in many inherited and acquired neurological disorders, including diabetic neuropathy (DN). Blocking this pathway has been shown to alleviate many animal and cell culture disease models, suggesting widespread molecular involvement in disease with important therapeutic potential. We investigated whether an inherited susceptibility to WD influences risk of DN.

Methods:
Using UK Biobank (UKB) extensive phenotypic data, and various types of genetic data including genome-wide genotype array and whole exome sequencing (WES) in 500,000 participants, we identified a cohort of Type 2 Diabetic patients with no other potential cause of neuropathy. Michigan neuropathy Screening Instrument (MNSI) score of 3 was used as cut-off to classify DN cases and controls. Controls were defined as type 2 diabetic patients without neuropathy. Regenie was used to identify genetic associations with DN in 2 steps using genotype calls and WES Plink files. Multiple quality control (QC) steps were conducted to exclude samples with sex mismatch, Sex chromosome aneuploidy, and related participants. To keep our cohort homogenous, we included only individuals from White British ancestry. Following QC checks, variants with a minor allele frequency (MAF) less than 0.01 were filtered out.

Results:
Our cohort consisted of 6708 individuals, of which 373 participants had MNSI score > 3. Following QC checks and variant filtering we performed Regenie on 410,690 SNPs from total 3669 samples, where cases group consisted of 193 DN participants, and the remaining 3476 comprise the Control group. Preliminary analysis did not identify statistically any significant hits in any gene.

Conclusions:
Further tailoring of selection and filtering criteria is ongoing and more through GWAS study will be conducted.

References:
No

Grant Support:

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Keywords: Diabetic Neuropathy, GWAS, Wallerian Degeneration, UK Biobank

Comparative analysis of cutaneous sensory innervation in human and mouse

Poster No:
P 143

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Introduction:
Current neuropathy and neuropathic pain studies have some major limitations: first, most clinical diagnosis and research focus on hairy skin in the leg with little effort on glabrous skin of the foot where neuropathy patients overwhelmingly experience pain; second, most experimental studies concentrate on the glabrous skin of the mouse footpad. Differences in normal nerve innervations between hairy and glabrous skin within humans, and importantly, species differences between human and mouse are poorly characterized. Therefore, this study aims to differentiate between hairy skin and glabrous skin in humans, and furthermore to recognize the differences and similarities between human and mouse.

Methods:
Three mm skin biopsies from distal leg (hairy skin) and foot plantar (glabrous skin) were obtained from healthy human subjects and normal C57BL/6 mice. Immunohistochemistry for pan-neuronal marker (PGP 9.5), myelinated nerves (NFH), peptidergic nerves (CGRP) was performed. Intraepidermal nerve fiber density (IENFD) and subepidermal nerve fiber density (SENFD) were quantified using conventional counting method and unbiased stereology protocol, respectively. Double immunostaining for those markers was performed.

Results:
First, there are prominent differences between hairy and glabrous innervation in humans. Their glabrous skin has marked lower ($p<0.0001$) IENFD than hairy skin. However, the glabrous skin has marked higher ($p<0.0001$) densities of NFH+ and nociceptive CGRP+ fibers in the dermis. CGRP+ or NFH+ nerve fibers are scarce in the epidermis in both glabrous and hairy skin in humans. Compared to human data, both the glabrous and hairy skin in mice have dramatically higher IENFD than their human counterparts. Furthermore, in sharp contrast to humans, the epidermis of both glabrous and hairy skin in mice has dense CGRP+ fibers which co-label majority PGP9.5+ fibers.

Conclusions:
This study revealed significant differences in cutaneous innervation between hairy and glabrous skin and between human and mouse that may account for some of the disconnect between preclinical models and human neuropathic pain studies.

References:
No

Grant Support:

Merkin PNNR Center

Keywords: cutaneous innervation, hairy skin, glabrous skin, human, mouse

Impact of PCSK9 Deletion in the Peripheral Nervous System, Insight on Peripheral Neuropathy

Poster No:
P 144

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Institutions:
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Introduction:
Neuropathy is the most common chronic complication of diabetes. It is characterized by peripheral nerve damage and can lead to pain, tingling or loss of sensation. Despite years of research, there is no effective treatment to prevent or slow the progression of diabetic neuropathy. In recent years, an increase number of studies have highlighted the possible impact of lipids and cholesterol in the development of diabetic peripheral neuropathy. Proprotein convertase subtilisin-kexin 9 (PCSK9) is a key regulator of lipid metabolism in the liver by enhancing the degradation of cell surface low-density lipoprotein family receptors such as LDLR, VLDLR, LRP1, APOER2 and CD36.

Methods:
A PCSK9 knockout (PCSK9 KO) mouse model was used to explore the role of PCSK9 in neuropathy using several methods such as sensory tests, immunohistochemistry, in situ hybridization, western blot and electron microscopy.

Results:
Here, we demonstrate PCSK9 mRNA and protein expression in sensory neurons and Schwann cells (SCs) of the mouse sciatic nerves. We observed a significant reduction of light touch and acute mechanical pain sensation associated with a decrease in sensory nerve conduction velocity. At the level of the peripheral nerve, we observed axonal swelling of small nerve fibers with electron microscopy analysis. In parallel, we observed an increase in lipid content in the nerves of PCSK9 KO mice.

Conclusions:
In conclusion, this study highlights a role of PCSK9 in the regulation of lipid content in the peripheral nerve. To further investigate this hypothesis, future studies will focus on the impact of PCSK9 inhibition in the expression of lipoprotein receptors in peripheral nerves and the analysis of conditional PCSK9KO mice.

References:
No

Keywords: Neuropathy, PCSK9, Dyslipidemia, Peripheral nerve

Ischemic Injury and Microvasculitis in Treatment Induced Neuropathy of Diabetes and Treatment Induced Diabetic Lumbosacral Radiculoplexus Neuropathy

Poster No:
P 145

Authors:
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Introduction:
Because both treatment induced neuropathy of diabetes (TIND) and diabetic lumbosacral radiculoplexus neuropathy (DLRPN) can be induced by rapid glycemic correction, we postulate similar pathophysiological mechanisms.

Methods:
We retrospectively identified TIND and treatment induced DLRPN (TI-DLRPN) patients with nerve biopsy (1996-2022). Clinical, electrophysiological, and pathological characteristics were compared.

Results:
Eight TIND and 22 TI-DLRPN patients were identified. TIND were: all males, median age 57.5 years (42-70) and TI-DLRPN were: male (12/22), median age 55.5 years (36-73). TIND had distal sensory neuropathy; TI-DLRPN had sensorimotor radiculoplexus neuropathy. Nerve biopsies showed perivascular inflammatory collections in 8/8 TIND and 22/22 TI-DLRPN (p=1), with similar collection sizes (large 3/8 TIND vs 10/22 TI-DLRPN, p=0.3; moderate 3/8 vs 4/22, p=0.1; and small 2/8 vs 8/22, p= 0.28). Findings diagnostic of microvasculitis were seen in 2/8 TIND and 6/22 TI-DLRPN biopsies (p=0.9), while findings suggestive of microvasculitis in 3/8 vs 8/22 (p=0.1). Ischemic injury was seen in most biopsies (7/8 vs 21/22; p=0.4): multifocal fiber loss (5/8 vs 14/22; p=0.95), neovascularization (5/8 vs 14/22; p=0.95), injury neuroma (2/8 vs 10/22; p=0.3) and perineurial thickening (3/8 vs 16/22; p=0.07). Teased fibers showed axonal degeneration in 6/8 TIND and 20/22 TI-DLRPN; p=0.1 (TIND, 5.9%, 2.9-60% and TIDLRPN, 15.2%, 1.6-74.7%;p=0.3) and of segmental demyelination in 5/8 TIND vs 19/22 TI-DLRPN; p=0.08 (TIND, 4.15% , 0-16.2% and TI-DLRPN, 14.1% , 0-34.5%; p=0.003).

Conclusions:
We find evidence of ischemic injury and microvasculitis in TIND and TI-DLRPN similar to typical DLRPN. We postulate that rapid hyperglycemia correction triggers an immune attack on nerves which presents as either TIND or TI-DLRPN. Why some patients develop TIND and others TI-DLRPN is unclear, but could relate to diabetes type (TIND more in type 1 and TI-DLRPN more in type 2). Larger studies are needed to confirm microvasculitis as the main cause of TIND.

References:
No

Keywords: Diabetes, neuropathy, DLRPN, TIND, microvasculitis

The association between detailed obesity measurements and peripheral neuropathy in persons with diabetes.

Poster No:
P 146

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Introduction:
We aimed to determine associations between detailed obesity metrics and peripheral neuropathy in a large population of persons with diabetes from the United Kingdom (UK).

Methods:
We performed a cross-sectional study of persons with diabetes enrolled within the UK Biobank. Obesity was assessed using anthropometric measurements, bioelectrical impedance analysis (BIA), abdominal MRIs, and/or dual x-ray absorptiometry (DEXA). Obesity metrics were categorized as measuring general obesity, central obesity, peripheral obesity, or the central-peripheral obesity ratio. Neuropathy was assessed using the Michigan Neuropathy Screening Instrument questionnaire (MNSIq). Logistic regression models were used to determine associations between neuropathy and each obesity metric separately, after adjusting for age, sex, height, systolic blood pressure, high-density lipoprotein, and triglycerides. To account for multiple comparisons, statistical significance was assessed using a Bonferroni corrected threshold. Areas under the receiver operating characteristic curves (AUC) were calculated to assess diagnostic capability of individual obesity metrics.

Results:
We identified 9,487 persons with diabetes in the UK Biobank that completed the MNSIq. All participants completed anthropometric measurements, 9,302 completed BIA, 370 completed abdominal MRI, and 200 completed DEXA. There were 1,558 (16.4%) with neuropathy (MNSIq≥4). The mean age was 57.8 (7.1), 41.0% were female and 93.6% were white. Regression models revealed that increased obesity on 5/10 general obesity metrics, 9/19 central obesity metrics, 5/13 peripheral obesity metrics, and 1/5 central-peripheral obesity ratio metrics were associated with increased odds of neuropathy. Metrics with the highest diagnostic capability were the abdominal subcutaneous adipose tissue volume (abdominal MRI, AUC=0.83), weight-to-muscle ratio (abdominal MRI, AUC=0.82), fat mass index (DEXA, AUC=0.82), body surface area (anthropometric, AUC=0.82), and the overall percentage of fat tissue (DEXA, AUC=0.82).

Conclusions:
In agreement with previous studies, many obesity metrics were significantly associated with neuropathy. We found that obesity metrics from abdominal MRI and DEXA generally had better diagnostic characteristics than those from anthropometric measurements or BIA.

References:
No

Grant Support:

This work was supported by the National Institutes of Health (K99DK129785)

Keywords: diabetes, obesity metrics, abdominal MRI, bioelectrical impedance analysis, dual x-ray absorptiometry (DEXA)

Co-culture of immortalized sensory neurons and Schwann cells for the study of peripheral neuropathies

Poster No:
P 147

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Introduction:
Co-culture systems of neurons and Schwann cells have been utilized for the study of axonal degeneration/regeneration and myelination/demyelination; in most of the previous studies, however, these cells were obtained by primary culture that needs a time-consuming process. IFRS1 Schwann cells established from long-term cultures of adult Fischer rat peripheral nerves possess fundamental ability to myelinate neurites in co-cultures with primary cultured rat dorsal root ganglion (DRG) neurons. Our current investigation focuses on the establishment of stable co-culture system with IFRS1 cells and immortalized rat DRG neurons ND7/23, and its usefulness as a model of peripheral neuropathies.

Methods:
1) ND7/23 cells were seeded at a low density (2 x 10^3/cm^2) and kept for 5-7 days in serum-containing medium supplemented with non-essential amino acids, nerve growth factor (NGF; 10 ng/mL), and a Rho kinase inhibitor Y27632 (5 μM). 2) When neurite outgrowth was observed under a phase-contrast microscope, the cells were treated with an anti-mitotic agent mitomycin C (1 μg/mL) for 48 h to suppress proliferation. 3) The cells were then co-cultured with IFRS1 cells (2 x 10^4/cm^2) and maintained in serum-containing medium supplemented with ascorbic acid (50 μg/mL), NGF (10 ng/mL), and ciliary neurotrophic factor (10 ng/mL) for up to 28 days. 4) The co-cultured cells were exposed to glycolaldehyde (GA; 0.5 mM), a precursor of advanced glycation endproducts, for 3 days and the expression of phosphorylated c-jun N-terminal kinase (pJNK) was examined by Western blotting.

Results:
1) At 28 days of co-culture, myelin formation was illustrated by double-immunofluorescence staining with the antibodies to myelin basic protein and βIII tubulin, and confirmed by Sudan Black staining. 2) GA induced axonal degeneration-like changes and enhanced pJNK expression in the co-cultured cells.

Conclusions:
ND7/23-IFRS1 co-culture system can be a valuable tool to study the pathogenesis of diabetic and other peripheral neuropathies.

References:
No

Keywords: Co-culture, IFRS1 Schwann cells, ND7/23 cells, myelination, glycolaldehyde

The Degree of Dietary Fatty Acid Saturation Impacts Neuropathy and Nerve Inflammation in Prediabetic Mice

Poster No:
P 148

Authors:
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Institutions:
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Introduction:
Peripheral Neuropathy (PN) is a morbid neurological complication that impacts up to 50% of diabetic patients and 30% of prediabetic patients and is characterized by loss of sensory function. Recent studies show that dyslipidemia contributes to PN pathogenesis in type 2 diabetes and prediabetes, thereby triggering inflammation that damages the nerves. Since dyslipidemia is characterized by elevated saturated fatty acids (SFAs) and low monounsaturated fatty acids (MUFAs), we sought to determine whether dietary SFAs and MUFAs differentially regulate PN and nerve inflammatory cytokines and chemokines in a high-fat diet (HFD) murine model of prediabetes.

Methods:
Our study included four groups of C57BL6J mice fed a 1) control standard diet (SD), 2) HFD rich in SFAs (HFD-SFA), 3) HFD rich in MUFAs (HFD-MUFA) from 5-30 weeks of age, and 4) HFD-SFA from 5-18 weeks of age followed by HFD-MUFA from 18-30 weeks of age. At 18 weeks and 30 weeks we evaluated metabolic function (body weight, fasting blood glucose level, glucose tolerance, and body composition) and PN phenotypes (hind paw withdrawal and nerve conduction). At 30 weeks sciatic nerves were collected, lysed, and submitted to Eve Technologies© for multiplex chemokine and cytokine quantitation.

Results:
Both HFD-SFA mice and HFD-MUFA mice had higher body weight, increased fasting blood glucose, impaired glucose tolerance, and increased body fat mass throughout the duration of study, indicating that both diets caused metabolic dysfunction, compared to SD mice. HFD-SFA mice displayed decreased hind paw withdrawal and impaired nerve conduction by 18 weeks of age which was reversed by HFD-MUFA by week 30, indicating that HFD-MUFA improves nerve function. Dietary fatty acids altered sciatic nerve inflammatory cytokine, C-X-C motif chemokine, and macrophage inflammatory protein levels relative to SD mice.

Conclusions:
These results indicate that dietary SFAs and MUFAs differentially regulate nerve function and impact nerve inflammatory pathways in PN and prediabetes.

References:
No

Grant Support:

Support for this study was provided by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (R00DK119366), the Columbia University Diabetes Research Center Pilot and Feasibility grant (P30DK063608), and the Thompson Family Foundation Initiative (TFFI) at Columbia University.

Keywords: Diabetic Peripheral Neuropathy, Dietary fatty acids, Inflammation, Murine model, Prediabetes

Towards a Practical Use of Text Mining Approaches in Electrodiagnostic Data

Poster No:
P 149

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Institutions:
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Introduction:
Introduction: Healthcare professionals generate extensive textual data daily, presenting a challenge for insight extraction. This study demonstrates the synergy between text mining and statistical methodologies, emphasizing electrophysiology and nerve conduction studies, to advance health information systems. The focus is on large EMG laboratories in tertiary hospitals, aiming to expedite electrophysiology research.

Methods:
Methods: A retrospective study, spanning May 2016 to February 2022, analyzed patients undergoing electrodiagnostic (EDX) evaluation in a tertiary hospital's large EMG laboratory. Extracted data included demographics, test results, and unstructured reports. Analyses, particularly in electrophysiology and nerve conduction studies, featured topic modeling for clinical impressions and age- and sex-related topic analysis. Integrating suspected clinical condition text enriched data, revealing associations between patients' past medical history (PMH) and emerging diagnosis topics.

Results:
Results: Among 6096 abnormal EMG results, 58% were male. The latent Dirichlet allocation (LDA) algorithm identified 25 topics representing distinct diagnoses in the context of electrophysiology. Sex-related differences surfaced in seven topics, with three male-associated and four female-associated. Notably, brachial plexopathy, myasthenia gravis, and NMJ Disorders exhibited statistically significant age and sex disparities within the realm of electrophysiology. The study extracted 37 keywords related to PMH, revealing close associations with specific electrophysiological topics, such as length-dependent symmetric axonal polyneuropathy (LDPN) with diabetes mellitus (DM) and brachial plexopathy with motor vehicle accidents (MVA).

Conclusions:
Conclusion: This study highlights the efficacy of advanced computational methods in analyzing textual data in practical use in the electrophysiology lab and for epidemiological and nosological research. Text mining integration facilitates clinical insights specific to nerve conduction studies, potentially aiding real-life decision-making in large EMG laboratories in tertiary hospitals. Summarizing visualizations enhance result accessibility, focusing on key electrophysiological findings.

References:
No

Keywords: Machine learning, Electrophysiology, EMG, Deep Learning, Textual visualization

THE EFFECTS OF PRE-CULTURING EXTRACELULAR VESICLES ON THE UPTAKE AND DELIVERY POTENTIAL TO SCHWANN CELL

Poster No:
P 150

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Institutions:
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Introduction:
Despite recent advancements in peripheral nerve transplant, many patients still experience suboptimal outcomes following peripheral nerve transplants due to the intricacies of axonal regeneration. Current practice involves the usage of peripheral nerve autografts or cadaveric allografts; however, the issue of Wallerian degeneration following the injury remains. Previous research has shown promising results, using extracellular vesicles (such exosomes) of neurons, Schwann cells, and endothelial cells to induce tissue regeneration.

Methods:
This project investigates mechanisms to utilize extracellular vesicles regenerative capability by exploring how different concentrations and conditions affect their uptake by other cell types. Further, we have postulated that pre-culturing the extracellular vesicles through co-culture with the respective cell type or target cell type for 24 hours prior to target cell introduction, will increase the extracellular vesicle's tendency for uptake and long-term cell survival; thus, minimizing the likelihood of axonal degeneration after injury. For that we tested several concentrations of Schwasnn cells- derived extracellular vesicles (10ul, 15ul, 25ul, 100ul per mL) with and without pre-culturing them with the target cells (Schwann cells and endothelial cells) and at different time points.

Results:
Our preliminary data demonstrates that when different concentrations of pre-cultured Schwann cells derived- extracellular vesicles were tested, the best dose response in 24hrs, 3 and 7 days of co-culture were 10uL/mL.

Conclusions:
Overall, the findings suggest that pre-culturing extracellular vesicles, the cell origin of the vesicles, and the dosage affect the uptake potential of Schwann cells-derived extracellular vesicles into specific cells such as Schwann cells and endothelial cells. Optimizing the extracellular vesicles uptake could serve a therapeutic benefit to peripheral nerve transplant and improve the success rate of peripheral nerve regeneration. Ultimately, we plan to next explore the drug delivery capabilities of Schwann cells-derived extracellular vesicles and thus improve the outcome of peripheral nerve trauma.

References:
No

Grant Support:

none

Keywords: extracellular vesicles, transplantation

Diagnosing Polyneuropathy using the Erasmus – Polyneuropathy Symptom Score: A Validation Study

Poster No:
P 151

Authors:
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Institutions:
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Introduction:
Chronic axonal polyneuropathy (CAP) is a common disease that, despite clinical symptoms, often remains undiagnosed. Early detection of CAP may enhance identification and treatment of risk factors, delay progression and potentially prevent long-term complications. The Erasmus-Polyneuropathy Symptom Score (E-PSS) is a fast and easy-to-use screening tool consisting of six questions about the presence and frequency of symptoms. It was previously validated in an academic hospital setting and this study aims to validate the E-PSS for use in non-academic hospital settings.

Methods:
This cross-sectional validation study was performed in two large non-academic hospitals in the Netherlands. Inclusion criteria were a visit to the outpatient neurology clinic, aged ≥18 years and ability to fill in the E-PSS and Michigan Neuropathy Screening Instrument (MNSI) in Dutch. All patients visiting the neurology outpatient clinic were eligible, but during inclusion we focused on patients referred with suspected polyneuropathy and controls with similar age and/or symptoms. Exclusion criteria were missing data on the E-PSS questionnaire and controls with subclinical or undiagnosed polyneuropathy. The discrimination performance was evaluated using the area under the curve (AUC) of the receiver operating curves (ROC).

Results:
From February 2020 until March 2022, 645 participants were included of whom 228 had polyneuropathy (35.5%). Median age was 60 years (IQR 46–72) and 58.6% was female (N=390). The median E-PSS score in polyneuropathy patients was 5 (IQR 3-8) and in participants without polyneuropathy 1 (IQR 0-2). The performance of the E-PSS was good (AUC 0.85, 95% CI 0.82–0.88) and higher than the MNSI (AUC 0.70, 95% CI 0.66–0.74).

Conclusions:
The E-PSS, developed to ameliorate early detection of chronic polyneuropathy, has good discriminating performance in non-academic neurology outpatient clinics. Further research will focus on determining a valuable cut-off point to enhance clinical usage.

References:
No

Grant Support:

Prinses Beatrix Spierfonds (W.OR17-10)

Keywords: polyneuropathy, screening, questionnaire, diagnosis, symptoms

Comparison Of Efficacy Of Carbamazepine And Duloxetine For The Treatment Of Diabetic Neuropathy

Poster No:
P 152

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Introduction:
To compare the efficacy of carbamazepine and duloxetine for the treatment of diabetic neuropathy in terms of improvement in pain and quality of life

Methods:
It was a single-center open-label study conducted with patients of diabetes mellitus type II diagnosed with PDPN. A total of 100 cases were randomized (50 in each group) to receive 60 mg/daily duloxetine or CBZ tablets were administered twice daily orally at the recommended dose of 400 mg daily. The daily dose was titrated gradually from 100 mg (day 1) to 400 mg by the end of the first week (days 6 and 7). The dose was later increased up to 800 mg daily, according to the clinical response and the tolerability of the drug. Each patient was followed up for a period of 12 weeks. Change in neuropathic pain at week 12 was compared with baseline and assessed by the pain severity score. The pain severity score was calculated by taking the mean of scores for pain at its worst, pain at its least, pain on average, and pain experienced at a particular time point. QoL was accessed American Chronic Pain Association QoL Scale at baseline and at the end of the trial.

Results:
In the duloxetine and CBZ group, the mean VAS score at baseline was 5.38+0.49 and 5.40+0.49 which reduced after 12 weeks of treatment to 3.26+0.44 in duloxetine and 3.82+0.89 in CBZ group, ($P<0.001$). duloxetine was superior in improving the quality of life along with control of pain after 12 weeks. ($p\text{-value}<0.01$)

Conclusions:
Treatment with duloxetine 60 mg/daily for neuropathic pain in adults with diabetes for 12 weeks demonstrated a substantial pain-relieving benefit, with lower mean pain intensity compared to treatment with CBZ, in this real-world experience trial; Qol index was also better after duloxetine treatment.

References:
No

Keywords: Neuropathic pain, Diabetes, Carbamazepine, Duloxetine, Comparison

Chronic Activation of the Innate Immune Receptor Toll-Like Receptor 4 Decreases Peripheral Nerve Integrity

Poster No:
P 153

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Introduction:
The most prevalent complication of diabetes is the development of pain, numbness, and tingling in the distal extremities – referred to as diabetic peripheral neuropathy (DPN). Although DPN significantly decreases patients' quality of life, there have been challenges in understanding its pathogenesis and developing targeted interventions that improve peripheral nerve health. Diabetes is a chronic inflammatory condition, and the innate immune system receptor toll-like receptor 4 (TLR4) is increasingly recognized as an important contributor to complications seen in diabetes. TLR4 can be activated by various agonists that are present in diabetic patients and promote the expression of downstream inflammatory mediators. These experiments explored how TLR4 activation affects peripheral nerve integrity and contributes to neuropathy development.

Methods:
A hallmark of DPN is the loss of epidermal axons in the distal limbs. To test whether activation of TLR4 drives the loss of peripheral nerve fibers, we intraperitoneally injected the TLR4 agonist lipopolysaccharide (LPS) into wild-type mice over three weeks. Mechanical and thermal thresholds were measured weekly over the course of the experiment and intraepidermal nerve fiber density (IENFD) was subsequently measured.

Results:
Mice tolerate LPS injections but display temporary reductions in weight, suggesting a sickness-associated response to LPS. We quantified intraepidermal nerve fiber density and assessed mechanical and thermal sensation. We found that a series of LPS injections significantly reduced peptidergic fibers (38 vs. 28 fibers/mm, $p = 0.012$) but did not significantly alter pain-like behavior.

Conclusions:
These findings suggest that TLR4-mediated neuroimmune interactions contribute to the integrity of peripheral nerve innervation but may not be sufficient to affect sensation. This indicates that epidermal c-fibers can respond to immune threats and inflammation by undergoing neurodegeneration. Current experiments are exploring the mechanism by which TLR4 contributes to IENFD loss, including identifying TLR4-relevant signaling pathways, innate immune cell involvement, and the time course of TLR4's effects on peripheral nerves and their soma.

References:
No

Grant Support:

1T32DK128770-01A1
NINDS R01NS043314-17

Keywords: diabetic neuropathy, small fibers, inflammation, toll-like receptor 4, peripheral nerve

Neuropathic Pain Consortium (NPC) Abstracts

P 154 - 165

V122I and Black Race Are Linked To Increased Mortality While Dual Therapy Confers No Added Benefit In A US Transthyretin Amyloidosis (ATTR/v) Cohort

Poster No:
P 154

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Institutions:
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Introduction:
Transthyretin (TTR) amyloid polyneuropathy (PN) progression has been dramatically altered by TTR tetramer stabilizers and reduced hepatic TTR synthesis. ATTRv PN trials focused on patients from endemic regions. Here we describe longitudinal follow up of US-based patients, including many with V122I who were poorly represented in registration trials.

Methods:
Longitudinal data pertaining to PN severity, mortality, labs, race, and treatment were abstracted from electronic medical records. Differences in survival were determined by chi squared analysis, factors associated with disease progression were assessed by a linear mixed effects model. Group differences were assessed by t-test.

Results:
Ninety-five subjects, 74 ± 8 years, 32% female were identified. Variants included V122I (28), L58H (25), T60A (11), V30M (12), other (6), and WT (13). Mean follow up was 4.9 ± 2.5 years and baseline neuropathy impairment score (NIS) was 42.7 ± 33.2 (range 5 - 131). 55% of subjects had mixed PN and cardiomyopathy while 42% had only PN. Most were on silencer monotherapy, 27% were on dual therapy (silencer and stabilizer). Twenty subjects died, predominantly from CHF; black race ($p=0.03$), male gender ($p=0.04$), and the V122I allele ($p=0.004$) were risk factors. PN progression was 1.3 NIS points/year; dramatically improved from historical natural history data. Male gender ($p=0.12$) and death ($p=0.09$) were associated with worsening PN progression. Compared to V30M, PN severity was similar in L58H patients ($p=0.7$), less severe in T60A ($p=0.002$) and V122I ($p=0.007$). There was no difference in PN progression between patients on silencer monotherapy vs. dual therapy ($p=0.3$).

Conclusions:
ATTRv PN progression has been dramatically altered with treatment compared to historical natural history data. 87% of patients progressed <4 NIS points/year while 37% had a durable improvement from baseline. Black race and V122I allele were associated with higher mortality. We observed no additional benefit from dual therapy over silencer monotherapy.

References:
No

Keywords: Transthyretin Amyloidosis, Polyneuropathy (PN)

Assessment of Small Fiber Involvement in Patients with Autoimmune Nodopathy by Quantitative Sensory Testing

Poster No:
P 155

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Institutions:
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Introduction:
Recent studies showed high frequency of neuropathic pain (NP) in patients with neurofascin 155-IgG-positive (NF155+) and contactin 1-IgG-positive (CNTN1+) autoimmune nodopathy (AN), suggesting that AN might involve the small fiber (SF) damage. However, conventional nerve conduction studies assess only large myelinated fibers and cannot detect any SF abnormalities. In this study, we aimed to clarify the presence of SF involvement in AN using quantitative sensory testing (QST).

Methods:
We enrolled 8 NF155+ and 3 CNTN1+ AN patients who underwent current perception threshold (CPT) testing which can elucidate the functional status of large myelinated fibers (Aβ fibers), small myelinated fibers (Aδ fibers), and unmyelinated fibers (C fibers) by measuring CPT at settings of 2000, 250, and 5 Hz, respectively, at the unilateral median, ulnar, peroneal, and sural nerves. CPTs that lay outside normal range were defined as abnormal. We also assessed their clinical characteristics and treatment response.

Results:
The disease duration of NF155+ patients was significantly longer than that of CNTN1+ patients (mean ± standard error; 5.9 ± 1.9 years vs 0.7 ± 0.3 years, $p = 0.03$). NP was observed in 3 out of 8 NF155+ and all the 3 CNTN1+ patients. The ratio of CPT abnormalities of Aβ, Aδ, and C fibers respectively in NF155+ patients were as follows; median nerve (100%, 50%, 62.5%), ulnar nerve (100%, 72.5%, 62.5%), peroneal nerve (100%, 62.5%, 37.5%), and sural nerve (75%, 50%, 25%), whereas those in CNTN1+ patients were as follows; median nerve (66.7%, 33.3%, 66.7%), ulnar nerve (66.7%, 0%, 33.3%), peroneal nerve (100%, 0%, 100%), and sural nerve (66.7%, 0%, 66.7%). Immunotherapy ameliorated NP and paresthesia in 2 NF155+ and 1 CNTN1+ patients, with CPT abnormality improvement of Aδ and C fibers as well as Aβ fibers.

Conclusions:
We revealed SF involvement in NF155+ and CNTN1+ patients by QST.

References:
No

Keywords: autoimmune nodopathy, small fiber, neuropathic pain, QST

From Antibody Selection to Automated Quantification: TRPV1 Staining on Human Skin using Immunofluorescence Staining

Poster No:
P 156

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Institutions:
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Introduction:
The transient receptor potential vanilloid-1 (TRPV1) receptor in the skin plays a pivotal role in pain signal detection and is associated with chronic pain conditions. Assessing TRPV1 expression on the skin has the potential to serve as a biomarker for predicting peripheral neuropathic pain outcomes, yet the lack of a dependable immunofluorescence protocol remains a challenge.

Methods:
In this study, six TRPV1 antibodies from different companies underwent validation using immunofluorescence staining on rat dorsal root ganglion (rDRG), hTRPV1-expressing human embryonic kidney (HEK) 293 cells, and human skin samples consecutively. To facilitate unbiased quantification of TRPV1-immunoactive expression on nerve fibers, two automated image analysis methods were developed. These included a deep-learning-based approach in Python and a machine-learning-based approach in FIJI. Both methods utilized a nerve fiber mask (PGP9.5) to filter and count TRPV1 immuno-active dots specifically on nerve fibers.

Results:
Among the six antibodies tested, two demonstrated superior sensitivity and specificity. Quantification revealed no significant differences in the average TRPV1 immuno-active dot counts between the deep-learning-based method (28.9±24.3), the machine-learning-based method (24.0±16.3), and a manual method (23.79±19.8). Strong positive correlations were observed between each pair of the three methods ($P<0.001$).

Conclusions:
In conclusion, two commercially available TRPV1 antibodies emerged as dependable tools for detecting TRPV1 expression in human skin. Furthermore, the newly developed deep-learning and machine-learning-based automated image analysis methods provided accurate quantification of TRPV1 immuno-active dots specifically on nerve fibers. These findings hold promise for advancing the quantification of TRPV1 expression in human skin and have potential implications for pain research and therapeutic strategies.

References:
No

Keywords: TRPV1, Immunofluorescence, Deep learning, Machine learning, Automated analysis

The Prevalence And Clinical Features Of Anti-Annexin A2 Autoantibodies In Neuropathic Pain.

Poster No:
P 157

Authors:
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Institutions:
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Introduction:
In mice, Annexin A2 (ANXA2) is expressed pain-conducting dorsal root ganglion (DRG) neurons and associated with neuropathic pain (NP). In human, although it is known that ANXA2 is expressed in endothelial cells and autoantibodies to ANXA2 (ANXA2-IgG) is pathogenic in antiphospholipid syndrome, relationship between ANXA2-IgG and NP and ANXA2 expression in DRG are not clear. We assessed the prevalence of ANXA2-IgG in patients with NP and its biological relevance.

Methods:
We screened local patients with neuropathy confirmed by nerve conduction studies and divided them by NP status. NP is diagnosed with International Association for the Study of Pain criteria. Patients with neurodegenerative diseases and healthy controls were also included in non-NP group. We assessed serum/cerebrospinal fluid (CSF) ANXA2-IgG and serum ANXA2-IgG subclasses using enzyme-linked immunosorbent assay and the demographic features of serum ANXA2-IgG-positive patients. Additionally, we checked serum IgG reactivity to mouse dissociated DRG neurons by immunocytochemistry, and ANXA2 expression in postmortem lumbar DRG and ventral root tissues by immunohistochemistry.

Results:
Prevalence of ANXA2-IgG was higher in NP group (4/37, 10.8%) than in non-NP group (1/82, 1.2%) ($p = 0.03$). Main antibody subclass was IgG1 in 80% (4/5) of the antibody-positive patients. CSF ANXA2-IgG was found in 80% (4/5) of serum ANXA2-IgG-positive patients. ANXA2-IgG-positive patients consisted chronic inflammatory demyelinating polyneuropathy (n=3), Guillain-Barré syndrome (n=1), and paraneoplastic syndrome (n=1). ANXA2-IgG-positive patients showed recurrent disease course (80%), decreased vibratory sensation (80%), weakness in the distal muscles of the limbs (60%), and response to immunotherapy (60%). Immunocytochemistry demonstrated serum IgG from all ANXA2-IgG-positive patients bound to ANXA2-positive mouse DRG neurons. In human, ANXA2 was expressed in the cytoplasm and plasma membrane of neurons and satellite glial cells in DRG and partial myelin sheath in ventral root.

Conclusions:
ANXA2-IgG is suggested to be associated with NP and a potential biomarker for immunotherapy-responsive NP.

References:
No

Keywords: Annexin A2, Neuropathic Pain, Anti-Annexin A2, autoantibody

Unraveling itch: Exploring the characteristics of pruritus in small fiber neuropathy

Poster No:
P 158

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Introduction:
Chronic itch, or pruritus, is a common discomfort of the skin with an irresistible urge to scratch in order to relief this unpleasant sensation. It can be caused by various conditions and approximately 8% of all chronic itch is caused by a neurological condition. Chronic itch has been described as a symptom of small fiber neuropathy, which is a disorder resulting from damage to the small myelinated Aδ- and unmyelinated C-fibers. Prior studies showed that itch is reported in 63-68% of SFN patients, which suggests that itch is a common symptom. However, no distinct pattern could be found. These studies solely focused on SFN patients and therefore it remains unknown if there is a difference in itch between SFN and non-SFN patients as well as certain characteristics of itch that could indicate SFN.

Methods:
All patients referred to our center were asked to fill out a specific questionnaire about their itch symptoms as well as questionnaires about their other complaints.

Results:
We collected data from 1456 patients and by analysing these patients this study aims to get a better view at the clinical characteristics of itch.

Conclusions:
The results will be presented at the conference.

References:
No

Keywords: Small fiber neuropathy, Itch, Characteristics

Phenytoin Cream For Painful Chronic Idiopathic Axonal Polyneuropathy: A Randomized Double-Blind Placebo-Controlled Trial

Poster No:
P 159

Authors:
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Institutions:
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Introduction:
Patients with chronic idiopathic axonal polyneuropathy (CIAP) may experience neuropathic pain that significantly diminishes their quality of life. Oral neuropathic pain medication often falls short in providing adequate relief and can cause undesirable side effects. Topical phenytoin cream could be a potential solution to these challenges. We performed the first randomized clinical trial in patients with CIAP and neuropathic pain to assess the efficacy and side effects of phenytoin cream.

Methods:
In a six-week randomized double-blind, placebo-controlled double cross-over trial we compared placebo cream with phenytoin creams (20% and 10%) in patients with CIAP and neuropathic pain with a mean daily pain score of at least 4 on the numeric rating scale (NRS, range 0-10). The primary endpoint was the change in pain intensity measured on the NRS between baseline and week 2 for phenytoin 20% versus placebo cream.

Results:
The trial was carried out between July 2020 and June 2023. From 689 patients screened, 80 patients were enrolled. There was 1 drop-out and 26 patients were documented non-responders to other treatments. There were small statistically significant differences in pain reduction on the NRS between the phenytoin creams and placebo cream, but these differences did not reach the predefined 1 or 2 NRS points in the sample size calculation. Phenytoin cream was safe, mild local side effects were uncommon and not more frequent compared to placebo cream.

Conclusions:
This was the first randomized controlled trial in carried out in patients with CIAP. Phenytoin cream was safe, and provided a limited reduction of neuropathic pain. The short 2-week treatment period could be one of the explanations for the observed small effect size. The 1-year open label phase study with 71 patients will provide more insights on long-term effectiveness.

References:
Yes

Reference 1: Kopsky DJ, van Eijk RPA, Warendorf JK, Keppel Hesselink JM, Notermans NC, Vrancken AFJE. Enriched enrollment randomized double-blind placebo-controlled cross-over trial with phenytoin cream in painful chronic idiopathic axonal polyneuropathy (EPHENE): a study protocol. Trials. 2022 Oct 22;23(1):888. doi: 10.1186/s13063-022-06806-8. PMID: 36273216; PMCID: PMC9587538.

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Keywords: idiopathic/cryptogenic axonal polyneuropathy, neuropathic pain, topical phenytoin, randomized trial, double-blind

Early Nociceptive Evoked Potentials (NEPs) in Hereditary Neuropathies

Poster No:
P 160

Authors:
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Institutions:
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Introduction:
Diagnosing small fiber neuropathy (SFN) poses challenges due to the limitations of current tests. A recent development is a surface electrode for small fiber-selective stimulation, featuring an interdigitated micropattern with conductive rails spaced 150µm apart (150IDE) and alternately connected to opposite stimulator poles. This small cathode-anode distance generates an electric field with a maximum penetration depth of 100µm, selectively activating intraepidermal nerve endings. Nociceptive evoked potentials (NEPs) can be recorded from the scalp through rhythmic stimulation with the 150IDE. We propose a novel SFN diagnosis protocol.

Methods:
The research involved 10 healthy individuals, 9 with Charcot-Marie-Tooth disease 1A (CMT1A), 6 with hereditary transthyretin-related amyloidosis (ATTRv), and 3 presymptomatic Phe64Leu-ATTRv carriers. Neurological examination, electroneurography, Sudoscan, and 150IDE-NEPs were performed.

Results:
In healthy individuals, NEPs were recorded after rhythmic stimulation with the 150IDE. These potentials exhibited earlier onset and smaller amplitudes than the more established N1, possibly indicating direct activation of the primary somatosensory cortex. CMT1A patients exhibited either non-recordable or delayed 150IDE-NEPs. Disparities were observed in the amplitude of N40 ($p=0.046$), P50 ($p=0.003$), and N60 ($p=0.020$) and the latency of P80 ($p=0.029$) between CMT1A and healthy subjects. Sudoscan results were altered in only two CMT1A patients, while five of six ATTRv patients exhibited abnormal results. High variability in 150IDE-NEPs was observed, possibly due to diverse TTR variants. Differences between ATTRv and healthy controls emerged in the latency of P50 ($p=0.006$) and the amplitude of N60 ($p=0.010$) and P80 ($p=0.015$). Presymptomatic ATTRv carriers displayed normal Sudoscan and NEP results. Individuals with neuropathic pain had longer N40 ($p=0.032$) and N60 ($p<0.001$) latency compared to those without, and subjects with thermal hypoesthesia exhibited lower N60 amplitude ($p=0.008$) than those without hypoesthesia.

Conclusions:
The 150IDE-NEPs could represent a valuable tool for SFN detection. Further patient enrollment and comparative analysis with skin biopsy would provide important insights.

References:
Yes

Reference 1: Leandri M, Marinelli L, Siri A, Pellegrino L. Micropatterned surface electrode for massive selective stimulation of intraepidermal nociceptive fibres. J Neurosci Methods. 2018 Jan 1;293:17-26. doi: 10.1016/j.jneumeth.2017.08.032

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Keywords: Nociceptive Evoked Potentials, NEPs, Interdigitated Electrode, 150IDE, Small Fiber Neuropathy

Dermal Vessel Innervation in Association with Cold Feet Symptoms in Skin of Bortezomib Induced Polyneuropathy Patients

Poster No:
P 161

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Introduction:
In this study, we aimed to investigate a possible pathophysiological mechanism underlying the symptom of cold feet in patients with bortezomib induced polyneuropathy (BIPN).

Methods:
Twenty-seven multiple myeloma patients with BIPN, 15 patients with demyelinating neuropathy and 24 healthy volunteers were included to the study. Dermal vessel and nerve fiber density in 40-µm skin sections immunolabeled with CD31 and PGP9.5 were evaluated by a newly developed automatic analysis tool created based on Fiji. TH+ sympathetic autonomic and CGRP+ somatic sensory nerve fibers around arterioles are also evaluated in 20-µm skin sections quantitatively. The results were compared between all groups and between BIPN subgroups according to cold feet symptom.

Results:
We found that almost half of BIPN patients complained about cold feet (48%). Mean duration after the last bortezomib dose was significantly longer and neuropathy severity grade was higher in patients in the cold feet group. No difference in vessel density (%) was observed in subepidermis and dermis between the subgroups. However, dermal nerve area (%) was significantly reduced in the cold feet group compared to patients without cold feet. The nerve and vessel connection area in the dermis tended to be lower in the cold feet group. Compared to the healthy and demyelinating neuropathy groups, the BIPN group had significantly reduced nerve density and vessel innervation (connection area %) in the subepidermis while vessel density (%) in both subepidermis and dermis was similar between all groups. Arteriole innervation analysis is ongoing.

Conclusions:
Reduced vessel innervation in skin might be a contributing pathological factor for the cold feet symptom in BIPN patients. Confirmation of those findings in a larger cohort and further investigation of thermoreceptors are needed to better understand the pathophysiology of the cold feet symptoms in neuropathy.

References:
No

Grant Support:

This study was part of KFO5001 ResolvePAIN, funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Project ID: 426503586.

Keywords: Cold feet, Vessel innervation, Autonomic fibers, Bortezomib, Skin biopsy

Diode laser evoked sensory pain threshold as a response biomarker in peripheral neuropathic pain

Poster No:
P 162

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Introduction:
Clinical biomarkers that accurately reflect change in ongoing neuropathic pain with therapy are lacking, likely because the nerve fibers involved in mediating the pain are not accessible by current means. We developed a Diode Laser (DLss) technique to selectively stimulate CMi or Aδ fibers in skin. DLss provides activation of dermal heat sensitive fibers without dangerous overheating. Here we describe technical advances and reliability for use in human subjects.

Methods:
17 healthy participants, ages 25 to 66 were screened to exclude neuropathy, then 12 completed 2 testing days, separated by at least 48 hours, at the foot dorsum: quantitative sensory testing (QST) for warm sensory threshold (WST) and heat pain threshold (HPT); DLss sensory and pain thresholds for C-fiber and Aδ-selective protocols; and DLss induced axon reflex flare, measuring flare area and intensity using reflectance imaging. The flare induction protocol has been optimized using repetitive stimulation and noise reduction. 5 participants performed baseline DLss and QST measures, then wore a 5% lidocaine patch on the foot dorsum for 12 hours, then repeated DLss and QST measures the following day.

Results:
Results: DLss ratio of amperage to CMi pain threshold vs. to Ad sensory threshold differed by (average percent;stdev) 8.1;10.7 from day 1 to day 2 baseline, compared to QST WDT (6.4;6.8)) and HPT (5.8;6.4). Optimized flare area under the curve differed by 15.1%stdev18.2 from day 1 to day 2 baseline. Following lidocaine (N=5) mean DLss thresholds changed by > 25%, while HPT changed by <10%.

Conclusions:
DLss sensory thresholds show high test-re-test reliability, similar to that of commercial QST, and greater response to lidocaine. CMi evoked axon reflex flare, while less reliable, shows even greater response to lidocaine. A combination of these DLss measures has potential as a biomarker correlate to neuropathic pain and analgesic efficacy.

References:
No

Grant Support:

NINDS R61 NS122298

Keywords: Biomarker, Neuropathic pain, Neuropathy

Scaled Out Human Induced Pluripotent Stem Cell Derived Sensory Neuron Production

Poster No:
P 163

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Introduction:
More effective, personalized treatment options are urgently required for chronic pain which affects one in five people worldwide. A scalable, rapid, and reproducible protocol to produce sensory neurons from multiple human induced pluripotent stem cell (hiPSC) lines would aid in better understanding the genetic basis of pain, and accelerate drug discovery platforms for novel analgesics.

Methods:
In this study, three different hiPSC lines (wild type - female, wild type - male, pain agnosia - female) were differentiated using a novel seven day directed differentiation protocol composed of daily combinations of small molecules and growth factors to recapitulate sensory neuron developmental stages. Initially, single cell seeding density titrations were carried out in 6-well plates to establish the best density for optimal differentiation before sensory neuron production was scaled up in flask format and banked. Sensory neurons were then thawed and matured before being molecularly and functionally characterized.

Results:
Sensory neurons generated from all lines expressed BRN3A, PRPH, ISLET1, and TUJ1 at a purity of greater than 95% via immunocytochemistry. The three different donor lines were found to have similar gene expression profile via qPCR for the pan-sensory neuron ion channels: NaV1.7, NaV1.8, NaV1.9, TRPV1, CAV3.2, P2RX3, and TRKA. Lastly, sensory neurons derived from each line show morphological similarities when matured on multi-electrode array plates, but have functional differences in baseline activity through 4 weeks.

Conclusions:
These findings show a rapid seven day directed differentiation protocol can be applied to multiple hiPSC donor lines and successfully produce functional, sensory neurons for downstream assays. This process would allow researchers to test many biological samples with diverse backgrounds to better understand the genetic differences in pain and develop more effective, personalized treatment options.

References:
No

Grant Support:

N/A

Keywords: sensory neurons, human induced pluripotent stem cells, pain, disease modeling, in vitro

Efficacy of Alpha-Lipoic Acid in Chronic Peripheral Neuropathic Pain

Poster No:
P 164

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Introduction:
Chronic peripheral neuropathic pain (CPNP) poses a significant clinical challenge, often unresponsive to conventional therapies. This study investigates the efficacy of alpha-lipoic acid (ALA), an antioxidant, in alleviating CPNP symptoms.

Methods:
A double-blind, placebo-controlled trial was conducted over a 12-month period, involving 150 CPNP patients. Participants were randomly assigned to two groups: one receiving ALA treatment and the other a placebo. ALA was administered orally at a dose of 600 mg/day. Pain intensity, functional status, and side effects were evaluated monthly using standardized scales and questionnaires.

Results:
At 6 months, the ALA group demonstrated a statistically significant reduction in pain intensity compared to the placebo group ($p < 0.05$). Improved functional status was also noted in 70% of patients in the ALA group. Additionally, a decrease in analgesic use was observed in this group. The treatment was well-tolerated, with minimal side effects reported, primarily gastrointestinal discomfort.

Conclusions:
The findings suggest that ALA is effective in reducing pain intensity and improving functional status in CPNP patients. This study highlights ALA as a promising therapeutic agent in the management of chronic neuropathic pain, warranting further exploration in larger-scale clinical trials. The tolerability and safety profile of ALA also make it a viable option for long-term management of CPNP

References:
No

Grant Support:

NA

Keywords: Peripheral Neuropathic Pain, Alpha-Lipoic Acid, Randomized Controlled Trial, Pain Management

Pain-related evoked potentials are a valuable biomarker for assessing small fiber damage in Hereditary Transthyretin Amyloidoses with Polyneuropathy

Poster No:
P 165

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Introduction:
Introduction: Pain-related evoked potentials (PrEP) constitute a valuable neurophysiological tool for screening small fiber (SF) neuropathy. They have proven useful in diagnosing certain neuropathies; however, its usefulness in the evaluation of SF damage in ATTRv-PN is yet to be proven. Our objective is to explore PrEP, as a non-invasive approach, in the evaluation of SF damage in ATTRv-PN patients

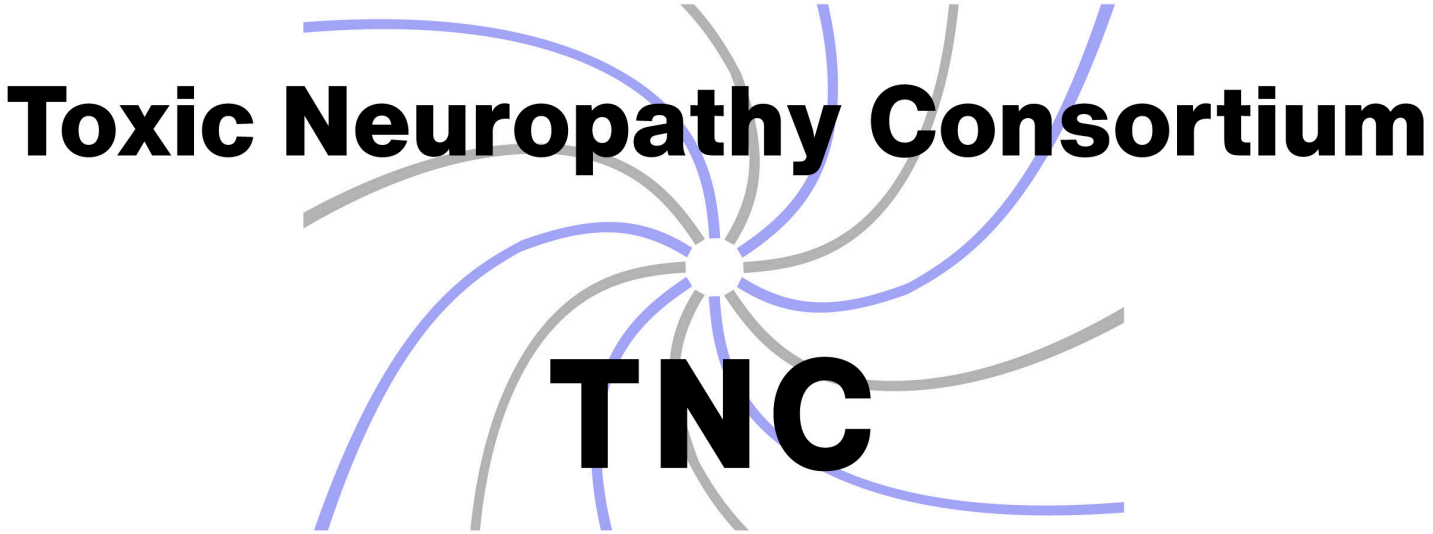
Methods:
Methods: We evaluated 23 genetically confirmed ATTRv-PN patients (12 symptomatic and 11 pre-symptomatic) and 23 age- and sex-matched healthy controls. The subjects underwent detailed clinical examinations and PrEP evaluations on sensory nerves of the arms (median) and legs (superficial fibular). PrEP latencies (negative peak) and the frequency of absent PrEP responses in nerves with abnormal sensory function were compared between groups. Additionally, we evaluated the stimulus perception threshold between the groups.

Results:
Results: The mean age was 47 for symptomatic and 45 years for pre-symptomatic patients. The main mutation was V30M (19 out of 23 cases). PrEP latency was significantly prolonged in the symptomatic group compared to the pre-symptomatic group (147.3+/-25.5 vs. 122.09+/-17.01 ms, p = 0.014) and to control group (218.2+/-35.68 vs. 193.08+/-22.24 ms, p=0.05). The proportion of absent PrEP responses was also higher in the symptomatic group compared to the pre-symptomatic group (50% vs. 18%, p = 0.032) and compared to controls (16% vs 83%, p = 0,003). Additionally, we evaluated the stimulus perception threshold, which was significantly higher in symptomatic patients compared to pre-symptomatic patients (3.317+/-2.406 vs. 1.636+/-0.825 uV, p=0.039).

Conclusions:
Conclusion: Although preliminary, these results suggest that PrEP may be a useful tool to assess SF damage in ATTRv-PN. Further studies are still required to better explore these findings.

References:
No

Keywords: Amyloidosis, PREP, Neurophysiology



Toxic Neuropathy Consortium (TNC) Abstracts

P 166 - 188

Ozone Therapy for Chemotherapy-Induced Peripheral Neuropathy, A pilot Study.

Poster No:
P 166

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Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) stands out as a significant non-hematologic adverse effect, involving damage to peripheral nerves resulting from exposure to neurotoxic chemotherapy drugs. The European Drugs Association sanctioned the use of Ozone for treating inflammation and ulcers in 2003, and subsequent studies have indicated its potential in addressing neuropathy. This pilot study aims to assess Ozone therapy's effectiveness in alleviating symptoms of polyneuropathy.

Methods:
Conducted as a case series study, this research focused on 11 patients with a history of gastrointestinal (GI) cancer, specifically involving the colon and stomach. Following 6 or 12 chemotherapy sessions (Oxaliplatin-based regimen) with confirmed neuropathy, all patients were referred for ozone therapy. Each patient underwent 30 sessions of ozone therapy. Comprehensive assessments, including the monofilament test and Dipazon exam, were conducted before and after treatment. Additionally, the quality of life was evaluated using a QLQ-C30 questionnaire.

Results:
Among 11 subjects (six female and five male), the mean age was 63.09±5.55. Dipazon exam remained unchanged post-treatment (Before Median=10, range: 8-10 vs After Median=10, range: 8-10). While the monofilament test revealed no changes for nine patients before treatment, two patients exhibited improvements after treatment. The QLQ-C30 mean before treatment was 0.56±0.09, and it increased to 0.65±0.12 after treatment (P-Value=0.02).

Conclusions:
The results from this pilot study suggest that Ozone therapy maintained the patients' neuropathic condition without progression. Positive changes were observed in QOL. However, a more extensive sample size with control is needed for conclusive findings in future studies.

References:
No

Keywords: Ozone, Chemotherapy-induced peripgeral neuropathy, Oxaliplatin

MOLECULAR CHARACTERIZATION OF OXALIPLATIN-INDUCED PERIPHERAL NEUROTOXICITY

Poster No:
P 167

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Introduction:
Oxaliplatin (OHP) is characterized by a peculiar neurotoxicity profile (oxaliplatin-induced peripheral neurotoxicity [OIPN]); apart from a chronic sensory neuropathy, it causes an acute syndrome with cold-induced paresthesia and cramps. Acute OIPN is due to ion channel dysfunctions and there is a growing body of evidence suggesting that the severity of acute OIPN is a predictor for more severe chronic neuropathy.

Methods:
OHP-treated (3 mg/Kg, 2qw4ws, iv) and a control group of female rats (n=12/group) were tested. The onset of acute OIPN was assessed via nerve excitability testing (NET), whereas chronic OIPN via behavioural test, nerve conduction studies (NCS), and neuropathology. The latter was performed on specimens collected at the end of treatment and after 6 weeks of follow-up: caudal nerves and dorsal root ganglia (DRG) underwent morphological and morphometric analysis; intraepidermal nerve fiber density (IENFD) was measured on paw skin specimens; immunohistochemistry for the transient receptor potential vanilloid type-1 (TRPV1) receptor was perfomed on lumbar spinal cord specimens.

Results:
Acute OIPN was demonstrated as soon as the first OHP administration, and it was resolved 1 week after the end of treatment. Chronic OIPN was demonstrated at the end of treatment; however, it nearly resolved at follow-up. Densitometric analysis of TRPV1 immunolabeling in the dorsal horn of the spinal cord at the end of treatment showed an increased density of TRPV1 staining in OHP animals (in lamina I and inner lamina II). This difference was maintained at follow-up.

Conclusions:
Acute OIPN (i.e., alterations of ion channels) is clearly different phenomenon respect to neuropathic pain manifestations due to chronic OIPN, as demonstrated by the mismatch between NET alterations and persistence of neuropathological alterations (spinal cord and IENFD). Acute and chronic OIPN should be explored as separate sides of the same coin in future studies, and NET is the ideal method in this regard

References:
No

Keywords: nerve excitability testing, neuropathology, animal models, chemotherapy induced peripheral neurotoxicity

Sound Waves of Relief: Unveiling Ultrasound's Potential against Chemotherapy-Linked Neuropathy

Poster No:
P 168

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Introduction:
Paclitaxel, a frontline chemotherapy medication for various cancers, disrupts microtubules during cell division, impeding cancer cell proliferation. Despite its efficacy, paclitaxel can cause adverse effects, including peripheral neuropathy, impacting normal cells and demanding intricate management. Managing and preventing paclitaxel-induced neuropathy are critical for patients' well-being and treatment completion.

Methods:
In the exploration of therapeutic avenues, Low-Intensity Ultrasound (LIUS) emerges as a potential solution for managing neuropathic conditions, especially chemotherapy-induced peripheral neuropathy (CIPN). Zebrafish embryos serve as a model for studying paclitaxel-induced neuropathy. LIUS treatments at varying frequencies and intensities are administered to these zebrafish embryos, setting the stage for investigating the potential of ultrasound therapy.

Results:
Preliminary findings from our experiments reveal an interesting observation. Paclitaxel-induced neuronal retraction, a hallmark of neuropathy, is significantly mitigated by ultrasound treatment. This suggests a promising strategy for preventing neuropathy associated with paclitaxel, offering a non-invasive and potentially effective therapeutic intervention.

Conclusions:
Ultrasound therapy implementation is an attractive candidate for future clinical trials aimed at preventing and managing neuropathy in cancer patients undergoing paclitaxel treatment. These results underscore the potential of LIUS as a valuable addition to neuropathy management strategies, encouraging further exploration and validation in more complex organisms and, ultimately, human clinical trials.

References:
No

Keywords: Chemotherapy, Neuropathy, Paclitaxel, Ultrasound

Impairment Of Sensory Function And Ethological Behaviors In A Rat Model Of Paclitaxel Induced Neuropathy

Poster No:
P 169

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Institutions:
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Introduction:
Paclitaxel-induced neuropathy is the major dose-limiting side effect of this widely used chemotherapy agent. Given the lack of effective preventive and therapeutic strategies, validating animal models becomes imperative for conducting translational mechanistic and treatment studies. This study aims to characterize multiple behavioral responses induced by clinically formulated paclitaxel in rats.

Methods:
Adult male Sprague-Dawley rats receiving either paclitaxel (4 mg/kg, ip) or vehicle were periodically weighted. Mechanical and cold-induced sensitivities were evaluated using von Frey filaments and acetone. Locomotor activity, anxiety-like behaviors and ethologically relevant parameters such as exploratory activity, thigmotaxis, rearing movements and grooming behaviors were also assessed in an open field.

Results:
Animals receiving paclitaxel showed a progressive attenuation in their weight gain. This attenuation was noticeable from the onset of the chemotherapy cycle and achieved statistical significance in the long term. In line with these findings, a pronounced reduction in food intake was detected during PAX administration period, with concomitant lower water consumption. Paclitaxel-injected animals developed both mechanical and cold hypersensitivities, with 13% and 40% of the rats evidencing patent mechanical and thermal allodynia. However, none of the animals exhibited pronounced piloerection, hind limb weakness, alterations in posture, limb retraction or guarding behaviors. There were no observable alterations in grooming behaviors and coat conditions. Animals receiving PAX also showed reduced spontaneous locomotor activity while anxiety-like behaviors were exacerbated. Remarkable reductions were detected in the time spent in the central area, the number of entries into the central zone, the ratio between time spent in the centre and time spent in the periphery, and the ratio between distance travelled in the centre and total distance travelled.

Conclusions:
This study offers valuable insights into the behavioral effects of paclitaxel on rats, particularly in the context of peripheral neuropathy. The thorough phenotypic characterization of this rodent model will hopefully enhance the development of translational mechanistic and treatment-oriented investigations.

References:
No

Grant Support:

This work was supported by Agencia Nacional de Promoción Científica y Técnica (PICT 2020-030), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET, PIP 297) and Universidad Austral (O05-PDISR098), Argentina.

Keywords: Paclitaxel-induced peripheral neuropathy, Mechanical and cold hypersensitivities, Ethologically relevant behaviors, Ongoing pain-like behaviours, Anxiety-related behaviours

Chemotherapy-Induced Peripheral Neuropathy in a Cohort of Pediatric Oncology Patients from "a specifi region".

Poster No:
P 170

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Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) stands out as one of the most frequent adverse reactions associated with cancer treatment, significantly affecting the patient's quality of life. However, the impact of this severe adverse effect has yet to be assessed in our country. Hence, the primary objective of this study was to examine the prevalence and clinical characteristics of CIPN within a local cohort of pediatric oncology patients. Additionally, the study aimed to assess the potential associations with demographic and treatment-related variables.

Methods:
A total of sixty-six patients diagnosed with malignant hematopoietic tumors and receiving vincristine were included in the observational, retrospective study. Variables analyzed included age, gender, tumor type, chemotherapy (type and number of neurotoxic agents), occurrence of CIPN, main symptoms, severity, and analgesic treatment.

Results:
The study population consisted of 39 boys and 27 girls. The predominant hematologic malignancy was precursor B-cell acute lymphoblastic leukemia (67%). Symptoms consistent with CIPN were identified in 15 children, reflecting a prevalence of 23%. All these patients also received methotrexate, while 90% received both these agents plus cytarabine. The main symptom was pain in the lower limbs, with some patients reporting jaw or generalized pain. Pain severity was categorized as mild in 13% of the children, while 60% and 27% experienced moderate or severe pain. In such cases, anticonvulsants and/or opioids were prescribed. Among the demographic and treatment-related variables analyzed as potential risk factors, only the concurrent administration of cytarabine demonstrated a significant association with vincristine-induced peripheral neuropathy. Incidence of neuropathy did not show associations with sex, age, tumor type, or the number of neurotoxic agents administered.

Conclusions:
Given the fluctuating prevalence of pediatric CIPN across different regions, understanding the characteristics of the local population becomes crucial for designing and implementing effective preventive and therapeutic interventions.

References:
No

Keywords: chemotherapy-induced neuropathy, vincristine-induced pain, pediatric oncology patients

Nitrofurantoin-induced polyneuropathy, a forgotten entity.

Poster No:
P 171

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Introduction:
We report a case of a nitrofurantoin- induced polyneuropathy presented as progressive chronic distal quadriparesis with complete sensory impairment to highlight the importance of clinical aspects and the resources available to make the right diagnosis in polyneuropathies and to identify treatable conditions.

Methods:
We described neurological features, laboratory tests, electro-physiological and pathological, findings of the patient.

Results:
We report 30-year-old women with medical history of recurrent urinary tract infections due to neurogenic bladder. She was diagnosed with spina bifida at age of 4 and because she has been admitted at least 2 times for parenteral antibiotic treatment she was prescribed with nitrofurantoin 100 mg TID which she has been consuming 2 years before admission to our hospital. 18 months before her admission she presented painful quadriparesis. It started as numbness and weakness in toes and it progressively ascended. 12 moths before hands were also affected. Limitations in daily live activities progressed the next months and at her hospital admission she had an asymmetric distal predominant quadriparesis with dropped feet, hyporeflexia and sensory impairment in multiple modalities. Electrophysiological studies were performed with unexcitable nerves and characteristics of chronic active axonal polyneuropathy in electromyography. Many exams failed to determine the underlying etiology and sural nerve biopsy reported characteristics of toxic neuropathy. The nitrofurantoin was suspended and in five months improvement was evident not only in sensory symptoms but motor as well.

Conclusions:
In conclusion, we report a case of toxic neuropathy due to nitrofurantoin. As this entity has not been reported from many decades it can be considerate a forgotten

References:
Yes

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Keywords: Toxic neuropathy, nitrofurantoin

Calpain-Mediated Disruption of Axon-Glia Interaction in Cisplatin-Induced Peripheral Neuropathy

Poster No:
P 172

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Introduction:
Chemotherapeutic-induced peripheral neuropathy (CIPN) serves as a primary constraint in cancer treatment, often leading to dosage reduction or discontinuation of chemotherapy. Several pathological mechanisms in CIPN focus on axonal dysfunction. However, the potential impact of alterations in axon-glia interaction remains unexplored. The axo-glia junction at nodes of Ranvier comprises protein sets with specific distribution, including ion channels, transmembrane proteins, and cell adhesion molecules. The spectrin cytoskeleton which forms the foundation for the axon-glia junction, is susceptible to calpain-mediated proteolysis, and activation of calpain is prominent in CIPN. Therefore, we hypothesize the disruption of the axon-glia interaction in a calpain-dependent manner in the CIPN model.

Methods:
CIPN was induced by cisplatin (cumulative 23mg/kg) in mice, and sensory behavioral assessments, including mechanical allodynia and thermal hyperalgesia, confirmed the development of CIPN. Additionally, sensory nerve conduction velocity was reduced in cisplatin-treated groups. Furthermore, intraepidermal nerve fiber density was decreased in the cisplatin-treated group. To investigate the molecular organization of the axon-glia junction, immunohistochemistry was performed on sural and tibial nerves using markers such as Caspr, Neurofascin, Ankyrin-G, and β-IV spectrin.

Results:
Interestingly, the cisplatin group exhibited disrupted paranodal structures with abnormal localization of nodal and paranodal proteins. To further support our hypothesis, we have used the calpain inhibitor MDL28170 (cumulative 100mg/kg) and observed improvements in both sensory behavior and electrophysiology. Currently, we are assessing the rescue effect of calpain inhibitors on the molecular organization of the axon-glia junction.

Conclusions:
Importantly, our results strongly suggest that the disruption of the axon-glia junction is involved in the pathogenesis of CIPN, and the use of calpain inhibitors might rescue the CIPN. Thus, our findings unveil a novel mechanism in the field of CIPN and the potential therapeutic relevance of targeting the axon-glia junction and calpain activity in managing CIPN.

References:
No

Grant Support:

This project is supported by the Department of Science and Technology (DST-INSPIRE), Government of India.

Keywords: Chemotherapeutic-induced peripheral neuropathy, Axon-glia interaction, Node of Ranvier, calpain inhibitor, paranodal junction

A Case Report of Acute Porphyric Neuropathy and Lessons for Interspecialty Care

Poster No:
P 173

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Introduction:
Acute porphyric neuropathy presents as a rapidly progressive, motor predominant neuropathy affecting upper more than lower limbs. We report a case of acute porphyric neuropathy, and the care coordination necessary between neuromuscular and hematology in fine tuning disease-targeted therapy.

Methods:
A woman in her 30s developed progressive arm weakness and numbness over 8 weeks, following one year of vague episodic abdominal pain and spells of presyncope and syncope. She also developed voice hoarseness as well as progressive dysphagia necessitating PEG placement. Examination showed essentially flaccid upper limbs, with 1/5 finger flexor movement and no extensor movement, and 4/5 ankle dorsiflexion. Patient described sensory symptoms, however had preserved sensory perception to all modalities on examination.

Results:
Electromyography demonstrated a severe axonal, motor neuropathy involving upper greater than lower limbs. Urine porphobilinogen was significantly elevated at 59.0 mg/L, urine ALA 13.2 mg/L, with ALA to creatinine ratio of 41.4. She was treated with oral glucose therapy and 5 days of intravenous hemin infusions. Following treatment, urine porphobilinogen and ALA improved (27.9 mg/L, 4.3 mg/L, respectively). Genetic testing showed a variant of uncertain significance in HMBS which is associated with autosomal dominant acute intermittent porphyria. Follow up at 2 months showed mildly improved proximal strength.

Conclusions:
Hematology led decision-making on hemin therapy (range 5-14 days), however duration of therapy in this rare disease was initially to be dictated by clinical improvement. Given the axonal nature her neuropathy, a clinical or electrophysiological improvement over the course of 1-2 weeks would be surprising. This was important to know for the treating teams, as it dictates need for other treatment response and disease biomarkers. It was imperative to combine interdisciplinary knowledge and tools to direct therapy frequency and duration. This case highlights the importance of natural history and outcomes data in rare neuropathies to guide therapy.

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Yes

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Grant Support:

NA

Keywords: neuropathy, outcome measure, porphyria, rare disease

Refinement Of Dorsal Root Ganglia Neurons Morphometry

Poster No:
P 174

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Introduction:
Oxaliplatin (OHP) is known to cause peripheral nervous system damage and it is a reliable model of neuronopathy, a condition in which it is crucial to quantify the effect size on morphometric changes in dorsal root ganglia (DRG) neurons. Since this measurement is operator-dependent, our aim was to refine our standard morphometry protocol allowing for better control of possible measurement bias and, potentially, for the development of an automated measurement method.

Methods:
The analyses were performed on DRG obtained from mice treated with OHP (3mg/kg twice a week for 4 weeks), compared to CTRL animals. Two blinded examiners evaluated light micrographs of methylene-blue stained DRG sections acquired at the end of the treatment and after 6 weeks of follow up. ImageJ software was used to manually trace the outline of neuronal soma, nuclei, nucleoli, and to calculate the corresponding areas. All traces were saved and labelled on the images using a specific ImageJ plug-in, allowing to check hereafter the accuracy of the measurement and to identify the outlined areas.

Results:
Both examiners found a statistically significant reduction in all elements of interest (soma, nucleus, nucleolus) in OHP-treated mice at the end of the treatment, while at the end of the 6-week follow up the reduction was statistically significant only in the nucleolar area. The same level of significance was obtained by both examiners.

Conclusions:
Since very little, non-significant, difference was observed between the examiners, confirming that our approach is reliable, no post-hoc correction was required. Therefore, it was confirmed that this algorithm, enabling a persistent mark defining soma, nucleus and nucleolus areas, could be the ideal basis to implement the automatic measurement method with machine learning algorithms we are developing.

References:
No

Grant Support:

Cariplo Foundation Grant to Paola Alberti (Biomedical Reasearch conducted by Young Researchers)

Keywords: chemotherapy induced peripheral neurotoxicity, neuronopathy, dorsal root ganglia, morphometry

Role Of Neurotransmitters In Perineural Invasion And Survival Of Cancer Cells

Poster No:
P 175

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Introduction:
Perineural invasion (PNI) is a characteristic feature of several cancers where cancer cells invade peripheral nerves, particularly, into the perineural space. PNI is a risk factor for cancer metastasis and recurrence; it also contributes to cancer-related neuropathic pain. However, the exact mechanisms that fuel-up PNI is understudied. Also, whether cancer cells participating in PNI has any survival advantage in response to chemotherapy agents is also not systematically studied. Here, using our newly developed ex-vivo model, we evaluated the effect of neurotransmitters on PNI occurrence and cell survival.

Methods:
Dorsal root ganglion (DRG)-nerve preparations were embedded in Cultrex in a 24-well plate to mimic extracellular matrix (ECM) and co-cultured with eGFP-tagged breast and prostate cancer cell lines. The preparations were then treated with the neurotransmitters norepinephrine and acetylcholine with or without the presence of chemotherapy agents cisplatin and paclitaxel. After 14 days, the DRG-nerve preparations were isolated and PNI cells were quantified. The interactions of PNI cells with intact axons, neuron cell bodies and glial cells were also examined.

Results:
We found increased occurrence of PNI in neurotransmitter treated groups compared to control preparations. In addition, we also found increased number of surviving PNI cells in combination groups compared to chemotherapy alone groups. In separate experiments, we found that PNI cells tend to migrate towards neuron cell bodies rather than localizing to the axonal compartment indicating that neuron cell bodies are enriched with chemotactic signals for cancer cells facilitating PNI.

Conclusions:
Our results provide evidence that autonomic neurotransmitters facilitate PNI and offer survival advantage to cancer cells and thus may contribute to cancer-related neuropathic pain.

References:
No

Grant Support:

Saskatchewan Health Research Foundation (Establishment Grant)
Prostate Cancer Fight Foundation and Ride for Dad
APP Devolved funding (from University of Saskatchewan)

Keywords: Perineural invasion, Cancer, Chemotherapy, Neuropathy, Metastasis

Acute intermittent porphyria related acute neuropathy- a case report

Poster No:
P 176

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Introduction:
Porphyrias are disorders of the biosynthetic pathway of heme. The neurological manifestations included acute on chronic peripheral neuropathy.

Methods:
A 28-year-old female presented with generalized weakness of all four limbs.The initial impression was AMAN subtype of GBS. However, further questioning revealed symptoms starting 5 years ago, with periods of exacerbation, and improvement seemingly with use of traditional medications. She also had a history of recurrent abdominal pain and passage of dark-colored urine. A physical examination revealed bilateral hand weakness with foot drop and a high steppage gait. Power was grade 4 in proximal muscles and was grade 1 in distal muscle group. Upper limb power was grade 3, with sensory examination normal in both limbs. A nerve conduction study showed absent radial and peroneal responses. The compound muscle action potentials of the other nerves were reduced with mild prolongation of distal latency and slowing of contusion velocity. Sensory studies were normal, except for prolonged distal latencies of both median nerves. Needle electrode examination revealed acute denervation in a number of proximal and distal muscles. Urine porphobillinogen was raised at 29 micromol/L. A diagnosis of acute intermittent porphyria related neuropathy was made.

Results:
Hemin, the specific treatment for AIP, is not available in the under-resourced setting where the patient was managed. She was given high-concentration parenteral glucose. Although there was no evidence for its use, a trial of corticosteroids was commenced. There was only mild improvement by grade 1 in both upper limbs. At the one-month review, her power remained static.

Conclusions:
The peripheral neuropathy associated with AIP often resembles GBS. Careful elucidation of previous episodes, muscle wasting, lack of sensory or cranial nerve involvement, history of abdominal pain with "negative laparotomy", and passage of dark urine are all clinical clues that should prompt urine testing for porphobilinogen.

References:
No

Grant Support:

No Grant Support.

Keywords: Porphyria, Acute Intermittent Porphyria, GBS(AMAN variant), Neuropathy, Developing countries Healthcare

A CASE OF ATYPICAL BORTEZOMIB INDUCED MOTOR PREDOMINANT NEUROPATHY IN A NON-LENGTH DEPENDENT PATTERN

Poster No:
P 177

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Introduction:
Bortezomib is a proteasome inhibitor used for chemotherapy in multiple myeloma (1). Bortezomib induced peripheral neuropathy (BIPN) is seen in 35% of exposed patients (2). Severe BIPN has a 71% rate of recovery/improvement (2). BIPN usually manifests as a painful small fiber neuropathy affecting the dorsal root ganglia (1). Rare motor predominant cases of BIPN have been reported (3). Management of BIPN typically consists of steroids and reduction/discontinuation of bortezomib (2). We present a case in which a patient developed progressive shoulder weakness attributed to bortezomib.

Methods:
This 66-year-old-man with lambda light-chain myeloma was hospitalized for melphalen and stem cell transplant. In the last 3 months he had 4 cycles of bortezomib. Around this time, he developed progressive right and then left shoulder weakness without sensory changes. Strength was 2/5 at right deltoid and biceps, 4/5 at left deltoid with diminished RUE reflexes. EMG revealed right axillary, musculocutaneous, and suprascapular axonal mononeuropathies. Other C5-C6 and upper trunk innervated muscles, such as the brachioradialis, were normal. In his legs he had a non-length-dependent, asymmetric, axonal, large fiber neuropathy with sensory involvement. Lambda light-chains were elevated to > 1000 mg/L at the time bortezomib was initiated but bellow 100 mg/L at that the time of neurology evaluation. Cervical and brachial plexus MRI and a PET CT showed no lesions to explain the clinical and EMG findings. His CSF was unremarkable. Infectious workup, rheumatological labs, and GM1 antibodies were negative.

Results:
Bortezomib was stopped, and his plasma cell dyscrasia improved with melphalen and stem cell transplant. IVMP was deferred due to myelosuppression. At 14 months the right biceps strength had improved to 4/5. The right deltoid strength remained 2/5 with improved passive ROM.

Conclusions:
Bortezomib often has an associated painful axonal neuropathy, however this case demonstrates that BIPN can occasionally manifest as a non-length dependent motor predominant neuropathy.

References:
Yes

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Keywords: Bortezomib, Axonal, Mononeuropathy Multiplex

West Yorkshire Experiences of Nitrous Oxide -N2O- Related Neuropathy and Sub-Acute Combined Degeneration Cases

Poster No:
P 178

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Introduction:
The purpose is to share our regional experiences of Nitrous Oxide related neurological complications in past two years. Recent UK official data suggested the use of laughing gas is now the second most used drug among the young people, with over 8% of 16- to 24-year-olds.

Methods:
Reports of peripheral neuropathy patients seen in two neurophysiology departments at West Yorkshire from April 2022 to July 2023 were reviewed.

Results:
Six cases (age 19 to 28 years/4 males and two females) of N2O related neuropathy cases including three with SACD were seen. They all exposed regularly to N2O of six months or more. All have gait ataxia and lower limbs sensory symptoms. Only one has hands symptoms. None of them manifested with motor or sphincter control symptoms. Reflexes are down in four and brisk with clonus in two SACD cases. Two cases showed macrocytosis. Only one has low B12 level. One has elevated MMA level. Four patients CSF studies were normal. EMG/NCS revealed predominantly axonal loss motor sensory polyneuropathy involving lower limbs. Sensory and motor axonal loss was seen in all three SACD cases. The rest had only motor fibres loss in legs. Upper limbs sensory motor fibres involvement is confined to SACD cases. MRI of spine revealed hyper intense T2 signals in C2-C7 level cervical spinal cord of two SACD cases. All received B12 treatment with good improvement. Two patients had follow-up NCS. One revealed neurophysiological improvement.

Conclusions:
The use of N2O among young people is an issue all across in UK. Despite the explained mechanism of functional B12 deficiency causing demyelination, our observation suggested more axonal loss type peripheral neuropathy (like many others). Nitrous Oxide consumption history can be considered as one potential etiology in any young patients with neuropathy or myelo-neuropathy.

References:
No

Grant Support:

No

Keywords: nitrous oxide related neuropathy, myelopathy

Chemotherapy Induced Peripheral Neuropathy: a possible neuroprotective role for HDAC6 inhibitors

Poster No:
P 179

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Introduction:
Chemotherapy induced peripheral neuropathy (CIPN) is one of the most frequent and serious long-term side effects of chemotherapy, affecting more than 50% of patients. Despite numerous preclinical and clinical studies, effective therapies for preventing or limiting CIPN severity remain elusive. Histone deacetylase 6 regulates gene expression, impacting in several cellular processes. Its inhibitors (HDAC6i) show potential for neuroprotection and anticancer effects. In this work we investigated the possible molecular mechanism by which HDAC6i exert a neuroprotective effect against neurotoxicity induced by different chemotherapy drugs (bortezomib, oxaliplatin, paclitaxel and vincristine). Specifically, we studied the involvement of the NMNAT2/SARM1 pathway, which is suggested to be associated with CIPN and the modulation of neurite degeneration.

Methods:
The neuroprotective effect of different HDAC6i (ricolinostat, SW-100 and tubastatin A) was evaluated in primary cultures of mouse sensory neurons. Neurons were treated with various concentrations and combinations of chemotherapy drugs and different HDAC6i. Neuronal survival and neurite elongation were measured to evaluate neurotoxic or neuroprotective effects. Modulation in protein expression were analyzed by western blotting. The non-interference of HDAC6i on drugs anti-tumor effect was assessed by MTT assay in different cancer cell lines.

Results:
All evaluated HDAC6i show a neuroprotective effect against all chemotherapeutics tested and none of HDAC6i showed interference with the anti-tumor effect of chemotherapy drugs against cancer cell lines. Moreover, we demonstrated that paclitaxel induces a reduction of protein expression of NMANT2 and SARM1, restored by the co-treatment with HDAC6i.

Conclusions:
The study suggest the neuroprotective effect of HDAC6i through the restoration of NMNAT2 levels (reduced by antineoplastic drugs). This allows to recover the correct NMNAT2/NAD ratio essential for preserving SARM1 in its inactive and non-pro-degenerative form.

References:
No

Grant Support:

Fondazione Serpero

Keywords: - Chemotherapy induced peripheral neuropathy (CIPN), - HDAC6 inhibitors, - NMNAT2, - SARM1

Chemotherapy-induced peripheral neuropathy is associated with reduced executive function in chemotherapy treated cancer survivors

Poster No:
P 180

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Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) is common and disabling among cancer survivors. Little is known about the association of CIPN with other measures of the nervous system's integrity, such as executive dysfunction. We compared measures of executive function in older chemotherapy-treated cancer survivors with and without CIPN.

Methods:
This cross-sectional study enrolled 50 chemotherapy-treated cancer survivors (65.6±11.5 years, 88% women) post chemotherapy treatment. Twenty-two participants (44%) had CIPN defined by patient reported distal paresthesia or numbness which began with chemotherapy and continued to the time of cognitive testing. Measures of executive function included Trails-B, Stroop, and rapid reaction accuracy (RRA) and were evaluated between cancer survivors with and without CIPN using T-tests. Multivariable models were then used to determine whether CIPN was an independent determinant of the measures of executive function (Trails-B, Stroop Incongruent, RRA). Models were adjusted for age, gender, history of anxiety, and benzodiazepine use due to their known associations with cognitive and executive function.

Results:
Cancer survivors with CIPN (CIPN+) had reduced executive function compared to survivors without CIPN (CIPN-) on Trails-B (CIPN+: 84.9s±44.1s, CIPN-: 59.1s±22.5s, p=0.01), Stroop (CIPN+: 100.6s±38.2s, CIPN-: 82.1s±17.3s, p=0.03), and rapid reaction accuracy (CIPN+: 60.3%±12.9%, CIPN-: 70.6%±15.7%, p=0.01). The association between CIPN and reduced executive function was found in multivariable models after adjusting for age, gender, anxiety, and benzodiazepine use for Trails-B (ß:17.9, p=0.046), Stroop (ß:16.9, p=0.02), and rapid reaction accuracy (ß:-0.072, p=0.03).

Conclusions:
CIPN is associated with reduced executive function in older cancer survivors treated with chemotherapy. Future research is required to further understand the association, causality, and potential risk factors. Nevertheless, neurotoxicity may concomitantly affect peripheral and central nervous systems and could confound interpretation of research evaluating chemotherapy's neurotoxicity.

References:
No

Grant Support:

P30AG02482

Keywords: Chemotherapy induced peripheral neuropathy, Neurotoxicity, executive function

Leprosy late-onset neuropathy: an uncommon presentation of an autoimmune reaction of pos treated leprosy isolated in the peripheral nerve system

Poster No:
P 181

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Introduction:
This abstract presents a case study of a 70-year-old male exhibiting symptoms of generalized weakness, body-wide pain, and difficulty sitting and standing. The patient's complex medical history includes a longstanding diagnosis of tuberculoid leprosy at 23, treated with 4 years of multidrug therapy, during which he experienced various leprosy reactions and was treated later with thalidomide for many years.

Methods:
The patient underwent a thorough clinical examination, revealing severe muscle atrophy and hypotonia in the left upper limb, along with asymmetrical sensory deficits in the lower limbs.

Results:
Additionally, nerve conduction studies showed an asymmetric axonal sensory-motor polyneuropathy and nerve biopsy of the superficial fibular nerve revealed moderate perineurial thickening, a focal inflammatory infiltrate with mononuclear predominance, an intense fibrosis of the perineurium and a negative Fite-Faraco stain sections for acid-fast bacilli (AFB).This case highlights the challenges in diagnosing and managing chronic neuropathy in the context of a post treated leprosy neuropathy patient.

Conclusions:
The combination of a progressive worsening of his neuropathic symptoms and the histopathological findings of an inflammatory process in the nerve lead us to the diagnosis of a Leprosy late-onset neuropathy, an uncommon presentation of an autoimmune reaction of a pos treated patients with leprosy isolated in the peripheral nerve system.

References:
No

Keywords: leprosy

Preclinical Model of Paclitaxel-Induced Neuropathy: A Combined Neuropathy and Breast Cancer Approach

Poster No:
P 182

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Introduction:
Paclitaxel-induced peripheral neuropathy (PIPN) and associated neuropathic pain are frequent adverse events that occur in breast cancer patients. PIPN is also an important long-term consequence for breast cancer survivors, profoundly affecting their quality of life. No drug is currently approved for prevention. Here, we induced a PIPN in an immunocompetent, syngeneic mouse model of breast carcinoma. No animal model of PIPN associated with breast cancer has yet been developed.

Methods:
A murine breast carcinoma cell line, EMT6 (ATCC® CRL-2755™), was injected subcutaneously in female Balb/C mice. Paclitaxel was administered upon the detection of a tumor measuring 3 mm in diameter (4 x 2 mg/kg, intraperitoneal). Subcutaneous tumors were excised at the end of the anticancer treatment. The impact of chemotherapy on tactile and thermal sensitivities was assessed by functional tests, respectively the von Frey filament test and the plate preference choice test, from the cell transplant to 7 days after tumor excision. Dorsal root ganglia, skin biopsies, and sciatic nerves were removed at the end of the experiments and proceeded for immunohistofluorescence and ultrastructural analyses.

Results:
Administration of paclitaxel restrained tumor growth and induced a sensory neuropathy characterized by tactile hypersensitivity and cold hypersensitivity.

Conclusions:
In conclusion, this model provides a valuable tool that enables the evaluation of both tumor response and sensory nervous system injury to paclitaxel. The development of a drug candidate in the context of PIPN implies that this molecule has neuroprotective properties and does not negatively influence the antitumor effect of chemotherapy.

References:
No

Keywords: Breast cancer, Syngeneic, Mouse mode, Paclitaxel, Neuropathic pain

Doxycycline induced neuropathy

Poster No:
P 183

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Introduction:
Doxycycline-induced neuropathy is a rare finding. We report a case of small fiber neuropathy secondary to doxycycline use

Methods:
we present a 30-year-old lady who presented with a gradual onset of severe burning sensation after the start of doxycycline as prophylaxis antimalarial. The patient had no known chronic illness and was not a vegetarian. Examination revealed mild hypoesthesia with differential warmth in the distal extremities. Normal power with intact vibration sense and no other neurological deficits.

Results:
The patient laboratory investigations revealed ESR-5mm fall/hr, HBsAg: negative HCV antibodies: negative, HBA1C; 5.1%, Thyroid Function test: normal anti-Ro: negative, anti-La: negative, ANA: negative, anti-CCP: negative, Vit B12: normal, Serum protein electrophoresis: normal, fecal calprotectin: normal, A Nerve Conduction study done on two occasions were normal. The patient was managed on Prednisolone by a rheumatologist but still had no relief of symptoms. A diagnosis of small fiber neuropathy secondary to doxycycline was made. The patient's symptoms improved remarkably after cessation of doxycycline.

Conclusions:
This case adds to the literature that doxycycline is a rare cause of neuropathy and its use should be stopped immediately patients develop neuropathy to prevent undue investigations which come with a cost to the patient.

References:
No

Keywords: doxycycline, small fiber neuropathy

Paclitaxel-induced neuropathy manifests differentially in different rat strains: a behavioral and histopathological assessment.

Poster No:
P 184

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Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting adverse effect of commonly used taxanes, which affects the cancer patients' overall survival and quality of life. Several in vivo models are used to explore the progression of CIPN; however, there are still inconsistencies regarding the choice of animal strain, route of schedule of drug administration, and evaluation method for the side effects. Thus, we aimed to compare CIPN development in three different rat strains, Lewis, Wistar and Sprague-Dawley rats, to determine a suitable strain for CIPN research.

Methods:
Rats received two consecutive intravenous doses of 18 mg/kg of paclitaxel (3 days apart) to induce neuropathy. To evaluate the development of neuropathy, von Frey, acetone evaporation and grip strength tests were performed at different time points and a 3-mm skin punch biopsy sample was collected from hind paw to assess intraepidermal nerve fibers on the last day of the experimental schedule. Furthermore, paclitaxel-induced stress behavior was evaluated concomitantly with an open field test.

Results:
Preliminary results of our study suggested that following the first paclitaxel injection, mechanical allodynia started developing on day 5 in both Lewis and Wistar rats. Neuropathic pain signs recovered on day 11 in Lewis rats while reaching peak levels on day 8 in Wistar rats and remaining steady for two weeks. Cold allodynia was first observed on day 5 and day 8 in Lewis and Wistar rats, respectively, and both strains remained sensitive to cold stimuli until the end of the experiments. However, there was no significant change in forelimb grip strength, a predictor of motor function in both strains.

Conclusions:
Consistent with existing literature, our preliminary findings demonstrate varying levels of responses to CIPN across different rat strains. This study aims to appoint the most suitable strain for subsequent experiments to investigate the contribution of stress in the progression of CIPN.

References:
No

Keywords: neuropathic pain, intraepidermal nerve fibers, taxanes, allodynia, von Frey

Cryoglobulinemic neuropathy in a Hepatitis B-Infected Patient: A Case Report

Poster No:
P 185

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Introduction:
A 48-year-old Brazilian woman complained of numbness on the lateral side of her right leg, which progressed to constant numbness in the left foot. Subsequently, she experienced intermittent numbness in her hands and weakness while writing.

Methods:
The patient underwent a comprehensive neurology consultation three months later.

Results:
Her medical history revealed a neonatal blood transfusion, a hepatitis B diagnosis at the age of 20 and the recent initiation of entecavir. Notably, she had skin lesions diagnosed as urticaria, a thyroid nodule, and a family history of Charcot-Marie-Tooth disease type 1A. The neurological examination included gait analysis, reflex assessment, sensory tests, and cranial nerve evaluation. Despite a normal gait and preserved muscle strength, the patient exhibited distal hypoesthesia, particularly in the lower limbs, with asymmetry and hyperchromic skin lesions. Nerve conduction studies revealed an asymmetric sensory axonal polyneuropathy, especially in lower limbs. Laboratory exams showed Hepatitis B virus with active replication (reactive Anti-HBe) and a detectable viral load. Cryoglobulin was also present in the blood test. Genetic test was negative for CMT1A. Following oral prednisone and entecavir, her neurological condition worsened, prompting the initiation of plasma exchange, leading to a significant improvement after one month.

Conclusions:
This case underscores the challenges in managing cryoglobulinemic neuropathy, refractory to corticosteroids, especially when related to hepatitis B-infected individuals, when the treatment with rituximab is restricted. We emphasize the efficacy of plasma exchange in improving symptoms in a short term. The association of the neuropathy with skin lesions and the presence of a history of hepatitis B should raise the suspicion of cryoglobulinemia. Although cryoglobulinemia is far more frequent with hepatitis C, it is important to emphasize that it can occur in patients with B virus as well. Further research is needed to elucidate the underlying mechanisms and optimize therapeutic approaches for such cases.

References:
No

Keywords: Hepatitis B, Peripheral Neuropathy, Cryoglobulinemia

Altered landscape of neuronal gene expression in skin biopsies from patients with paclitaxel-induced peripheral neuropathy

Poster No:
P 186

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Introduction:
Late effects from chemotherapy-induced peripheral neuropathy (CIPN) are often sensory-predominant and their severity may be out of proportion to impairments observed on clinical testing. Pathomechanisms underlying these persistent sensory symptoms are poorly understood.

Methods:
Skin punch biopsies from distal legs were collected from 3 patients with symptoms of paclitaxel-induced neuropathy and 3 age/sex-matched non-neuropathy controls. Neuropathy was quantitated via NIS-LL and QLQ-CIPN20. Epidermal nerve fiber density was performed at the Mayo Clinic Peripheral Nerve Laboratory. RNA isolation and quality control were achieved, and paired-end Illumina sequencing (HiSeq 2x150bp) was conducted (Azenta/Genewiz).

Results:
We enrolled 3 female subjects who received standard adjuvant paclitaxel therapy (12 weekly infusions of 80 mg/m2) for breast cancer and developed neuropathic symptoms. For individual patients, QLQ-CIPN20 totals were 31, 34, 25 and NIS-LL were 2, 12, 4. Epidermal nerve fiber density were 8.9, 5.3, and 9.6, which is normal by lab standards and did not differ statistically from matched control subjects. Despite similar epidermal nerve fiber density, RNAseq analysis demonstrated 2,277 genes with statistically significant differential expression between those exposed to paclitaxel and controls. K-means cluster analysis revealed 8 clusters of upregulated (6) and downregulated (2) gene sets, two of which included genes involved in nervous system function. These genes included those implicated in schwann cell and neuronal function (examples: SCN9A, TRPM7, NEFL, TUBB3, STMN2).

Conclusions:
Late neuropathic effects of paclitaxel-induced peripheral neuropathy correlate with dramatic changes in gene expression of distal leg skin biopsies, despite normal epidermal nerve fiber density. We hyopthesize that in addition to alterations in skin and metalloproteinases, which we previously reported, neuronal gene derangements and distal neuronal translation contribute to neuropathic symptomatology in this patient population. The primary limitation of this study is the small sample size and a larger study should be completed to confirm results.

References:
Yes

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Grant Support:

This research was supported by the National Institutes of Health, grant number 1R01CA215973 (SR) and 1R01CA21887 (NPS), 1R01CA275870 (NPS)

Keywords: CIPN, skin biposy, transcriptome

Neuroinflammation Drives Acute Lymphoblastic Leukemia Therapy-Induced Neuropathy

Poster No:
P 187

Authors:
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Introduction:
Acute Lymphoblastic Leukemia (ALL) is one of the most frequently diagnosed cancers in the pediatric population. Due to advances in cancer treatment, the survival of ALL is estimated to be 90%. ALL survivors experience long-term, debilitating neuropathies from treatment with life-saving cancer therapy. Currently, there is limited knowledge about neuropathies caused by chemotherapy, and current treatment approaches insufficiently control the symptoms without addressing the actual cause. We have discovered that chemotherapy-induced neuropathy (CIPN) is driven by the activation of the Nod-Like-Receptor 3 (NLRP3) inflammasome and can be prevented using anti-inflammatory drugs. However, current simplified preclinical models for CIPN do not consider the contribution of cancer and combination chemotherapy to CIPN development. Additionally, CIPN treatments may impact cancer progression and chemotherapy efficacy.

Methods:
Therefore, to address these gaps, the aim of this study was to investigate the effects of MCC950, a specific NLRP3 inhibitor, in our novel clinically relevant model of sensory-motor neuropathy, based on the administration of combination chemotherapy in cancer-bearing rodents. Specifically, we have established ALL-19 Patient Derived Xenograft in NOD scid gamma (NSG) mice and treated these animals with vincristine, L-asparaginase, and dexamethasone combination (developed in collaboration with clinicians). Following the treatment, we assessed tumor progression and animal survival and performed an extensive behavioral assessment using an Electronic von Frey apparatus (TopCat Metrology), Parallel Rod Floor (Stoelting & Anymaze), and Grip strength meter (Stoelting).

Results:
MCC950 treatment prevented ALL-19 combination regimen-induced mechanical allodynia, motor impairment, and muscle weakness without negatively affecting chemotherapy efficacy or ALL-19 progression.

Conclusions:
MCC950 is therefore a safe preventative treatment for CIPN that was tested for the first time in a clinically relevant model of CIPN. The outcomes of this study are expected to form the basis for future investigator-driven clinical trials aimed at repurposing MCC950 for the treatment of peripheral neuropathies.

References:
No

Grant Support:

NHMRC – National Health and Medical Research Council Australia

Keywords: Chemotherapy-induced neuropathy, Acute-Lymphoblastic Leukaemia, Combination chemotherapy, Novel model, MCC950

A Case of Early-Onset Painful Lumbosacral Plexopathy after Pelvic Radiation

Poster No:
P 188

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Introduction:
Radiation-induced neuropathy occurs at a rate of less than 1% with current irradiation doses. Lumbosacral plexopathy may occur as a result of radiation to pelvic tumors. Case series suggest typical onset latency from 4 months to 23 years post radiation. We report a case of painful, progressive, asymmetric, radiation induced lumbosacral plexopathy that developed 4 weeks after pelvic radiation for prostate cancer.

Methods:
62-year old man with local prostate cancer developed painful weakness and numbness initially in the left leg after 4 weeks of completing 7 rounds of 70 Gy radiotherapy treatments that progressed over 7 months to involve the right leg. Examination showed left > right and distal > proximal leg weakness, absent lower extremity reflexes, and sensory loss to all modalities in the left leg to the knee and in the right to the mid-calf.

Results:
Electromyography and nerve conduction studies showed asymmetric left > right sensory motor neuropathy with acute on chronic distal > proximal neurogenic changes. CSF showed no WBC, no RBCs, protein 107, glucose 53, and negative flow cytometry and cytology. MRI lumbar spine and plexus showed left greater than right lumbosacral plexus, obturator, femoral and sciatic nerve hyperintensities and enhancement. Whole body PET was normal. Left sciatic nerve biopsy showed chronic axonal loss, neovascularization, perineural edema without evidence of infiltrative process or inflammation. His pain improved approximately 9 months after symptom onset. He was trialed on methylprednisolone 500mg IV weekly for 4 weeks (after improvement in pain) without objective improvement in strength. His exam 15 months after onset is stable.

Conclusions:
This case represents an atypical presentation of early-onset painful radiation induced lumbosacral plexopathy. The differential for painful progressive asymmetric neuropathy typically includes infiltrative process, vasculitis and amyloidosis, but radiation should be considered early should work up for alternative causes be negative.

References:
Yes

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Keywords: Radiation, lumbosacral plexopathy, toxicity

Inflammatory Neuropathy Consortium

Inflammatory Neuropathy Consortium (INC) Abstracts

P 189 - 310

Hyaluronidase-facilitated Subcutaneous Immunoglobulin 10% For CIDP: Final Results From A Long-term Safety And Tolerability Study

Poster No:
P 189

Authors:
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Institutions:
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Introduction:
Hyaluronidase-facilitated subcutaneous immunoglobulin (fSCIG; human immunoglobulin G [IgG] 10% with recombinant human hyaluronidase) recently received US approval as maintenance therapy in adults with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and European approval for adults and children with CIDP post-stabilization with intravenous immunoglobulin. This study investigated long-term safety and efficacy of fSCIG 10% in patients with CIDP.

Methods:
ADVANCE-CIDP 3 (NCT02955355) was a long-term extension of ADVANCE-CIDP 1 (NCT02549170),1 a phase 3, double-blind, randomized, placebo-controlled study evaluating fSCIG 10% as maintenance therapy for CIDP. Patients who completed ADVANCE-CIDP 1 were eligible for ADVANCE-CIDP 3 to receive open-label fSCIG 10%. Primary outcomes were safety, tolerability and immunogenicity. Efficacy was an exploratory outcome.

Results:
The study included 85 patients (mean age 54.3 years, 54.1% male) with total follow-up of 220 patient-years; 3487 infusions were administered. Median (range) exposure was 33 (0–77) months. The majority of patients (88.2%) received fSCIG 10% every 4 weeks. Mean (standard deviation [SD]) dose equivalent was 77.9 (41.6) g/4 weeks and mean (SD) infusion duration was 135.5 (62.8) minutes. Most adverse events (AEs) were mild or moderate and self-limiting, consistent with the established fSCIG 10% safety profile. Overall, 1406 AEs (48 severe, 30 serious) were reported. Of these, 798 AEs (20 severe, 3 serious) were fSCIG 10%-related, occurring in 51 patients (60.0%); approximately two thirds were local reactions (64.0%), such as infusion site redness and pain. Overall, 14 patients (16.7%) had ≥1 positive anti-hyaluronidase antibody titer (≥1:160); antibody positivity was not associated with increased incidence of any AEs. Relapse occurred in 10 of 77 patients (13.0%); annualized relapse rate was 4.5%.

Conclusions:
ADVANCE-CIDP 3 demonstrated favorable long-term safety and tolerability of fSCIG 10%, and a low relapse rate, supporting its use as maintenance treatment for CIDP. Study/writing funding: Takeda Development Center Americas, Inc./Takeda Pharmaceuticals International AG.

References:
Yes

Reference 1: Bril V, Hadden RDM, Brannagan TH III et al. Hyaluronidase-facilitated subcutaneous immunoglobulin 10% as maintenance therapy for chronic inflammatory demyelinating polyradiculoneuropathy: the ADVANCE-CIDP 1 randomized controlled trial. J Peripher Nerv Syst 2023;28:436–49.

Keywords: chronic inflammatory demyelinating polyradiculoneuropathy, facilitated subcutaneous immunoglobulin, safety and tolerability, efficacy, ADVANCE-CIDP 3

A patent with CIDP in Ghana- diagnostic and therapeutic limitation in third world countries.

Poster No:
P 190

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Introduction:
Distal acquired demyelinating symmetric polyneuropathy is a rare variant of Chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods:
We report a 67-year-old woman who presented with a gradual onset of numbness followed by weakness of the distal extremities over a 3-month period, which rendered her wheelchair-bound. Examination revealed distal weakness with hypoesthesia in glove and stockings distributions and impaired vibration sense.

Results:
Lumbar puncture showed albuminocytologic dissociation. Nerve conduction revealed unexcitable nerves and prolonged distal latencies of the axillary nerves. She had negative anti-MAG antibodies and protein electrophoresis was negative. Paranodal antibody tests are not available. The patient did not respond to prednisolone but improved modestly to 4 cycles of intravenous immunoglobulin over 3 months. She was able to walk using a Zimmer frame. However, a lack of financial resources limited the use of IVIg in Ghana. The patient was switched from intravenous immunoglobulin to pulse methylprednisolone 1g for 3 days every 3 weeks on account of lack of funds.

Conclusions:
This case highlights the difficulty in characterizing and optimally managing CIDP in a resource-limited setting, there is indeed a need for research into less expensive alternatives such as small-volume plasmapheresis.

References:
No

Keywords: Chronic inflammatory demyelinating polyneuropathy, IVIG, small-volume plasma exchange

THE VALUE OF NERVE ULTRASOUND IN THE DIFFERENTIAL DIAGNOSIS OF DIABETIC SENSORIMOTOR NEUROPATHY, CIDP OR A COMBINATION OF BOTH DISEASES

Poster No:
P 191

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Introduction:
Diabetic sensorimotor polyneuropathy (DSP) usually manifests as a symmetrical, length-dependent sensorimotor polyneuropathy, with predominantly axonal features. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired autoimmune neuropathy, commonly presenting with proximal and distal weakness, areflexia and demyelinating changes in nerve conduction studies (NCS). Diagnosis is challenging when both diseases coexist (DSP+CIDP), as patients with DSP may have demyelinating features in NCS. Nerve ultrasound (US) may help differentiate those patients by uncovering structural changes, but is an underutilized tool. We aimed to investigate the value of nerve US to differentiate patients with DSP, CIDP and DSP+CIDP.

Methods:
We prospectively included adult patients diagnosed with CIDP, DSP or DSP+CIDP based on clinical assessments and NCS, who had US of the main upper and lower limb nerves (median at the wrist/forearm/arm, ulnar at the wrist/ulnar groove/arm, fibular at the fibular head and tibial at the ankle). Patients with DSP+CIDP were defined as presenting with unexpected disease progression in a pattern consistent with CIDP and supportive changes in NCS, MRI or CSF.

Results:
Of 57 patients (20 DSP, 20 CIDP and 17 DSP+CIDP; 17 female), 3 had Type1 DM and 34 Type2 DM. There were no differences in the age, sex and neuropathy duration between the groups ($p=0.42$, 0.72 and 0.87 respectively). Patients with CIDP or CIDP+DSP had larger cross-sectional areas (CSA) in three proximal sites: left median nerve at mid-arm ($p=0.001$), right ulnar ($p=0.002$) and left ulnar ($p=0.009$) nerves at mid-arm. Patients with CIDP+DSP also had increased median CSA in the left mid-forearm ($p<0.001$). There were no differences in the median CSA at the wrists ($p=0.62$), or ulnar CSA at the elbows ($p=0.84$).

Conclusions:
Nerve US was helpful to differentiate patients with CIDP or CIDP+DSP from those with DSP only. Proximal and intermediate upper limb nerve segments showed enlarged areas only in CIDP/CIDP+DSP patients.

References:
No

Keywords: CIDP, DPN, Nerve ultrasound

A Quantitative Study on the Patient Journey and Experience in Patients with CIDP and MMN

Poster No:
P 192

Authors:
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Introduction:
Multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyneuropathy (CIDP) are life-altering peripheral neuropathies with a substantial burden. This study aimed to understand the effect of MMN and CIDP on quality of life (QoL) and evaluate patients' diagnostic and treatment journeys.

Methods:
This cross-sectional mixed-methods study included US adult patients with self-reported MMN or CIDP. These quantitative study findings are based on an online survey developed from qualitative patient insights.

Results:
Patients with CIDP (n=173) indicated significantly more lower body symptoms (legs/feet) than patients with MMN (n=31) (numbness/tingling, 87% vs 32%; weakness, 80% vs 58%; pain, 56% vs 16%, respectively; $P<0.05$ for all). Patients with CIDP or MMN frequently reported difficulties with performing lower body strength activities and dexterous tasks, respectively. Many patients reported caregiver involvement (CIDP:61%; MMN:52%), generally with housework (CIDP:86%; MMN:81%) and attending medical appointments (CIDP:59%; MMN:44%). Patients recalled experiencing symptoms >6 months before diagnosis (CIDP:51% MMN:90%), visiting ≥3 healthcare providers (CIDP:55%; MMN:65%), and undergoing several tests. Most patients specified neurologists as the diagnosing and/or treating physician (CIDP:92%; MMN:97%); approximately half were neuromuscular specialists (CIDP:54%; MMN:57%). Patients often consulted other specialists to manage symptoms, although few sought mental health support. Most patients received intravenous immunoglobulin therapy (CIDP:75%; MMN:74%), resulting in frequent travel and disruptions to work (CIDP:41%; MMN:29%) and personal life (CIDP:69%; MMN:48%). Dose adjustments, such as dose amount (CIDP:43%; MMN:60%) or frequency (CIDP:57%; MMN:64%), were common and may further hinder patients' ability to maintain treatment schedules.

Conclusions:
Patients with CIDP and MMN experience burden related to diagnosis, treatment, symptoms, and functional limitations. Half of patients report seeing a neuromuscular specialist, with care being fragmented across different specialty providers. This study, while limited by unconfirmed CIDP and MMN diagnoses, points to the need to broadly educate providers on these neuropathies as patients continue to seek information at various points of care.

References:
No

Grant Support:

Sponsorship: Takeda Pharmaceuticals USA, Inc. funded the study and writing support.

Keywords: MMN, CIDP, Quality of life, Immunoglobulin, Patient journey

Leveraging Real-World Data To Understand Treatment Patterns And Disease Burden in Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Poster No:
P 193

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Introduction:
Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) is a progressive autoimmune disease that causes inflammation of the nerve roots and peripheral nerves. There are limited published scientific literature on the disease burden and treatment patterns in patients with CIDP. This retrospective observational cohort analysis therefore aimed to describe the demographic characteristics of CIDP patients and analyze the treatment patterns and healthcare resource utilization (HCRU) associated with the condition in the US.

Methods:
Integrated data from the Optum® Market Clarity linked EHR-claims dataset was used to identify adults with CIDP diagnoses between 2008 and 2020. Demographic characteristics were described for the diagnosed cohort (n=3,187) and treatment patterns and HCRU were described for the treatment cohort (n=1,942).

Results:
The diagnosed cohort (n=3,187) was characterized by a high prevalence of patients aged ≥50 years (78% of the cohort) and a slight predominance of male patients (55% of the cohort). Hypertension and dyslipidemia were among the top 10 comorbid conditions in the diagnosed cohort. In the treated cohort (n=1,942), first-line therapies prescribed to patients included immunoglobulin (43%), systemic glucocorticoids (32%), immunoglobulin and systemic glucocorticoids in combination (11%), immunosuppressive therapy (4%), and plasma exchange (3%). In the two years after the date of initial treatment, 39% of patients made a CIDP-related outpatient visit and 3% of patients made a CIDP-related inpatient visit.

Conclusions:
This real-world data analysis provides novel and detailed insights into the clinical characteristics of a large cohort of CIDP patients. Real-world evidence can be used as a tool to understand the treatment patterns and disease burden in a small population of patients with a rare disease such as CIDP.

References:
No

Keywords: CIDP, real-world evidance, epidemiology, treatment patterns, immune neuropathy

Validation of EGRIS score in Iraqi patients during COVID-19 pandemic

Poster No:
P 194

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Introduction:
Guillain-Barre syndrome (GBS) is an acute flaccid paralysis due to autoimmunity, characterized by progressive weakness and areflexia, reaching plateau within 4 weeks with variable severity, disease course, clinical variants, and outcome. As an auto-reactive disease, it is incidence increases after pandemics of infections. Patients with GBS had a high risk of developing acute respiratory insufficiency and may need ventilatory support. Early recognition of respiratory failure in GBS is of paramount importance.

Methods:
Methods: we prospectively followed 73 GBS patients at major 2 hospitals in Baghdad/Iraq between (20th July 2020 to 20th of January 2022).

Results:
Results: total patients were 73, (50 (68.5%) males vs 23 (31.5%) females). Of them, 49 (67.1%) were COVID-19 positive. The mean age was 45.7 (+/- 18.0) years. Forty patients had facial or bulbar involvement but only 22 patients (30.1%) required mechanical ventilation. MV patients scored higher on the EGRIS score with statistical significance (4.68 ± 1.61 vs 2.98 ± 1.39; $p < 0.001$). Area under the ROC curve, which was 0.80. COVID-19 state did not affect the EGRIS score.

Conclusions:
Conclusion: EGRIS is a clinically useful prediction tool among Iraqi GBS patients whether they have COVID-19 infection or not and it can be used to guide management plans, especially in pandemics where resources may become limited.

References:
No

Keywords: Guillain-Barre syndrome, COVID-19, EGRIS score

Olfactory Mucosa Mesenchymal Stem Cells and Biomaterials Promoting Peripheral Nerve Regeneration

Poster No:
P 195

Authors:
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Introduction:
Despite recent advances in promoting peripheral nerve regeneration after injury, it has not yet been possible to establish an alternative treatment to supplant traditional surgical methods as gold-standard approaches [1]. Regenerative medicine drew attention due to its versatility, multifactorial approach, and potential to revolutionize different medical fields, including Peripheral Nerve Injury (PNI) and regeneration [2,3]. The beneficial effects of MSCs secretome in combination with neural guide-tubes (NGCs) in promoting nerve regeneration were previously confirmed [4]. The aim of this work was to test this therapeutic combination in a more complex model, the sheep model, as a step prior to its application in clinical trials.

Methods:
Twelve sheep were subjected to neurotmesis of the common peroneal nerve and received different therapeutic approaches: (a) EtE suture; (b) NGC (c) NGC + OM-MSCs secretome. Over 24 weeks, the animals were regularly monitored through functional tests, ultrasounds, electromyography, and kinematic assessment. At the end of the study period, the nerves and effector muscles were collected for stereological and histomorphometric evaluation.

Results:
The results of the functional assessment allowed to identify a progressive functional improvement over the study period and in all evaluated parameters. Over time, there was a recovery of sensitivity to pain, a recovery of proprioception and the ability to reposition the hind limb. Ultrasound and electromyography also revealed improvements in nerve regeneration and muscle electrical activity. The muscles and nerves collected for stereological and histomorphometric evaluation and the results of the kinematic evaluation are currently under analysis and should be available soon.

Conclusions:
The therapeutic combination discussed in this work shows promising results in a more complex model such as the sheep, reinforcing the potential of cell-based combined therapies in promoting peripheral nerve regeneration after injury. The results of nerve stereological and muscle histomorphometric evaluation will help confirm whether functional recovery equally translates into effective histological and ultrastructural reorganization.

References:
Yes

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Reference 3: Alvites R, Branquinho M, Sousa AC, Lopes B, Sousa P, Maurício AC. Mesenchymal Stem/StromalCells and Their Paracrine Activity—Immunomodulation Mechanisms and How to Influence theTherapeutic Potential. Pharmaceutics. 2022;14(2):381.

Reference 4: Alvites RD, Branquinho MV, Sousa AC, Lopes B, Sousa P, Prada J, Pires I, Ronchi G, Raimondo S, Luís AL, Geuna S, Varejão ASP, Maurício AC. Effects of Olfactory Mucosa Stem/Stromal Cell and Olfactory Ensheating Cells Secretome on Peripheral Nerve Regeneration. Biomolecules. 2022 Jun 11;12(6):818.

Keywords: Peripheral Nerve Injury, Mesenchymal Stem Cells, Biomaterials, Secretome, Animal Models

Patient-Reported Outcomes With Hyaluronidase-Facilitated Subcutaneous Immunoglobulin 10% And Intravenous Immunoglobulin 10%: The ADVANCE-CIDP 1 Study

Poster No:
P 196

Authors:
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Institutions:
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Introduction:
Hyaluronidase-facilitated subcutaneous immunoglobulin (fSCIG) 10% and GAMMAGARD LIQUID (GGL; intravenous immunoglobulin [IVIG] 10%) are under investigation to treat chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). This study assessed patient-reported outcomes (PROs) associated with fSCIG 10% and GGL during ADVANCE-CIDP 1.

Methods:
During the phase 3, randomized, multicenter ADVANCE-CIDP 1 study, adults with CIDP who received ≥12 weeks of IVIG were randomized to fSCIG 10% or placebo (at the same dose/interval as previous IVIG) for 6 months or until relapse/discontinuation (Epoch 1). Patients experiencing relapse entered the open-label GGL rescue phase (Epoch 2). PROs were assessed using the Rasch-built Overall Disability Scale (R-ODS), EQ-5D-3L, EQ-VAS, 36-item Short Form Health Survey (SF-36), 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9), treatment preference (unavailable for Epoch 2) and Patient Global Impression of Change (PGIC) instruments.

Results:
Overall, 132 patients received fSCIG 10% (n=62) or placebo (n=70); 20 patients relapsed and received GGL (n=4 [fSCIG 10%-relapse], n=16 [placebo-relapse]). In Epoch 1, all PROs indicated stable/improved health-related quality of life (HRQoL) and increased treatment satisfaction with fSCIG 10%, versus stability/deterioration or reduced satisfaction with placebo. Compared with previous IVIG, 66.7% of patients preferred fSCIG 10% and 53.7% of those with available PGIC data reported improved ability to perform activities. From pre-GGL baseline through 24 weeks in Epoch 2, mean change in R-ODS centile scores for all patients was 12.9. For patients receiving GGL, SF-36 and EQ-VAS scores indicated improved HRQoL, mean EQ-5D-3L scores were decreased/maintained and TSQM-9 scores increased for all domains. Based on PGIC scores, 65.0% of patients indicated improved ability to perform activities with GGL, relative to pre-GGL baseline.

Conclusions:
fSCIG 10% and GGL maintained or improved HRQoL for patients with CIDP, demonstrating favorable treatment satisfaction and Patient Global Impressions of Change scores. Study/writing support funder: Takeda Development Center Americas, Inc./Takeda Pharmaceuticals International AG.

References:
No

Keywords: chronic inflammatory demyelinating polyradiculoneuropathy, facilitated subcutaneous immunoglobulin, patient reported outcomes, health-related quality of life, ADVANCE-CIDP 1

Electrodiagnostic subtyping in Guillain-Barré syndrome patients in the International Guillain-Barré Outcome Study

Poster No:
P 197

Authors:
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Institutions:
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Introduction:
Various electrodiagnostic criteria have been developed in Guillain-Barré syndrome (GBS). Their performance in a broad representation of GBS patients have not been evaluated. We used motor conduction data from the International GBS Outcome study (IGOS) cohort to compare two widely used criterion sets and to relate these to diagnostic ALS criteria, an axonal neuropathy.

Methods:
Methods: From the first 1500 patients in IGOS, NCS from 1137 (75.8%) were available for the current study. These patients were classified according to the NCS criteria proposed by Hadden and Rajabally.

Results:
Results: Of the 1137 studies, 68.3% (N=777) were classified identically according to criteria by Hadden and Rajabally: 111 (9.8%) axonal, 366 (32.2%) demyelinating, 195 (17.2%) equivocal, 35 (3.1%) inexcitable and 70 (6.2%) normal. Thus, 360 studies (31.7%) were classified differently. The main areas of differences were: (a) 155 studies (13.6%) classified as demyelinating by Hadden and axonal by Rajabally, (b) 122 studies (10.7%) classified as demyelinating by Hadden and equivocal by Rajabally and (c) 75 studies (6.6%) classified equivocal by Hadden and axonal by Rajabally. Due to more strictly defined cutoffs fewer patients fulfilled demyelinating criteria by Rajabally than by Hadden, making more patients eligible for axonal or equivocal classification by Rajabally. In 234 (68.6%) axonal studies by Rajabally the revised El Escorial (ALS) criteria were fulfilled, in cases with axonal studies by Hadden this was 1.8%.

Conclusions:
Conclusions and discussion: This study shows that electrodiagnosis in GBS is dependent on the criterion set utilized both of which are based on expert-opinion. Reappraisal of electrodiagnostic subtyping in GBS is warranted.

References:
No

Grant Support:

none

Keywords: Guillain-Barré Syndrome, Electrodiagnostics, Hadden criteria, Subtyping, Rajabally criteria

Evaluating Clinical Response In Relation To Treatment Alterations In The International CIDP Outcome Study (ICOS)

Poster No:
P 198

Authors:
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Institutions:
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Introduction:
Some patients with chronic inflammatory demyelinating polyneuropathy (CIDP) need treatment for a short period, but most require maintenance treatment for several years. Treatment can be tapered in a subgroup while others need treatment intensification for the disease to remain stable. Dynamics of treatment, functioning, and clinical outcome are not well reflected in the CIDP Disease Activity Status (CDAS). We aim to evaluate clinical outcome in relation to treatment alterations to improve future treatment choices.

Methods:
The International CIDP Outcome Study (ICOS) is a prospective, observational, multicenter study. Treatment-naïve and previously treated patients, fulfilling the EFNS/PNS 2010 criteria for CIDP, are included. Study visits are every 6 months for the first 2 years, and annually thereafter. At each visit, we evaluate clinical outcome with validated scales, and treatment alterations. Changes in clinical outcome are classified as improving, stable or deteriorating (using proposed cut-off values described in the EAN/PNS 2021 CIDP guideline). Treatment regimens are classified as unchanged, tapered, intensified, stopped, started, or switched. At 1, 2 and 5-year follow-up we will evaluate clinical response and patterns of change in treatment regimens and outcome.

Results:
By December 2023, 315 CIDP patients were included in ICOS. After excluding 27 patients, most often for a revised diagnosis, 288 patients remain. At study entry, 176 (61%) patients were already treated for CIDP (median duration 1 year, IQR 0.3–4.5 years), while 108 (38%) were treatment-naïve. The 1-year follow-up visit was completed by 219 patients, and 2- and 5-year follow-up visits by 168 and 46 patients respectively. Of patients receiving treatment at the 2-year visit, treatment was adjusted in 90/99 patients (91%) during follow-up. During 2-years of follow-up, treatment was intensified at least once in 72/99 (73%), and tapered in 59/99 (60%) patients.

Conclusions:
Clinical response corresponding to alterations in treatment regimens and factors related to treatment dependency or successful tapering will be presented.

References:
Yes

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Keywords: Chronic Inflammatory Demyelinating Polyneuropathy, CIDP, Clinical outcome, Treatment response

Inflammatory Neuropathy Driven By A Pathologically Expanded, Clonal Lineage of IL-21 Producing CD4$^+$ T cells

Poster No:
P 199

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Introduction:
Chronic inflammatory demyelinating polyneuropathy is a debilitating immune-mediated neuropathy characterized by progressive weakness and sensory loss. Peripheral nerves from affected patients and mouse models show infiltrating CD4$^+$ T cells, and CD4$^+$ T cells from affected mice are sufficient to transfer neuropathy to immunodeficient recipients, suggesting an important role for CD4$^+$ T cells in disease pathogenesis. Yet, key properties of pathogenic CD4$^+$ T cells remain incompletely understood.

Methods:
Single-cell RNA sequencing analysis revealed clusters of T cells from the peripheral nerves of six neuropathic mice with NOD background and partial loss-of-function G228W mutation in the Autoimmune regulator gene (NOD.Aire$^{GW/+}$). T cell receptor sequencing identified the clones of individual T cells and monitored clonal expansion amongst clusters. Spontaneous autoimmune peripheral polyneuropathy was modeled by NOD.Aire$^{GW/+}$ mice in experiments and, specifically, NOD.Aire$^{GW/+}$ IL21R$^{-/-}$ mice were used to demonstrate the importance of IL21R in disease pathogenesis. Mice were phenotypically assessed, and their condition was confirmed by electromyography. Immunostaining of mouse forelimbs was used to visualize the localization of key components in disease pathogenesis. Flow cytometry assessed the cellular characteristics of sciatic nerve, lymph node, and splenic samples.

Results:
We report that IL-21 expression is highly expressed and a unique feature of terminally-differentiated effector CD4$^+$ T cells within peripheral nerves of neuropathic mice. IL-21-expressing CD4$^+$ T cells are comprised of two transcriptionally distinct, clonally-expanded populations, which express genes associated with Tfh and Tph subsets. Remarkably, TCR clonotypes were shared between these two IL-21-expressing populations, suggesting lineage differentiation from a common progenitor. Finally, we demonstrate that IL-21 signaling is required for pathogenic T cell infiltration into peripheral nerves through upregulation of CXCR6, a chemokine receptor that promotes CD4$^+$ T cell localization in peripheral nerves.

Conclusions:
These findings highlight IL-21 signaling, Tfh and Tph differentiation, and CXCR6-mediated cellular localization as key pathogenic pathways and potential therapeutic targets in inflammatory neuropathies.

References:
Yes

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Keywords: Chronic Inflammatory Demyelinating Polyneuropathy, Inflammatory Neuropathies, IL-21 Signaling, Single-Cell RNA Sequencing, T Cell Receptor Sequencing

Detection Of Anti-MAG Antibodies With ELISA – The Impact Of Different Detergents On Performance And Stability

Poster No:
P 200

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Institutions:
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Introduction:
ELISA is a common and reliable method for the detection of autoantibodies in inflammatory neuropathies. The use of detergents is of particular importance for removal of unspecific binding events, ensuring the specificity of the assay. In Anti-MAG Neuropathy, the BÜHLMANN Anti-MAG Antibodies ELISA is the accepted gold standard. However, in its current form, it contains the detergent Triton X-100, which has recently been identified as an environmental toxin, particularly affecting aquatic life forms.

Methods:
Here, we present performance and stability data on the Anti-MAG Antibodies ELISA containing different ecofriendly detergents. For a method comparison, we included 41 samples across the measuring range and performed Bland-Altman and Passing-Bablok Regression Analysis, contrasting reagents containing either Tergitol 15-S-9 or Tween-20 with the Triton X-100 containing standard. The reference interval was determined using sera from 116 healthy controls and 40 sera from patients with a differential diagnosis, e.g. Myasthenia Gravis, Rheumatoid Arthritis, Systemic Lupus Erythematosus, and others.

Results:
The overall agreement between methods was good, with a mean bias of -17.4% and -10.4% for Tergitol 15-S-9 and Tween-20, respectively. All measured negative controls were well below the cut-off of 1000 BTU for both alternative detergents. Accelerated stability studies at elevated temperatures do not indicate a negative effect of the choice of detergent on reagent stability and kit shelf life. Considering all parameters, Tween-20 slightly outperformed Tergitol 15-S-9 as an alternative for Triton X-100.

Conclusions:
In conclusion, our results demonstrate that Triton X-100 can be fully replaced by more ecofriendly detergents in the Anti-MAG Antibodies ELISA, without affecting assay performance or reagent stability. Importantly, the high specificity of the assay remains intact, ensuring reliable diagnosis of anti-MAG neuropathy.

References:
No

Keywords: Myelin Associated Glycoprotein, Anti-MAG Antibodies, Molecular Diagnostics, ELISA

Quantifying the Opportunity Cost of Transitioning Patients from IVIg to SCIg

Poster No:
P 201

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Introduction:
The delivery of care for patients with inflammatory Neuromuscular Diseases (NMD) involves individualizing therapy, including access to home-based treatments. Subcutaneous Immunoglobulins (SCIg) have been shown to be as effective as Intravenous Immunoglobulins (IVIg) in treating inflammatory NMD but require nursing support not previously funded in our region. Transition to SCIg can lead to potential cost savings of $5000-6000 per patient per year. However, reducing the use of the infusion center for IVIg does not translate into savings for the hospital since the time is filled by other patients. We therefore sought to understand the opportunity cost of IVIg appointments, and consider the impact on other patients requiring that space.

Methods:
The infusion center provides infusions, transfusions, procedures and wound care and is open 7 days/week for 12 hours/day. Electronic health record data from 2022 was analyzed to determine the number of appointments and duration of time used for IVIg for 19 patients with inflammatory NMD as well as all other appointment types. Financial statements were cross referenced. Results were validated with the patient care manager and clinical nurse leader.

Results:
A total of 210 appointments totaling 72,045 minutes were used by 19 patients with inflammatory NMD for IVIg infusions in 2022. This cost the unit $107 347 (excluding physician time and IVIg product) and accounted for 4.6% of the total minutes in 2022. The time spent on these 210 IVIg appointments is equivalent to time needed for 2318 antibiotic infusions, 610 chemotherapy infusions, or 591 bone marrow biopsies.

Conclusions:
Calculating the opportunity cost of transitioning inflammatory NMD patients from IVIg to SCIg home treatment demonstrates value when there are no actual dollar cost savings. Presenting this data along with the stability in outcomes and improvement in quality of life of patients transitioned to SCIg therapy led to approval of funding for a permanent regional inflammatory NMD program.

References:
No

Keywords: IVIg, SCIg, health economics, opportunity cost

Quality of life in patients with multifocal motor neuropathy: a five-year longitudinal study

Poster No:
P 202

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Introduction:
Multifocal motor neuropathy (MMN) is a rare, chronic, and immune-mediated disease, characterized with slowly progressive, asymmetric weakness of limbs. However, even treated MMN continues to represent a significant burden in patients' everyday functioning and may continuously affect their quality of life (QoL). Thus, the aim of this prospective study was to analyze health related QoL in MMN patients during a five-year follow-up period in real-life settings.

Methods:
All 17 patients were initially tested in 2017 and 12 retested during 2022. The SF-36 questionnaire was used to evaluate patients' QoL. In order to address patients' functional status, the Inflammatory neuropathy cause and treatment (INCAT) score and Rasch-built Overall Disability Scale (I-RODS) were applied, followed by the Beck's depression inventory (BDI) and Fatigue severity scale (FSS).

Results:
The average age at disease onset was 38.8 ± 13.9 years (2:1 male to female ratio). Three patients were without any therapy at the moment of retesting, while the rest was treated with intravenous immunoglobulins. Out of eight health concepts of SF-36, only physical functioning (PF) (74.7±27.5 vs 70.1±25.7) and bodily pain (BP) (79.8±26.3 vs 75.4±22.4) worsened during the follow up period, while other QoL concepts were without a significant change. The INCAT and I-RODS scores were not significantly changed during the follow-up period. Increase in both BDI (4.6±8.5 vs 6.5±7.1) and FSS (21.0±14.7 vs 25.1±15.2) was noted during the follow-up period.

Conclusions:
QoL in patients with MMN was reduced both at initial testing and at retesting, especially in the physical domains such as FP and BP, which showed a more clear trend of worsening. Although an overall significant progression of patients' functional disability was not observed during the five-year follow-up period, longer disease duration should not be underestimated as a psychological burden for these patients.

References:
No

Keywords: Multifocal motor neuropathy, Quality of life, Longitudinal study

Severe Contactin-Associated Protein 1 (Caspr1) Nodopathy in a Child

Poster No:
P 203

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Institutions:
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Introduction:
Chronic inflammatory demyelination polyradiculoneuropathy (CIDP) was recently described to be associated with antibodies targeting nodal and paranodal proteins such as contactin-associated protein 1 (Caspr1). These antibodies have allowed for the stratification of CIDP. There are a limited number of patients reported in the literature with nodopathies, and an exceedingly small number of children.

Methods:
We describe the case of a young boy with onset of symptoms at age 12.

Results:
A 12-year-old boy with a history of autism initially presented with hearing loss and subacute weakness. He became profoundly weak over the course of several months with a symmetric proximal and distal phenotype that ultimately led him to a 3-month long hospitalization requiring ventilatory assistance. He was diagnosed with Guillain-Barre syndrome at that time and was treated with intravenous immunoglobulin (IVIg). He had slow improvement initially. However, over the course of 5 years, he experienced worsening weakness, imbalance, neuropathic pain, and worsening motor function. Diagnostic studies included EMGs fulfilling EAN/PNS diagnostic criteria for definite CIDP, normal MRI imaging of the brain and spine, normal CSF protein, and unremarkable neuropathy genetic panel testing. He was treated with IVIg and high-dose weekly prednisone with no significant change. He was ultimately found to have positive anti-Caspr1 IgG antibodies by Western blot and was subsequently treated with rituximab.

Conclusions:
This case illustrates that pediatric anti-Caspr1 nodopathy presents similarly to previously described adult patients, with a rapid-onset CIDP phenotype with cranial nerve involvement, early axonal involvement, significant ataxia, and poor response to IVIg. Our patient thus far remains stable with rituximab but continues to be nonambulatory with significant ataxia, likely due to secondary axonal degeneration.

References:
Yes

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Keywords: CIDP, Caspr1, nodopathy, pediatric

Brentuximab Vedotin Treatment Associated Chronic Inflammatory Demyelinating Polyradiculoneuropathy in a Teenager with Hodgkin's Lymphoma

Poster No:
P 204

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Introduction:
Brentuximab vedotin (BV) is a drug composed of an anti-CD30 monoclonal antibody and an anti-microtubule agent monomethyl auristatin E, used for the treatment of relapsed/refractory Hodgkin's lymphoma and non-Hodgkin's lymphoma. Adverse effects of BV can commonly cause peripheral neuropathy but can also rarely cause inflammatory polyradiculoneuropathies. There are a limited number of adult patients reported in the literature with no cases of children.

Methods:
We describe the case of a teenage girl with BV associated chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Results:
A 14-year-old girl was diagnosed with Hodgkin's lymphoma stage 2A. She was treated with 4 cycles of AHOD0031 therapy (doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, prednisone) but had recurrence at 9 months off treatment. She then started salvage therapy with ifosfamide and vinorelbine (AHOD00P1), underwent autologous transplantation, received radiation therapy, and was treated with BV. Approximately 6 months after starting BV, she developed subacute left arm weakness with sensory loss and subsequent gait abnormalities. Nerve conduction studies and electromyography showed an asymmetric, diffuse demyelinating process fulfilling EAN/PNS diagnostic criteria for definite CIDP. BV was discontinued and she was treated with IVIg and high-dose weekly prednisone. After approximately 10 months of treatment, she was able to return to baseline neurologic function except for very mild left intrinsic hand weakness. Her immune therapy was weaned off and she has remained stable since.

Conclusions:
This case illustrates a pediatric case of BV associated CIDP. This particular case was complicated by the significant asymmetry at presentation and the history of radiation therapy. The mechanism for BV associated CIDP is still unknown. It is important for providers to recognize and promptly treat these patients as most respond well to immune therapy.

References:
Yes

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Keywords: CIDP, brentuximab, lymphoma, pediatric

Predominance of Axonal Electrophysiological Abnormalities in Early Guillain-Barré Syndrome: A Single-Centre Study in Greece

Poster No:
P 205

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Institutions:
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Introduction:
Early diagnosis of GBS is largely based on neurophysiological evaluation. GBS shows great heterogeneity depending on factors such as precedent infections and geographical location. Aiming to identify the demographic/clinical characteristics and early neurophysiological abnormalities in patients living in southwestern Greece, we reviewed our records for the last 5 years.

Methods:
Uncini's criteria were used to classify cases into the 2 main sub-groups: acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor/sensory axonal neuropathy (AMAN/AMSAN).

Results:
Forty patients (24 males, mean age of 53.1±15.28 years) were analysed. The occurrence in winter/spring months was 73%, a preceding infection/vaccination was reported in 63%, and an increasing trend in annual incidence from 4 in 2019 to 12 cases in 2023 was found. The average time from symptoms' onset to hospitalization was 4.45±2.93 days. At nadir, the mean Hughes'functional disability score was 2.9±0.8, 4 patients required mechanical ventilation and 2 deaths occurred during hospitalization. On admission, mean time from symptoms onset 5.84±3.39 days, complete neurophysiological study was available in 38 patients, from whom 10 fulfilled the criteria for AIDP, 11 for AMAN and 1 for AMSAN. On repetition, within 2 weeks, 6 more cases of AIDP and 2 of AMAN were recognised. In the 1st study, the percentage of patients with abnormalities in at least 2 nerves were: compound muscle action potential (CMAP) latency 18%, CMAP duration 13%, CMAP amplitude 47%, motor conduction velocity 5%, motor conduction block 16%, F-wave persistence 65%, F-wave latency 8% and sensory potentials amplitude/velocity 21%.

Conclusions:
In brief, neurophysiological abnormalities supporting axonal features i.e. F- wave persistence, CMAP amplitude and conduction block, rather than demyelinating features i.e. CMAP latency, duration, velocity, and F-wave latency, appeared more frequent in the admission study. The percentage of patients eventually diagnosed with AMAN/AMSAN was 36.8% being at the higher edge of the previously reported rates for European countries.

References:
No

Grant Support:

None

Keywords: nerve conduction study, acute inflammatory polyneuropathy, Guillain Barre Syndrome, Electrodiagnosis

Non-Interventional Study On Safety & Tolerability Of Intravenous Immunoglobulin (IVIg 5% & 10%): Subanalysis Of Patients With Neurological Diseases

Poster No:
P 206

Authors:
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Institutions:
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Introduction:
Intravenous immunoglobulin (IVIg) is applied for antibody substitution in immunodeficiencies and for immunomodulatory therapy in autoimmune diseases. It is recommended for the treatment in different neurologic indications including chronic inflammatory demyelinating neuropathy (CIDP), multifocal motor neuropathy (MMN), and myasthenia gravis (MG). From 2014 to 2019 a multicenter, non-interventional safety study was conducted in Germany to assess the tolerability and safety of octagam 5 % and octagam 10 %.

Methods:
A subgroup analysis of the study population focused on CIDP, MMN, and MG was performed.

Results:
A total of 149 patients received in total 5604 IVIg infusions (5% or 10% solution) for treatment of CIDP, MMN, or MG. Most patients (78 %) were treated with IVIg 10 %. The median IVIg dose was similar across the analyzed indications: It ranged from 0.83 g/kg body weight (BW) per treatment cycle and a median treatment interval of 3.6 weeks (MMN) to 0.91 g/kg BW per cycle (CIDP) or 0.94/kg BW per cycle (MG), respectively, with a median time of 4.4 weeks between treatment cycles. The median (and maximum number = N°max) of treatment cycles varied from 2 treatment cycles in MG (N°max = 41) over 11 cycles in CIDP (N°max = 111) to 34.5 in MMN (N°max = 266). ADRs were reported for 19 out of 5604 applied infusions (0.34 %). Serious ADRs were documented for 2 infusions equivalent to 0.04 % of all infusions for the described indications. Most frequent symptoms were headache, chills and various skin reactions.

Conclusions:
This subgroup analysis demonstrates that the use of both IVIg concentrations was well tolerated and safe even in long-term and high dose immunomodulatory treatment of CIDP, MMN, and MG.

References:
No

Grant Support:

THis NIS was sponsored by Octapharma GmbH, Germany

Keywords: CIDP, Myasthenia gravis, MMN, IVIG, Tolerability

ANTI-CASPR1 AUTOIMMUNE NODOPATHY AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION

Poster No:
P 207

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Institutions:
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Introduction:
Autoimmune nodopathies are a rare and disabling subgroup of autoimmune neuropathies defined by the presence of specific antibodies targeting proteins within the node of Ranvier. Anti-Caspr1 nodopathy is clinically characterized by an acute presentation with neuropathic pain, ataxia, and cranial and respiratory involvement. Patients tend to respond poorly to immunoglobulins but show a good and long-lasting response to rituximab. To date no specific triggers have been described in anti-Caspr1 nodopathy. Here we describe a patient that developed anti-Caspr1 nodopathy after an allogeneic bone marrow transplantation.

Methods:
We report the case of a 70-year-old woman who developed gait instability nine months after undergoing an allogeneic bone marrow transplantation as treatment for acute myeloid leukemia. During the following months she further developed bilateral ptosis, dysarthria, facial, tongue and neck extensor weakness plus proximal muscle weakness, distal hypoesthesia with loss of vibratory sensation, areflexia and intense neuropathic pain.

Results:
Electrophysiological studies showed minor alterations, but were compatible with an acquired demyelinating polyradiculoneuropathy. Serological studies were positive for antinuclear antibodies with a nucleolar pattern and anti-Ro52, as well as for anti-Caspr1 antibodies. A paranodal and Cajal band staining pattern was noted on immunohistochemistry. CSF studies showed elevated protein levels, which increased in parallel to the clinical deterioration. Five methylprednisolone 1g/24h doses were started, followed by prednisone 1mg/Kg. As no improvement was noted, treatment with plasma exchange and rituximab was started, with excellent clinical response and an almost complete resolution of the symptoms.

Conclusions:
When suspecting an acquired polyradiculoneuropathy, a subacute or acute onset together with the presence of cranial nerve or respiratory involvement, ataxia and intense neuropathic pain should lead the physician to consider anti nodo/paranodal antibody testing, even if the clinical context does not suggest a primary autoimmune neuropathy. The early identification and prompt treatment of these disorders is crucial to avoid permanent axonal damage and to improve clinical outcomes.

References:
No

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Keywords: Autoimmune nodopathy, Anti-Caspr1, Inflammatory neuropathy

Heterogeneous Real-life Strategies In Therapeutic Approach Of Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Poster No:
P 208

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Introduction:
Despite the existence of therapeutic recommendations in the 2010 EFNS/PNS and 2021 EAN/PNS guidelines for managing Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), the sequence of therapy to be used in CIDP remains unsettled. We used data from a comprehensive registry to unveil the attitude used in the choice of therapy in patients followed at different Italian centers, and if there were factors that might have influenced the choice of therapy.

Methods:
A comparative analysis was conducted, examining therapeutic strategies and responses in 524 CIDP patients from tertiary referral centers included in a large national database.

Results:
Intravenous immunoglobulins (IVIg) emerged as the most commonly used first-line therapy (53%), followed by steroids (33%) and plasmapheresis (3%). A consistent proportion of patients (8%) received a combined first-line therapy with IVIg and steroids or (3%) monotherapy with immune suppressants. In acute-onset CIDP, IVIg and plasmapheresis were often used. There were also differences in relation to the early or late age at onset of CIDP and to CIDP variants. Despite the lack of evidence of efficacy from randomized trials, immune suppressants were often used as maintenance monotherapy (10%). There was a substantial variability among different centers in the choice of first- and second-line therapy, the number of therapies performed, the use of immunosuppressants, and subcutaneous immunoglobulin (SCIg). A consistent proportion of patients responded to IVIg (86%) or steroid (85%) when used as second line therapy and only 7% of the patients failed to respond to two first-line therapies. There

was no distinctive features between responder and not responder patients beside a more frequent ataxia at onset and greater disability at enrollment.

Conclusions:
The absence of specific indications from the guidelines may explain the notable heterogeneity in the therapeutic choice in CIDP patients. Therapeutic response significantly decreases after two failed attempts, but the identification of non-responders remains challenging.

References:
No

Keywords: Chronic inflammatory demyelinating polyradiculoneuropathy, Guidelines, Therapy, Management

Pediatric-Onset Chronic Inflammatory demyelinating Polyneuropathy : a French National Survey

Poster No:
P 209

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Introduction:
Childhood-onset CIDP is a rare condition with a prevalence estimated between 0.4 and 1.6/100000 habitant. Objective: To describe clinical and therapeutic aspects of pediatric-onset CIDP patients. To give prognostic outlines and long-term therapeutic approach.

Methods:
Multi-centric French retrospective study. Inclusion criteria: CIDP with definite/ probable CIDP (2021 EFNS/PNS criteria) with onset <18 years.

Results:
65 patients were collected in 15 French pediatric and adult tertiary neuromuscular centers. Results of the first 35 patients are presented here (the rest of the analysis still ongoing). 19 girls and 16 boys. Symptoms-onset median age of 12 years (range 2-18). 3 patients presented with previous Guillain-Barre syndrome a with a symptom-free period interval of 8 to 16 years. Mean diagnostic delay:10 months. 68% had an acute/subacute onset. 60% had a common form, 31% motor presentation, 8% distal form and MADSAM in 1 patient. Cranial nerves symptoms were involved in 31%. Mean CSF protein level: 1.1 g/L. anti-ganglioside positivity: 5, anti-NF 155/186 Ab: 1, Spinal roots or cranial nerves gadolinium-enhancement in 34% . Course was chronic in 64%, monophasic in 30% and relapsing 6%. All patients had IgIV : 51% were responders and 2/3rd of these were long-term weaned. 12 patients had plasma exchange, efficacious in 4 patients. 25 patients had corticosteroids, 40% were responders, 4 patients long-term dependent. Rituximab efficacious in 6/10 patients, azathioprine in 5/10, Mycophenolate-mophetil in 3/ 4 patients, 3 patients had autologous stem cell transplantation with a positive impact and no serious adverse events. 43% patients had a long-term treatment. 34% patients had no sequela.

Conclusions:
Pediatric-onset CIDP differs from adult-onset CIDP by a high frequency of acute/subacute onset, a predominant motor form and favorable course with few residual deficit

References:
No

Keywords: CIDP, Pedtriac-onset

Monitoring The Short-Term Effect Of IV Immunoglobulins In CIDP: What Are The Most Relevant Biomarkers?

Poster No:
P 210

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Introduction:
There is a pressing need to establish short-term assessment of the efficacy of intravenous immunoglobulins (IVIg) in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Our aim was to identify relevant disability-related biomarkers highly sensitive to change shortly after IVIg infusions.

Methods:
Twenty-nine patients with CIDP on chronic IVIg therapy were enrolled. First, several clinic, biological and electrophysiological biomarkers were screened to identify which ones were correlated (Spearman's correlation test) with patient's disability as measured by the Rasch-built Overall Disability Score (RODS) and the Overall neuropathy limitation score (ONLS). Then, the selected biomarkers were assessed before and 21 days after IVIg infusions and the measurements were compared using the non-parametric Wilcoxon test for paired data.

Results:
MRC sum score, grip test, 10 meters walk, 4 steps test, CMAP sum score, motor unit number index (MUNIX) sum score, tibial motor distal latencies, peroneal CMAP duration and serum neurofilament light chain (NfL) levels were significantly related to patients' disability. Significant modifications were observed, 21 days after IVIg infusions, only for the ONLS score (-18%, p=0.01), MUNIX sum scores (+11%, p=0.039) and NfL levels (-11%, p=0.014). The intrinsic variability of these biomarkers was good according to the standardised response means (SRM) which were 0.70, 0.62 and 0.61 respectively.

Conclusions:
ONLS, MUNIX, and NfL are related to disability and sensitive to change shortly after an IVIg infusion. These assessments could be valuable tools for evaluating treatment efficacy and guiding decisions regarding the optimal protocol of IVIg in CIDP.

References:
No

Grant Support:

no

Keywords: CIDP, Biomarkers, IVIg, MUNIX, Neurofilament light chain

Autonomic Neuropathy Improving after Intravenous Immunoglobulin Therapy. Report of two cases

Poster No:
P 211

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Introduction:
Autoimmune autonomic neuropathies, encompassing immune-mediated autonomic dysfunction, have witnessed an expansion with recent reports including seronegative cases and limited forms of presumed autoimmune autonomic failure.

Methods:
We present two cases of limited autonomic neuropathy that demonstrated marked improvement post intravenous immune globulin (IVIg) therapy. Diagnostic delays and incorrect initial management marked both cases.

Results:
Case 1 involves a 24-year-old Caucasian woman with a ten-year history of length-dependent, symmetric leg paresthesia, xerophthalmia, xerostomia, orthostatic tachycardia, chronic headache, urinary retention, and pseudo-obstruction post-vaccination. Misinterpreted initially as spinal cord dysfunction, leading to an ineffective spinal stimulator implantation, subsequent referral to a gastroenterologist suggested colostomy, which she declined. Diagnosis revealed Sjögren's disease and POTS, with a notable response to IVIg treatment. Case 2 features a 35-year-old Caucasian man with limb pain, altered sensitivity, constipation, abdominal distension, incomplete bladder emptying, and pseudo-obstruction post-Herpes Zoster infection. His general practitioner referred him to a gastroenterologist, who prescribed natural laxatives without benefit. The patient visited the emergency room multiple times and was eventually admitted to the Neurology department. Acetylcholine receptor ganglionic antibody, CT scans, and paraneoplastic markers were negative. Cardiovascular autonomic function tests revealed POTS. IVIg therapy resulted in a remarkable clinical response.

Conclusions:
Both cases underscore the diagnostic challenges of limited autonomic neuropathy, often misattributed, leading to significant diagnostic delays and suboptimal initial interventions. This report emphasizes the frequently overlooked autoimmune basis of autonomic neuropathy, urging heightened awareness for timely and appropriate therapeutic interventions.

References:
No

Keywords: autoimmune autonomic neuropathy, intravenous immunoglobulin

A patient with chronic inflammatory demyelinating polyneuropathy and nephrotic syndrome in Ghana.

Poster No:
P 212

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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) is associated with nephrotic syndrome. It is believed that immunopathology against shared or similar epitopes in peripheral nerves and glomerular podocytes underlies this association. Antibodies against contacting 1 protein (CNT1) that cluster around the nodes of Ranvier are detected in some but not all of the cases of CIDP associated with nephrotic syndrome. We described a patient in Ghana with CIDP and nephrotic syndrome.

Methods:
A 32-year-old male with myasthenia gravis(MG) and systemic lupus erythematosus(SLE) who presented with nephrotic syndrome. Three weeks prior he had developed paresthesia and weakness of his hands and feet, This progressed within few weeks to bilateral wrist and foot drop.

Results:
Lumbar puncture showed an albiminocytologic dissociation. Nerve conduction studies showed absent motor responses and sural sparing pattern of sensory deficits. CIDP was diagnosed. Paranodal antibodies such as those against anti CNT1 are not available in Ghana. Patient did not repose to corticosteroids or plasma exchange. With a suspicion of paranodopathy subtype of CIDP , he was switched to rituximab. Within 3 months he improved to the point of walking without an aid

Conclusions:
Careful phenotyping of peripheral nerve disorders is especially important in underserved regions like Ghana, where tests such as paranodal antibodies are unavailable; facilitating timely selection of the most appropriate therapeutic modality for optimal patient outcomes.

References:
No

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Keywords: Chronic inflammatory demyelinating polyneuropathy, paranodopathy, contacting 1 protein

Assessment of diagnostic criteria for multifocal motor neuropathy.

Poster No:
P 213

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Introduction:
To assess the diagnostic criteria, ancillary investigations, and treatment response using real-life data in MMN patients.

Methods:
A web-based database included 110 clinically diagnosed MMN patients from specialized centers. Data, including clinical assessments, nerve conduction studies, anti-GM1 IgM antibodies, cerebrospinal fluid analysis, MRI, and ultrasound, were collected and analyzed based on EFNS/PNS criteria.

Results:
The EFNS/PNS diagnostic criteria were variably applied. In 17% of the patients only CMAP amplitude, but not area, was measured and subsequently recorded in the database by the treating physician. The supplementary diagnostic investigations recommended by the EFNS/PNS guidelines significantly contributed to improving the diagnostic accuracy in our cohort, exhibiting sensitivities ranging from 50% to 61%. Anti-GM1 IgM antibodies and nerve ultrasound demonstrated the highest sensitivity. Additional tests were frequently performed outside the EFNS/PNS guidelines recommendations. There was no difference in terms of clinical and laboratory findings, and response to therapy between patients with definite, probable or possible MMN. Fifty-three patients (78%) received IVIg maintenance treatment at the time of this study. Most patients with MMN were reported to stabilize after treatment with SCIg. Three out of 8 (37%) patients improved after cyclophosphamide.

Conclusions:
Real-life application of EFNS/PNS criteria in MMN diagnosis showed variations, with potential underutilization of CMAP area data and the frequent use of supplementary investigations beyond the recommendations outlined by the EFNS/PNS guidelines. Ancillary investigations, especially anti-GM1 IgM antibodies and nerve ultrasound, proved valuable in enhancing diagnostic

precision. The study underscores the challenges and utility of current diagnostic strategies in MMN within a real-world clinical practice setting and provides insights into its management strategies.

References:
No

Keywords: multifocal motor neuropathy, diagnostic criteria

Dissecting the genetic architecture of CIDP. Study protocol for an international collaborative genome-wide association study

Poster No:
P 214

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Introduction:
The aim of this study is to characterize the genetic landscape within a substantial cohort of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) patients. We seek to assess whether specific alleles or haplotypes are implicated in CIDP risk, its clinical and immunological variability, severity, therapeutic response, and its association with diabetes and other autoimmune disorders.

Methods:
This multicenter, collaborative investigation involves the Italian CIDP database study group, the Inflammatory Neuropathy Consortium Base study (INCbase), and the International CIDP Outcome Study (ICOS). A large cohort of CIDP patients will undergo screening using a genome-wide association study (GWAS). Additionally, 5000 healthy controls from the Italian population have already undergone GWAS genotyping. Participants include those meeting CIDP diagnostic criteria and individuals with autoimmune nodopathies. All patients will undergo a comprehensive clinical history using a dedicated questionnaire. Enrolment assessments will encompass outcome measures, concurrent medical illnesses, and laboratory testing for anti-paranodal protein antibodies and anti-ganglioside IgM antibodies. Blood samples will be collected for DNA extraction, followed by genotyping. GWAS results will be compared across various CIDP patient groups to discern genetic influences on disease phenotypes.

Results:
The study involves twenty Italian centers, two Dutch centers, one Spanish, one Serbian, and one Swiss center. Sixteen of these centers have obtained ethics committee approval. Blood samples from 186 CIDP patients have been collected, with DNA extraction completed in 62 patients.

Conclusions:
By comprehensively evaluating a diverse and well-characterized cohort of CIDP patients, this study aims to elucidate the role of genetics in CIDP. Insights into the genetic architecture of CIDP may pave the way for new preventive and therapeutic strategies, as well as the identification of diagnostic and prognostic biomarkers.

References:
No

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GBS CIDP Foundations

Keywords: CIDP

Different epitopes in anti-CNTN1-associated autoimmune nodopathy and their association with clinical phenotypes

Poster No:
P 215

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Introduction:
Autoimmune nodopathy with autoantibodies against the paranodal protein Contactin1 (CNTN1) is characterized by a distinct clinical phenotype of severe sensorimotor peripheral neuropathy. However, certain typical clinical features like glomerulonephritis are only found in some but not all of the patients and the course of disease varies. As epitopes in the Fibronectin-III (FnIII) as well as 6Ig domain have been described, binding to certain domains may be associated with distinct symptoms.

Methods:
Our study included sera of 13 patients with anti-CNTN1 autoantibodies. First, epitopes within the FnIII or 6Ig domain were identified by binding to HEK293 cells transfected with truncated CNTN1 constructs. An effect of glycosylation on autoantibody binding was tested by binding assays using HEK293 cells transfected with deglycosylated CNTN1 mutants. Peptide microarrays were run to confirm linear epitopes and to identify the exact binding site.

Results:
We could identify sera with binding to the FnIII domain (n=3) and with binding to the 6Ig domain (n=10). Glycosylation was required in one patient only. Linear epitopes within these domains were identified by peptide microarray in seven patients (2 FnIII, 5 6Ig). Comparison with clinical data revealed that glomerulonephritis was only found in patients with an epitope in the 6Ig domain (6/10). Six patients with 6Ig epitopes had a monophasic course of disease whereas 2/3 patients with FnIII epitopes developed a chronic course of disease and all three suffered from diabetes mellitus.

Conclusions:
Our data suggest that anti-CNTN1 autoimmune nodopathy is not a homogenous disease, and that different epitopes may be associated with different courses of disease and symptoms.

References:
No

Keywords: autoimmune nodopathy, autoantibody, epitope, contactin, node of Ranvier

Comparison of the Diagnostic Accuracy of the 2010 EFNS/PNS and the 2003 AAEM Diagnostic Criteria for Multifocal Motor Neuropathy

Poster No:
P 216

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Introduction:
To compare the sensitivity and specificity of the 2010 EFNS/PNS diagnostic criteria for multifocal motor neuropathy (MMN) with those of the 2003 AAEM.

Methods:
Sensitivity and specificity of the two above-mentioned criteria were evaluated in 53 MMN patients and 225 controls with axonal peripheral neuropathy or motor neuron disease. Comparison of the utility of nerve conduction studies with different number of nerves examined and of the sensitivity of the AAEM criteria considering conduction blocks as either amplitude reduction or area reduction was assessed.

Results:
EFNS/PNS criteria had a sensitivity of 47% for definite MMN and 57% for probable/definite MMN, while the AAEM criteria had a sensitivity of 28% for definite MMN and 49% for probable/definite MMN. Using extended nerve conduction study protocol, sensitivity of the EFNS/PNS criteria remained relatively stable while sensitivity of the AAEM rose to 31% for definite MMN and 55% for probable MMN. Using supportive criteria, the sensitivity of the EFNS/PNS criteria for probable/definite MMN increased to 64%, while an additional 36% of patients fulfilled the criteria for possible MMN. Upon revisiting the analysis of the sensitivity of the AAEM criteria, considering only amplitude reduction versus solely area reduction, the latter parameter demonstrated greater sensitivity. Specificity of the EFNS/PNS criteria for probable/definite MMN was 99.5%, while specificity of the AAEM criteria for probable/definite MMN was 100%. Using extended nerve conduction study protocol, specificity of the two sets of criteria remained the same. The diagnostic accuracy of the EFNS/PNS criteria was slightly higher than that of the AAEM.

Conclusions:
In our patient populations, the EFNS/PNS criteria were more sensitive and showed similar specificity compared to the AAEM criteria. With the AAEM criteria, more extended nerve conduction studies are recommended to obtain an acceptable sensitivity while maintaining a very high specificity.

References:
No

Keywords: multifocal motor neuropathy, diagnostic criteria

Neuroinflammation and neurodegeneration in a mouse model of chronic neuritis

Poster No:
P 217

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Introduction:
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is one of the most common autoimmune disorders of the peripheral nervous system (PNS) and presents as clinically heterogeneous disease affecting the peripheral nerves and nerve roots. The disease is defined by immune mediated damage of myelin and axonal structures, however processes of dedifferentiation and degeneration may further contribute to the clinical damage. The ICAM-1-deficient NOD mouse represents a spontaneous model of chronic neuritis that shares several pathological and clinical features with CIDP, including responsiveness to IVIg. Here, we aimed to better understand to what extent neuroinflammation, neurodegeneration and dedifferentiation in the sciatic nerves determine disease progression.

Methods:
To characterize key immune cell populations including T-lymphocytes (CD3, CD4, CD8), B-lymphocytes (B220) and macrophages (CD11b) by means of quantity and localization immunohistochemistry was performed. In addition, Sox2 was analyzed as a marker for dedifferentiation of Schwann cells. Morphometric analyses were used to investigate myelin integrity and axonal density.

Results:
Accumulation of infiltrating immune cells in the sciatic nerves was more prominent in moderate and severely affected animals indicating a correlation with disease severity. These finding were paralleled by an increased number of dedifferentiated Schwann cells. Axonal density was lower in more severely affected animals compared to animals with mild clinical signs. While only minor differences in myelin thickness were measured, we observed more "onion bulb"-like structures in severely affected animals.

Conclusions:
Although the disease severity is heterogenous in the chronic neuritis model of ICAM1-deficient NOD mice, these findings indicate that severity of clinical symptoms was not just paralleled by inflammatory infiltration, but also by Schwann cell dedifferentiation, which may make a relevant contribution to myelin and axonal damage. The clinical relevance of neurodegeneration and dedifferentiation in immune mediated neuropathies is to be investigated in further studies.

References:
No

Keywords: CIDP, NOD-ICAM1, Neuroinflammation, Neurodegeneration, Dedifferentiation

Autoimmune Nodopathies – Clinical And Serological Characteristics Of Patients From A UK Diagnostic Laboratory

Poster No:
P 218

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Introduction:
The existing literature on the clinical and serological characteristics of patients with autoimmune nodopathies (AN) derives from small case series, and thus conclusions about clinical patterns and treatment responses may be less confidently applied to clinical practice.

Methods:
Between 2015-2023 we identified 121 patients (6.2% of the 1940 screened) with (para)nodal antibodies (NF155, NF186, CNTN1, Caspr1). Standardised clinical data was available for 88 AN and 194 seronegative patients.

Results:
AN patients had a severe, motor and sensory, proximal and distal symmetrical neuropathy. They were more likely to present acutely (53% vs 30%, p=0.0015), and were more disabled at nadir (79% modified Rankin score >=4 vs 21%, p= 0.0001) than the seronegative group. Nephrotic syndrome was more common in the nodopathy group (61% vs 3%, p=0.0001), and most frequently observed in the pan-neurofascin antibody group. Anti-panNF and anti-Caspr1 antibody patients presented most acutely. Respiratory failure, autonomic insufficiency, and cranial nerve palsies were strongly associated with panNF, and neuropathic pain with Caspr1 patients. Ataxia and tremor were comparable between groups. IgG1 was at least as dominant as IgG4, and the most frequently observed antibody subclass in all groups; the panNF group were almost exclusively IgG1. At a group level, antibody titres did not correlate with disease severity, but longitudinally they tended to correlate with clinical disease course on an individual level. Over half of nodopathy patients were deemed to have a 'good' response to Rituximab versus only a minority receiving standard immunotherapy (7-19%).

Conclusions:
Our dataset strengthens the established core phenotype of AN patients, but suggests clinical features previously reported to be characteristic of individual antibody groups are not necessarily specific. We add to the emerging literature that antibody titres correlate with clinical disease activity and are likely to be useful in disease monitoring. The frequent presence of IgG1 subclass antibodies warrants further investigation.

References:
No

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Keywords: Autoimmune Nodopathies

Population Pharmacokinetic Simulations In CIDP And MMN: Hyaluronidase-Facilitated Subcutaneous Immunoglobulin And Intravenous Immunoglobulin G 10%

Poster No:
P 219

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Introduction:
A population pharmacokinetic (popPK) model was used to simulate pharmacokinetic profiles in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) or multifocal motor neuropathy (MMN), after administration of different dosing regimens of hyaluronidase-facilitated subcutaneous immunoglobulin (fSCIG) 10% or intravenous immunoglobulin (IVIG) 10%.

Methods:
A popPK model was developed using total circulating immunoglobulin G (IgG) levels from phase 3 studies in CIDP (NCT02549170; n=132) and MMN (NCT00666263; n=44). The final popPK model was a one-compartment linear model with a subcutaneous depot compartment, and was used to simulate total serum IgG concentration–time profiles during 6 months of continuous IVIG 10% treatment, or 9 months of fSCIG 10% maintenance therapy for patients with CIDP or MMN (after 3 months IVIG 10% and fSCIG 10% ramp-up dosing). During model development, no patient characteristic distinguished between pharmacokinetic profiles in patients with CIDP or MMN. Simulated dosing regimens were: 0.4, 0.8, and 1g/kg every 2 weeks (Q2W); 1 and 2g/kg Q3W; 0.4, 0.8, 1, and 2g/kg Q4W; and 2g/kg split into four daily infusions Q4W.

Results:
For the same dosing regimen, average IgG concentrations during dosing intervals at steady state were lower in patients receiving fSCIG than IVIG 10%. For fSCIG 10%, the ramp-up period led to maintenance of trough concentrations at higher levels and controlled maximum concentrations. For IVIG 10%, accumulation was observed for Q2W and Q3W dosing, while Q4W regimens with doses below 2g/kg showed almost no accumulation, and trough values approached off-treatment levels. Splitting the 2g/kg dose into four daily infusions did not markedly affect serum IgG concentration–time profiles for either treatment.

Conclusions:
Simulations demonstrated that subcutaneous fSCIG 10% combined with a ramp-up period of administration may maintain IgG levels with less peak-to-trough fluctuation than IVIG 10% administration, in patients with CIDP or MMN. Study/writing support funder: Takeda Development Center Americas, Inc./Takeda Pharmaceuticals International AG.

References:
No

Keywords: population pharmacokinetic modelling and simulations, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, hyaluronidase-facilitated subcutaneous immunoglobulin 10%, intravenous immunoglobulin 10%

Serum Glycobiomarkers Defining Therapeutic Response to Intravenous Immunoglobulin in Chronic Inflammatory Demyelinating Polyneuropathy

Poster No:
P 220

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Introduction:
We conducted a comprehensive glycan analysis of serum to explore glycan biomarkers defining the pathophysiology and treatment response in chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods:
Of the 81 consecutive patients with CIDP, we included untreated typical CIDP patients (n=27) at the initial presentation and healthy controls (HC, n=20). N- and O-glycans in pretreatment serum were quantitatively analysed by mass spectrometry. We investigated the relationship between clinical parameters and glycans. Treatment response was evaluated by the degree of improvement in the modified Rankin Scale two weeks after the first dose of intravenous immunoglobulin (IVIg). We also assessed serum neurofilament light chains (NfL).

Results:
Compared to HC, the total amount of N-glycans, especially sialylated N-glycans, was significantly lower in the CIDP group (CIDP vs. HC, 973.3 vs. 1124.0 pmol/μL; $p < 0.05$, 898.0 vs. 1064.4 pmol/μL; $p < 0.01$, respectively). In contrast, there were no significant differences in O-glycans between the two groups. Treatment response was not associated with serum NfL levels, but low levels of N-glycans, especially sialylated N-glycans and O-glycans, were significantly associated with resistance to initial IVIg treatment ($p < 0.05$, $p < 0.05$, $p < 0.01$, respectively). For individual glycans, low levels of Hex2HexNAc2NeuAc2 [α2,6/α2,6] + Man3GlcNAc2, α2,6-linked sialylated N-glycans discriminated the treatment response group with an area under the curve of 0.802 ($p < 0.05$).

Conclusions:
Our findings indicated that low levels of N-linked glycans, particularly α2,6-linked sialylated, serve as a novel glycan biomarker reflecting pathophysiology and therapeutic resistance in typical CIDP.

References:
No

Grant Support:

This work was supported in part by JSPS KAKENHI (23K14751).

Keywords: chronic inflammatory demyelinating polyneuropathy, biomarker, glycoanalysis, intravenous immunoglobulin, N-glycans

Deep Data Extraction from Nerve Biopsy Reports: Evaluating the Accuracy of Generative Artificial Intelligence

Poster No:
P 221

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Introduction:
Deep data mining of narrated diagnostic reports, e.g. in radiology or pathology, has been instrumental in revealing new insights into disease pathogenesis and outcomes. Our study presents results from extracting pathologic features from nerve biopsy reports using an advanced natural language processing system.

Methods:
We collected semi-structured (i.e., based on standardised reporting templates) nerve biopsy reports (n=868) from 2006 to 2023 from our institution. The Generative Pre-trained Transformer 4 (GPT4) model was used to extract 45 parameters as categorical or ordinal variables. After developing prompts and instructions on 10 benchmark cases, we applied these to 50 selected cases across various diagnoses and compared the results to human data extraction. Model performance was evaluated using accuracy for all fields and weighted kappa metrics for ordinal fields only.

Results:
GPT4 demonstrated an overall accuracy of 0.87 (range 0.62-1) in the 50 test cases, accomplishing the task in 41 minutes vs 5 hours of manual data extraction. High accuracy (≥0.95) was noted for features such as "onion bulbs", "macrophage activity", "fibrinoid necrosis", "vessel wall infiltration", and "demyelination" on reported teased fibre or electron microscopy results. Lower accuracy was observed for "distribution of fibre loss" (0.62) or "inflammation distribution across the nerve" (0.64). Categorical fields yielded higher accuracy (mean 0.92) than ordinal fields (mean 0.81), but the mean weighted kappa for ordinal fields was 0.82, indicating minor discrepancies between human and GPT4 classifications.

Conclusions:
Our findings demonstrate the utility of using GPT4 for automated data extraction from nerve biopsy reports without specific pre-training. High accuracy was achieved for critical clinical findings, particularly in demyelination and vasculitic features. However, complex fields such as ordinal data and abstract concepts, such as fibre loss and inflammation distribution, still require prompt refinement for optimal accuracy.

References:
No

Keywords: neuropathies, nerve biopsy, GPT4, artificial intelligence

Rasch-built Ataxia Rating Sale for IgM-associated Polyneuropathy With and Without Anti-MAG Antibodies (IgM-PNP RB-ARS)

Poster No:
P 222

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Introduction:
IgM-associated polyneuropathy with and without anti-MAG antibodies (IgM ± anti-MAG PNP) is generally a slowly progressive disorder with clinical features ranging from mild foot numbness to severe neuropathic pain, ataxia, and limb weakness. While sensory and strength impairments have been the main focus for explaining functional deficit in IgM PNP, some patients show gait ataxia with balance disorders which has not been systematically addressed. The international, multi-center, collaborative IMAGiNe study consortium which includes 21 hospitals in 10 countries, presents a modern clinimetric analysis of a disease-specific interval-level scale specific for the assessment of ataxia.

Methods:
The IMAGiNe study is a prospective, observational cohort study with a 3-year follow-up period. Subjects completed a face/content validity fitting pre-selected list of items originating from the Modified International Cooperative Ataxia Rating Scale (MICARS) and Scale for the Assessment and Rating of Ataxia (SARA). The IMAGiNe ataxia entry data consisting of 237 records of participants with IgM ±anti-MAG PNP (Netherlands: 103, USA: 31, Denmark: 31, Spain: 24, France: 21, Italy: 19, Serbia: 8) will be subjected to Rasch analyses to determine model fit by transforming the ordinal data obtained into an interval metric. Various clinimetric aspects of the final ataxia scale will be examined, including differential-item functioning, local

dependence and cross-cultural validity. Reliability and validity studies will be performed. The IgM-RODS scores will be used to examine whether the functional deficit could be explained to some extent by the presence of ataxia.

Results:
The results will be presented at the meeting.

Conclusions:
This is the first large scale, international study to describe and quantify ataxia in patients with IgM ± anti-MAG PNP as well as its impact on functional deficit. These results will influence potential clinical trial endpoints in this disease.

References:
Yes

Reference 1: Hamadeh T, van Doormaal PTC, Pruppers MHJ, et al. IgM anti-MAG(+/-) peripheral neuropathy (IMAGiNe) study protocol: An international, observational, prospective registry of patients with IgM M-protein peripheral neuropathies. J Peripher Nerv Syst 2023;28(2):269-275.

Grant Support:

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Keywords: Monoclonal gammopathy, IgM polyneuropathy, Outcome research, anti-MAG, Rasch-built scale

Characterizing Treatment Patterns And Healthcare Use In Patients And Subgroups With Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Poster No:
P 223

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Introduction:
Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) is a progressive autoimmune disease that causes inflammation of the nerve roots and peripheral nerves. This retrospective observational cohort analysis aimed to explore the treatment patterns and healthcare resource utilization (HCRU) in US patients with CIDP and identify a subgroup of patients who move to a new therapy in the 2 years following first-line treatment.

Methods:
Integrated data from the Optum® Market Clarity linked EHR-claims dataset was used to identify adults with CIDP diagnoses between 2008 and 2020. Clinical characteristics, treatment patterns, and HCRU were described for the treatment cohort (n=1,942) and for a subgroup of patients who moved to a new therapy treatment class during the 2 years post first-line CIDP therapy initiation (n=605).

Results:
Out of the CIDP treatment cohort (n=1,942), 605 patients (31%) had moved to a new therapy during the 2 years post first-line treatment initiation. Out of the subgroup of patients who had moved to a new therapy, the first line treatment was, immunoglobulin in 51% of patients, systemic glucocorticoids in 27%, and immunosuppressive therapy in 8% patients. Compared with CIDP patients who did not move to a new therapy, this subgroup of patients had more CIDP-related healthcare encounters (6.5 vs 5.0 average encounters per year) in the two years post CIDP treatment initiation.

Conclusions:
This real-world data analysis provides detailed insights into the treatment patterns and HCRU of a large cohort of CIDP patients. A group of patients moved to a new therapy during the 2 years following treatment initiation, suggesting that first-line treatments in this patient population may be suboptimal. In this subgroup of patients, high rates of changing treatments and healthcare encounters are suggestive of unmet need in this population which may be refractory to standard of care.

References:
No

Keywords: CIDP, real-world evidance, epidemiology, treatment patterns, immune neuropathy

Patient-reported Health-related Quality of Life in Guillain–Barré Syndrome: A Prospective Cohort Study in Bangladesh Using i-RODS

Poster No:
P 224

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Introduction:
Guillain–Barré Syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy with several chronic sequalae including restricted mobility, self-care, fatigue and depression. However, health-related quality of life (HRQoL) data in GBS is still scarce. The study aimed to compare the HRQoL in GBS patients who received specific or supportive treatments.

Methods:
We included 147 patients with GBS who were enrolled between 2013–2018 and who completed follow-up at 1-month (baseline) and 6-month. We measured HRQoL using Inflammatory Rasch-built Overall Disability Scale (i-RODS). The i-RODS is a patient-reported scale comprising 24-items having scores 0-48. Higher scores represent better patient-reported HRQoL and vice-versa. We performed descriptive analyses to compare i-RODS scores between GBS patients who received specific or supportive treatment.

Results:
Among 147 patients with GBS, 67% (n=99) were male with a median age of 30 years (IQR 17,45). Two-thirds (64%, n=94) of the patients did not receive any specific treatment. Intravenous immunoglobulin (IVIg) and plasma exchange (PE) were given to 9% and 27% patients respectively. Around 76% (n=40) and 73% (n=69) of the patients who received specific or supportive treatment correspondingly were bedridden (GBS-DS 4) during enrollment. At baseline, the median (IQR) i-RODS sumscore of the patients who received specific treatments or supportive care were 8 (0,28) and 7 (1,22); P=0.794 respectively. At 6-month, the median (IQR) i-RODS sumscore of these patients were 38 (15,42) and 36 (28,41); P=0.591 respectively. Similarly, the median centile scores were not statistically significant at the studied time-points between patients who received or did not receive specific treatment.

Conclusions:
We did not find any statistically significant difference in patient-reported HRQoL in GBS patients who received or didn't receive any specific treatment. Further, controlled studies are required to evaluate HRQoL in larger GBS cohorts. This study reinforces the need of better treatment options and importance of patient-reported outcome for management of GBS.

References:
No

Keywords: Guillain–Barré syndrome, Patient-reported outcome measures, Health-related Quality of Life, Inflammatory Rasch-built Overall Disability Scale, i-RODS

Association of Gut Microbial Diversity with Inflammation in Patients with Guillain-Barré Syndrome

Poster No:
P 225

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Introduction:
Guillain-Barré syndrome (GBS) is an acute, immune-mediated paralytic illness of peripheral nervous system and has strong association with inflammation. In the current study, we aimed to investigate the association of gut-microbial diversity and inflammation in order to uncover possible microbial biomarker(s) in GBS inflammation.

Methods:
We investigated, gut-microbiome diversity in 60 GBS-patients compared to 60 age-sex-matched healthy controls. Blood and fecal specimens were collected from patients at baseline and 6-months of follow-up (n=46). Fecal DNAs were extracted and sequenced for bioinformatics analysis through QIIME2-DADA2 pipeline. Serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), neutrophil-to-lymphocyte ratio (NLR) and ferritin were measured and analyzed to assess association between sub-groups ($p<0.05$; significant).

Results:
Most of the patients were male adult (67%; IQR, 36[26-52]) and severely-affected (97%) with history of antecedent events (73%). CRP, ESR, NLR and ferritin were significantly increased in GBS compared to controls at baseline and 6-months follow-up ($p<0.0001$ for all comparisons). Firmicutes/Bacteroidetes (F/B) ratio was significantly high in GBS compared to controls and 6-months follow-up (GBS vs. HC, 73.43±160.3 vs. 36.64±100.7 (mean±SD); p=0.003 and GBS (baseline) vs. GBS 6-months follow-up (73.43±160.3 vs. 55.33±178.5 [mean±SD]; p=0.0269). Considering serum inflammatory markers induction at baseline of GBS regarding high CRP, ESR, NLR and ferritin, gut-microbial diversity revealed significant decreases of Bacteroidetes compared with 6-months follow-up (p=0.013, p=0.021, p=0.005, p=0.012). Phylum Euryarchaeota was decreased significantly with low CRP, ESR and NLR at 6-month (p=0.0265; p=0.006 & p=0.0005). Significant abundance of Proteobacteria and high F/B ratio was found in high level of ESR (Proteobacteria, p=0.0004; F/B, p=0.0206) and NLR (Proteobacteria, p=0.0240; F/B, p=0.0343) at baseline compared to low level at 6-month.

Conclusions:
Low abundance of Bacteroidetes is common in disease induction of GBS with inflammation. High F/B ratio might be considered as biomarker of inflammation in GBS. However, expression profiling of gut-microbiome is prerequisite to validate the findings.

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Yes

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Keywords: Guillain-Barré syndrome, Gut Microbial Diversity, Inflammatory biomarker, C-reactive protein, Neutrophil-lymphocyte ratio

Genomic Epidemiology of Campylobacter Jejuni Associated with Guillain-Barré Syndrome

Poster No:
P 226

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Introduction:
Campylobacter jejuni (C. jejuni) is the leading cause of bacterial gastroenteritis and is responsible for post-infectious sequelae, Guillain-Barré syndrome (GBS). We intended to investigate a genome-based global epidemiological analysis with all publicly accessible sequences of C. jejuni associated-GBS to determine bacterial-genomic features and baseline diversity associated with GBS.

Methods:
A comparative genomic analysis was performed in 90 GBS-associated C. jejuni strains; 38 strains were isolated and sequenced from Bangladesh and other 52 strains (global) were retrieved from NCBI database. Geographical structural diversity and similarities were performed using diverse bioinformatics approaches. Statistical analysis (GraphPad Prism, chi-square, Bioconductor/R package) was performed and $p<0.05$ considered as significant.

Results:
A total of 10 clonal complexes (CC) and 24 sequence types (STs) were found among all C. jejuni strains. Globally, sequence type ST-22 was prevalent while a widely diversified lineage was found in Bangladesh. Clonal complex CC362 (23%, [33/141]), CC22 (20%, [28/141]), CC21 (12%, [17/141]) were most frequently found worldwide whereas CC403 was prevalent in Bangladesh. Correlation matrix of virulence gene showed LOS genes nueC2 and nueB2 were highly correlated with flagellar genes, ptmA and ptmB. Type VI secretion system (T6SS) was significantly prevalent (29%, $p=0.0001$) among Bangladeshi strains; whereas, globally T6SS was found least (2%). C. jejuni integrated elements (CJIE) was found in total 37% of GBS-associated strains; but, CJIE-1 (30%) was more prevalent. Phase variation (PV) was significantly higher in clonal complex ST-403 ($p<0.0001$) strains comparing with ST-21, ST-22 and ST-362. Among phase variable genes, protein containing aminopeptidase domain was found in all GBS associated strains except one.

Conclusions:
Global diversity of C. jejuni isolated from patients with GBS from five different continents showed divergence of genomic features. Future studies should focus on the association between clinical features and sequence characteristics of GBS-associated C. jejuni strains.

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Yes

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Grant Support:

Fogarty International Center (FIC), National Institute of Neurological Disorders and Stroke of the National Institutes of Health (NIH), USA under Award Number K43 TW011447

Keywords: Guillain-Barré syndrome, Campylobacter jejuni, Clonal complex, Genomic epidemiology, Virulence gene

Effectiveness And Safety Of Ofatumumab In Autoimmune Nodopathy: A Prospective Cohort Study

Poster No:
P 227

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Introduction:
Autoimmune nodopathy is a peripheral neuropathy characterized by acquired motor and sensory deficit with autoantibodies against the node of Ranvier or paranodal region in the peripheral nervous system. Previous studies suggested the therapeutic potential of CD20-depleting treatment in the disease. However, some patients did not respond well to rituximab, a widely-used treatment in autoimmune diseases. Ofatumumab is the first fully human anti-CD20 monoclonal antibody, and may bring benefits to patients with autoimmune nodopathy.

Methods:
This prospective observational study included 7 patients with autoimmune nodopathy, receiving subcutaneous ofatumumab 20 mg every 4 weeks (q4w) (from Week 4, after initial doses on Days 1, 7, and 14). The Inflammatory Neuropathy Cause and Treatment (INCAT) disability score, Inflammatory Rasch-Built Overall Disability Scale (I-RODS), grip strength, and 3m-Time Up and Go (TUG) were collected at entry and every 4 weeks. Antibodies against neurofascin 155 (NF155) and contactin-1 (CNTN1) were tested every 4 weeks, using cell-based assay at a titer of 1:100.

Results:
Six patients with anti-NF155 antibodies and one patient with anti-CNTN1 antibodies were included in the studies. The median time of observation was 12 weeks (range: 4 - 24). At the last visit, six of the seven patients showed clinical improvement on either the INCAT, centile I-RODS or grip strength. Three of the six patients did not respond well to rituximab. The median time of reaching minimal clinically important difference was 16 weeks. Six of the seven patients improved in the 3m-TUG, and the median time of the first improvement was 4 weeks. The paranodal antibodies in these patients remain positive during the follow up visit. No severe adverse events were observed.

Conclusions:
Ofatumumab 20 mg q4w subcutaneously was effective and safe in a part of patients with autoimmune nodopathy. The association between clinical improvement and anti-paranodal antibodies needs further investigation.

References:
No

Keywords: Autoimmune nodopathy, Chronic inflammatory demyelinating polyradiculoneuropathy, Treatment, Ofatumumab

Decreased serum albumin levels are association with severe Guillain-Barré syndrome: an update of a prospective cohort study

Poster No:
P 228

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Introduction:
Guillain-Barre syndrome (GBS) is an immune-mediated polyneuropathy with varied clinical presentations and outcomes. Despite the efficacy of intravenous immunoglobulin (IVIg), one-third patients persist functional disability after 6 months. Identifying biomarkers for prognosis is crucial. Consequently, our study aimed to investigate the role of serum albumin as predictive biomarker for disease severity and IVIg clinical outcomes specially in LMICs.

Methods:
We included 184 GBS patients in a prospective cohort study during 2019-2023 in Bangladesh. Detailed neurological examinations, serological investigations including serum albumin and serum IgG were performed at baseline and pre-defined follow-up. Statistical comparisons between intended biomarkers and disease prognosis were performed using spearman correlation, ANOVA and student t-test.

Results:
The median age of patients was 31 years (IQR: 22-40) with male predominance (70%); 99 patients were treated with either IVIg and 85 patients received only supportive care. Severe GBS (GBS-DS>3) was found among 86% patients and 34% patients required mechanical ventilation (MV). Lower serum albumin levels were associated with higher GBS disability score at enrolment, 2, 4,13, 26 weeks ($p<0.001$). Severely affected patients with GBS were associated with hypoalbuminemia compared to mild GBS ($p=<0.001$) at enrolment. Low level of serum albumin was associated with patients with MV compared to non-MV patients ($p<0.001$). 84% patient with MV had reported hypoalbuminemia, while 87% non-MV had normal level of serum albumin. Significant increase of serum albumin was found at 13 and 26 weeks among IVIg treated patients compared to supportive care patients ($p<0.0001$ and <0.0001). 88% patients with GBS had poor outcome at 4 weeks after IVIg treatment, which was significantly associated with hypoalbuminemia compared to good outcome patients ($p<0.0001$).

Conclusions:
Reduced serum albumin can be considered as potential marker for severe GBS and predictors of IVIg treatment response of GBS. Further investigation is warranted to validate the clinical relevance of these biomarkers.

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Yes

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Grant Support:

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Keywords: Guillain-Barre syndrome, Intravenous immunoglobulin, Serum albumin, Predictive biomarker

The Regulatory B Cells Association with the Pathogenesis and Clinical Course of Guillain– Barré syndrome

Poster No:
P 229

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Introduction:
Antibodies and B-cells to peripheral nerve targets play a key role in the pathogenesis of Guillain-Barré syndrome (GBS). However, B-cells with regulatory function are yet unexplored in GBS. In this study, we aimed to investigate the frequency of IL10-producing subsets of regulatory B-cells (B10) in relation to GBS and their clinical association with the disease course.

Methods:
A prospective study was conducted in 63 GBS patients, 45 healthy controls (HCs) and 17 enteritis controls (ECs) during 2021-2023. B10 cells were measured in CpG-stimulated peripheral blood mononuclear cells using flow cytometry with surface staining for CD3, CD45, CD19, IgD, CD24, CD38, and CD20 and intracellular staining for IgG, IgM, IgA and IL10.

Results:
The median age of patients was 35 years (IQR: 44-25), with male predominance (71%). 48 patients had antecedent events, mostly diarrhea (40%) and 54 patients (86%) were unable to walk. GBS patients had an increasing frequency of CD19+ B-cells compared with both HCs and ECs. Unswitched CD19+IgM+ B-cells increased (p=0.03), whereas, switched B-cells and transitional B-cells decreased significantly in acute-GBS compared with ECs (p=0.03 and 0.015). IL10-producing CD19+CD38hiCD24hi, IgA+ and IgG+ B10 increased significantly at acute-stage of GBS compared with HCs (p=0.0006, 0.04 and 0.03), but were not different from ECs. GBS patients with gastroenteritis preceding events had significantly higher CD19+CD38hiCD24hi B10 than patients with other preceding events (p=0.04). During disease course, CD19+CD38hiCD24hi, IgM+ and CD19+ B10 were gradually declined till 4 weeks and raised significantly at 26 weeks. Positive correlation was found between frequencies of IgM+ and CD19+ B10 expression and IL-1β secretion in lymphocyte supernatant in GBS (p=0.02 and 0.046).

Conclusions:
Different IL10-producing B-cell subsets are expanded in the acute stage of GBS and are associated with gastroenteritis preceding infection and IL-1β cytokine secretion. Further studies require to understand the functional role of B10 in GBS.

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Yes

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Grant Support:

National Institute of Neurological Disorders and Stroke (NINDS), NIH, USA (5R21TW012184-02)

Keywords: Guillain-Barré syndrome, Regulatory B-cells, IL10-producing cells, Transitional B cells, clinical disease course

FoxP3 expressing regulatory T cells as a cellular marker for clinical course and response to Intravenous Immunoglobulin in Guillain-Barré syndrome

Poster No:
P 230

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Introduction:
Guillain–Barré syndrome (GBS), an immune-mediated polyneuropathy involving aberrant immune response to a preceding infection. Regulatory T cells (Tregs) play crucial role in maintaining self-tolerance and preventing autoimmunity. Intravenous immunoglobulin (IVIg), the most commonly used therapy for GBS that promotes the proliferation of Tregs. In this study, we investigated Treg phenotypes and their association with GBS pathogenesis and IVIg treatment response.

Methods:
A prospective case-controlled study was conducted involving 65 GBS patients and 65 healthy controls (HCs) during 2019-2023. Treg cells were measured in peripheral blood mononuclear cells using flow cytometry by surface-staining for CD4, CD25 and intracellular-staining for FoxP3. Mann–Whitney U test and pairwise t test were performed.

Results:
The median age of patients was 35 years, with male predominance (64%) and. 47 patients (74%) had antecedent events, mostly diarrhea (36%). Severe GBS was observed in 88% of cases, with 29% requiring mechanical ventilation. IVIg treatment was administered to 49% of patients, while others received supportive care. In acute GBS, the proportion of CD4+FoxP3+ Tregs ($p= 0.008$) and CD4+CD25+FoxP3+ Tregs ($p= 0.015$) was reduced compared to healthy controls. Decreased CD4+CD25+FoxP3+ Tregs correlated with higher GBS-disability scores (GBS-DS) ($p= 0.039$) and associated with mechanical ventilation ($p= 0.014$). IVIg treatment increased CD4+CD25+FoxP3+ Tregs at 2 weeks ($p= 0.014$), and CD4+FoxP3+ and CD4+CD25+FoxP3+ Tregs at 4 weeks ($p= 0.02$ and $p= 0.008$) compared to supportively treated patients. Patients with a 1-grade improvement in GBS-DS at 2 and 4 weeks after IVIg displayed elevated CD4+CD25+FoxP3+ Tregs ($p= 0.012$ and $p= 0.026$).

Conclusions:
Reduced FoxP3+ expressing Tregs are associated with GBS development and disease severity. IVIg treatment induces an increase in FoxP3+ expressing Tregs within 2 weeks, which was associated with clinical improvement. Further investigations are warranted to validate Tregs as a biomarker and elucidate their function in GBS treatment response

References:
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Grant Support:

This research activity was funded by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (USA), under award number R21TW012184.

Keywords: Guillain–Barré syndrome, Intravenous immunoglobulin, Regulatory T cells, GBS-disability scores, Mechanical ventilation

THE IMPORTANCE OF ULTRASONOGRAPHY IN THE TREATMENT OF LEPROSY NEURITIS

Poster No:
P 231

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Introduction:
Neuropathy of leprosy cause deformities and disabilities. Ultrasonography(USG) emerges as a complementary modality in the evaluation of peripheral nerves, being useful for guiding diagnostic and therapeutic decisions, in addition to electrodiagnostic(BROWN et al., 2016). Nerves are enlarged in leprosy patients, especially those with reaction, possibly blood flow being the first sign of neural injury(JAIN et al., 2009).

Methods:
Prospective cross-sectional study carried out at the specialized center. Selected patients with type 1 or 2 reaction with pain in a neuro-anatomical area with motor and/or sensory impairment of the median, ulnar, peroneal and tibial nerves. Clinical neurological examination was perfomed. Realized nerve conduction study(NCS) and those with signs of demyelination will be defined as neuritis and refer to USG. Classified as neuritis: increase crosssectional area(CSA) of the nerve(mm^2), loss of fascicular pattern, hyperechogenicity and/or thickening of the epineurium, flow on Power Doppler. These parameters was evaluated monthly and correlated to the dose of the corticosteroid, as well as every three months with the electrophysiological findings, until complete 6 months of treatment.

Results:
Twelve patients with leprosy neuritis were selected. Eight were undergoing polychemotherapy. The most affected nerve was the ulnar(8)>fibular(3)>median(1)=tibial(1). All were treated with oral corticosteroid 1mg/kg/day with weaning according to protocol. Clinical response to pain was 2 months, in agreement with absence of flow on PD (~ 2/3 months). The ECN did not show significant improvement of follow-up. USG helped to define neuritis in 2 cases with suggestive clinical signs, without response to NCS and other two with recurrent neuritis(D6). All patients showed reduction in CSA, but without normalization. Subjective improvement in fascicular arrangement and echogenicity. Only 2 use medication for neuropathic pain.

Conclusions:
The increased use of USG can help in understanding the pathophysiology of acute leprosy neuropathy, adding to the NCS to confirm and find more data and individualize treatment.

References:
No

Keywords: Leprosy, Neuritis, Neuropathy, ultrasound

A Case of POEMS Syndrome Masquerading as CIDP

Poster No:
P 232

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Introduction:
POEMS syndrome is a rare multi-system disorder that manifests clinically with polyneuropathy, organomegaly, endocrinopathies, monoclonal plasma cell disorder, and skin changes. The diagnosis is often missed or delayed due to its complexity and rarity.

Methods:
Case report and literature review.

Results:
We present a case of a 46-year-old male who complained of yearlong difficulty with walking with weakness and paresthesia in his feet. His neurological exam was significant for mild distal motor and sensory deficits in his lower extremities, diffuse areflexia, and a steppage gait. The EMG/NCS and CSF study, was consistent with chronic inflammatory demyelinating polyneuropathy (CIDP). He was first treated with IVIG and prednisone. After an initial stabilization for a few months, his neuropathy suddenly worsened to the point where he could not stand or walk and required a wheelchair. He continued to decline despite escalating doses of IVIG and steroids. He started to notice hyperpigmentation in the fingers and toes with associated edema and pain. His HbA1c increased from 6.9 to 9.3% within 5 months. He had unexplained weight loss. Imaging studies showed diffuse sclerotic and lytic bone lesions, abdominal ascites, suspicious for metastatic disease. An SPEP/IFE showed IgG lambda monoclonal protein. A clavicular biopsy revealed a plasmacytoma. This patient meets the criteria for POEMS syndrome. He was treated with chemotherapy and stem cell transplantation. His plasmacytoma is currently in remission. His strength has improved with now only residual foot drop, and skin changes and swelling have resolved.

Conclusions:
The diagnosis of POEMS is often delayed in early stages when patients exhibit only isolated polyneuropathy mimicking CIDP due to similar clinical and electrodiagnostic findings. This case underscores the value of re-evaluating the diagnosis when patients stop responding or worsen with indicated treatments for CIDP. The high clinical suspicion of POEMS and underlying malignancy are clues to diagnose this multifaceted syndrome.

References:
No

Keywords: POEMS, CIDP, EMG, Plasmacytoma

Electrophysiologic features of anti-neurofascin-155-positive autoimmune nodopathy

Poster No:
P 233

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Introduction:
Anti-neurofascin-155 (NF-155) antibody is one of the autoantibodies associated with autoimmune nodopathy (AN). Patients with anti-NF-155 antibody positive AN (NF-155 AN) have been reported to exhibit distinct clinical features: younger age at onset, distal motor involvement, sensory ataxia, tremor, and poor response to intravenous immunoglobulin (IVIg). However, electrophysiologic features of NF-155 AN remain unclear.

Methods:
Sera from 147 patients who fulfilled the diagnostic criteria for CIDP were tested for antibodies associated with AN, and 13 were positive for NF-155. The clinical features and results of nerve conduction studies (NCS) were investigated retrospectively. The clinical features and electrophysiological data of 13 NF-155 AN patients were compared to those of 36 CIDP patients without antibodies (seronegative CIDP).

Results:
NF-155 AN patients were younger at onset and more frequently presented with a subacute onset, sensory ataxia, tremor, and cranial nerve involvement, compared to seronegative CIDP patients. They were often exhibited a poor response to IVIg and corticosteroids. In motor NCS, NF-155 AN had significantly lower frequency of conduction block (15.4% vs. 77.8%, $p < 0.001$) and abnormal temporal dispersion (0 % vs. 58.3 %, $p < 0.001$) than seronegative CIDP. NF-155 AN had significantly lower terminal latency indices in the median (0.19 vs. 0.31, $p = 0.006$), ulnar (0.22 vs. 0.37, $p = 0.001$), peroneal (0.21 vs. 0.31, $p < 0.001$), and posterior tibial nerve (0.16 vs. 0.28, $p < 0.001$) than seronegative CIDP. NF-155 showed significantly higher modified F-ratios in ulnar (1.73 vs. 1.18, $p = 0.031$) and posterior tibial nerves (2.76 vs. 2.00, $p = 0.034$) than seronegative CIDP.

Conclusions:
Our study revealed unique electrophysiological features of NF-155 AN, highlighting prominent proximal and distal slowing. These findings can contribute to further exploration into the pathophysiological mechanisms underlying autoimmune nodopathy.

References:
No

Keywords: Inflammatory neuropathies, Autoimmune nodopathy

Intravenous Immunoglobulin Cessation Trials in Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Poster No:
P 234

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Introduction:
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is the most common autoimmune neuropathy worldwide. Most patients improve with first-line immunotherapy, including intravenous immunoglobulin (IVIg). After 6-12 months, a significant proportion enter spontaneous remission, remaining stable without treatment. We examined the success rate of IVIg cessation trials in patients with stable CIDP and calculated the financial impact.

Methods:
We identified patients on a stable maintenance IVIg regimen (g/kg/month) over 12 months from 2021-2023, excluding patients with >minimally clinically important difference (MCID) in ≥1 CIDP-specific outcome measure, or contiguous sub-MCID change in ≥2 measures, ≥12 months apart. We noted the proportion of eligible patients that underwent cessation trials, and of those, the proportion who remained stable off treatment for ≥6 months.

Results:
Of 125 individuals, 76 were on a stable IVIg regimen, and 66 had outcomes documented ≥12 months apart. 45/66 (68.2%) met criteria for clinical stability. Median (range) age was 58(38-81) years, disease duration 9(1-38) years and annual treatment cost was £107,000/person (£26,000-£714,000). Nine individuals had recent cessation trials indicating active disease and not re-challenged, leaving 36 eligible individuals. 12/36 (33.3%) had cessation trials and 8/12 (66.7%) remained stable off treatment for ≥6 months. Successful IVIg cessation in 8 patients resulted in an annual cost saving of £855,000. Based on previous experience and the current study, between 9-16 of the remaining 24 eligible patients would be expected to be in remission, potentially saving a further £962,000-£1,710,000/year.

Conclusions:
Overtreatment of CIDP has clinical and financial implications. In this real-life study, 8/12 (66.7%) clinically stable CIDP patients were revealed to be in remission, resulting in a cost saving of £800,000/year going forwards, with a potential further saving of £1.7 million/year if all eligible patients underwent cessation trials. Early counselling about the natural history of CIDP and future treatment cessation trials is recommended. A dedicated clinical infrastructure is vital to safely perform cessation trials.

References:
Yes

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Reference 2: Adrichem ME, Eftimov F, van Schaik IN. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyradiculoneuropathy, a time to start and a time to stop. J Peripher Nerv Syst 2016;21:121-127.

Reference 3: Kapoor M, Hunt I, Spillane J, et al. IVIg-exposure and thromboembolic event risk: findings from the UK Biobank. J Neurol Neurosurg Psychiatry 2022;93:876-885.

Reference 4: Kapoor M, Compton L, Rossor A, et al. An approach to assessing immunoglobulin dependence in chronic inflammatory demyelinating inflammatory polyneuropathy. J Peripher Nerv Syst 2021;26:461-468.

Keywords: CIDP, IVIG, Cost, Cessation trial

Paediatric-onset Chronic Inflammatory Demyelinating Polyradiculopathy: Epidemiology, Natural History and Disease Mimics

Poster No:
P 235

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Introduction:
Chronic inflammatory demyelinating polyradiculopathy (CIDP) usually presents in adulthood. Childhood, or paediatric, onset CIDP is rare. Its prevalence is unknown and natural history remains poorly understood. It can be difficult to distinguish from inherited or metabolic neuropathies. We aimed to study the natural history and epidemiology of CIDP, as well as alternative diagnoses in patients with atypical features.

Methods:
We interrogated the national immunoglobulin database for patients treated with immunoglobulin for a diagnosis of CIDP ≤ 18 years between 2006-2023. After removing duplicates, 183 individuals (102 male) were identified. We studied in detail individuals who had been referred to our center, a national neuromuscular center, upon transition to adult services, noting their initial presentation, treatment response, and final diagnosis.

Results:
Thirteen individuals (seven male) were seen at our center. Median age at onset was 13 years (range 1-18) with a follow up interval of 15 years (range 3-39) from disease onset. All but one patient who improved spontaneously had immunotherapy, including IVIg (n=11), steroids (n=8), mycophenolate/azathioprine, cyclophosphamide, plasma exchange, and rituximab (n=2-3 patients). Ten patients retained a diagnosis of CIDP at final review. Of these, seven patients were stable off treatment and three patients had ongoing immunotherapy. Three patients had alternative diagnoses. One patient presenting age 13 with lower limb symptoms with relapsing-remitting cranial neuropathies had a heterozygous NOD2 mutation, suggesting an inherited autoinflammatory disease. Another patient presenting with bilateral facial weakness and lower limb weakness shortly after infancy, with no clear response to treatment was diagnosed with a probable distal hereditary motor neuropathy with conduction block. Another patient presenting age 11 had Contactin/CASPR-1 antibody associated paranodopathy, stabilizing after rituximab.

Conclusions:
Paediatric-onset CIDP patients with atypical features and a lack of response to initial immunomodulatory treatment should have alternative diagnoses explored, including the more recently described paranodopathies, auto-inflammatory diseases, and other inherited and metabolic neuropathies.

References:
No

Grant Support:

This study was supported by a gift from the Christos Lazari Foundation (UCL, Queen Square Centre for Neuromuscular Diseases, c/o Prof Mary Reilly)

Keywords: Paediatric, CIDP, Immunotherapy, Epidemiology, Mimics

Ultrastructural Basis for Separating CIDP from Autoimmune Nodopathy with Antibodies against Neurofascin-155, Contactin-1, and Caspr1

Poster No:
P 236

Authors:
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Introduction:
The guideline established by the European Academy of Neurology/Peripheral Nerve Society for chronic inflammatory demyelinating polyneuropathy (CIDP) defines autoimmune nodopathy as a distinct condition separate from CIDP. This study aimed to differentiate these two diseases on pathological basis.

Methods:
Electron microscopy was used to examine transverse and longitudinal sections of sural nerve biopsy specimens from 16 patients with CIDP and 15 patients with autoantibodies against paranodal junction components. The tested antibodies included anti-neurofascin-155, anti-contactin-1, and anti-Caspr1 in 11, 2, and 2 patients, respectively.

Results:
Within the CIDP group, demyelination resulting from phagocytosis of myelin sheaths by macrophages and onion bulbs were found in 10 and 8 patients, respectively. Cases with numerous onion bulbs indicated the formation process of onion bulbs linked to repeated demyelination by macrophages and subsequent remyelination. In contrast, no instances of demyelination by macrophages were observed in cases with autoantibodies, and only one case with anti-neurofascin-155 antibodies displayed one onion bulb. Longitudinal section assessments revealed detachment of myelin terminal loops from the axolemma at the paranode in all antibody-positive cases, except for one with anti-contactin-1 antibodies. This case deviated from autoimmune nodopathy characteristics due to markedly elevated serum IgG4 (2040 mg/dL) and epineurial IgG4-positive plasma cell infiltration. In the CIDP group, detachment of myelin terminal loops from the axolemma was confined to remyelination areas and exhibited a very mild degree of detachment.

Conclusions:
Patients with anti-neurofascin-155, contactin-1, and Caspr1 antibodies share common pathological features distinct from conventional CIDP cases.

References:
Yes

Reference 1: Koike H, et al. Paranodal dissection in chronic inflammatory demyelinating polyneuropathy with anti-neurofascin-155 and anti-contactin-1 antibodies. J Neurol Neurosurg Psychiatry 2017;88:465-473.

Reference 2: Koike H, et al. Ultrastructural mechanisms of macrophage-induced demyelination in CIDP. Neurology 2018;91:1051-1060.

Keywords: autoimmune nodopathy, CIDP, Caspr1, contactin-1, neurofascin-155

Comparative Efficacy: ANX005's Potential Advantage over Intravenous Immunoglobulin in Guillain-Barré Syndrome

Poster No:
P 237

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Institutions:
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Introduction:
Guillain-Barré syndrome (GBS) is associated with significant morbidity and mortality despite intravenous immunoglobulin (IVIg). ANX005, an inhibitory monoclonal antibody against C1q, may prevent neuronal damage early in GBS disease progression. Early muscle strength recovery is prognostic of long-term functional outcome improvement. The objective of this study was to compare efficacy of ANX005 versus IVIg in GBS patients from historical datasets.

Methods:
Results from a placebo-controlled study in Dhaka, Bangladesh (BGD) involving a single dose of ANX005 (18-75mg/kg; N=18) were compared to observational IVIg-treated BGD patients (N=13) via direct comparison and IVIg-treated patients in the European SID-GBS study (N=44) via indirect comparison. For the direct comparisons, patients were matched for age, baseline GBS-Disability Scale (GBS-DS) and Medical Research Council scale (MRC), and time from onset of weakness.

Results:
By week 1, mean MRC sum score (SD) in ANX005-treated BGD patients improved by 11.8 (±11.4) points compared to 0.2 (±11.2) points in IVIg-treated BGD patients (p=0.0081). In total, 5/17 patients (88%) showed muscle strength improvement with ANX005 compared to 6/13 BDG patients (46%) on IVIg. Early muscle strength improvement at week 1 was associated with improvement in GBS-DS at week 4, with an adjusted common odds ratio of 2.50 (95%CI: 0.625, 10.007; p=0.1949). At week 4, 6% of ANX005-treated patients required ventilation compared to 39% of IVIg-treated patients (p=0.03). Compared with SID-GBS patients, ANX005-treated patients showed an improved MRC sum score versus IVIg (median score: 33 vs 23) and a substantial decrease in percentage of patients requiring ventilation: 32% (14/44) of patients from Europe versus 6% (1/18) of patients receiving ANX005 (p=0.02).

Conclusions:
ANX005 treatment was associated with a significant improvement in muscle strength over IVIg at week 1, which translated into gain in function on the GBS-DS at week 4, as well as reduced need for ventilation. ANX005 presents a promising alternative to IVIg.

References:
No

Grant Support:

Supported by Annexon Biosciences

Keywords: Guillain-Barré Syndrome, Intravenous Immunoglobulin, Classical comeplement pathway

Coexistence of Acute Motor Axonal Neuropathy and Acute Inflammatory Demyelinating Polyneuropathy in Guillain-Barré Syndrome

Poster No:
P 238

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Introduction:
Complement-fixing autoantibodies target gangliosides in axons and/or myelin of peripheral nerves, leading to clinical manifestations of Guillain-Barré syndrome (GBS). Disease severity and recovery vary by patient and geography, which is often attributed to differing neuro subtypes. However, the binary classification into acute motor axonal neuropathy (AMAN) and acute inflammatory demyelinating polyneuropathy (AIDP) does not consider that the two subtypes likely coexist. Molecular profiling can be used to more accurately describe the underlying disease process and identify prognostic markers. The objective of this study was to investigate the metabolic profile of AMAN and AIDP in GBS patients.

Methods:
Serum and CSF samples were collected at baseline and week 1 (Day 5–8) from GBS patients in Bangladesh with either AMAN (n=15) or AIDP (n=10) and were profiled using metabolomics and proteomics. Serum neurofilament light chain (sNfL), a marker of axonal damage, and sphingomyelin in CSF (CSFSM), a measure of myelin involvement in GBS, were evaluated.

Results:
Baseline sNfL was above the normal range in all patients, with higher median levels in AMAN (434.0 pg/ml) than AIDP (108.5 pg/ml). Higher sNfL was associated with lower muscle strength. Baseline CSFSM levels were elevated, expectedly more so in AIDP than AMAN patients. CSFSM increased further in patients whose muscle strength declined during the first week. The NfL/sphingomyelin ratio was 5× higher in AMAN vs AIDP (p=0.002), reflecting the extent of axonal vs. myelin damage. Independent of subtype, sNfL was the most prognostic biomarker, followed by CSFSM.

Conclusions:
GBS patients, regardless of neurotype, have elevated biomarkers indicative of axonal damage and demyelination, suggesting that the two pathological processes coexist to varying degrees in patients. NfL is the most prognostic biomarker, suggesting the extent of axonal damage is important to patient function. This study emphasizes the need to move beyond traditional binary neurotype classifications to explain GBS disease heterogeneity.

References:
No

Grant Support:

Supported by Annexon Biosciences

Keywords: Guillain-Barré Syndrome, AMAN, AIDP

Feasibility And Reliability Of A Monitoring App For Chronic Inflammatory Neuropathies

Poster No:
P 239

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Introduction:
Multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyneuropathy (CIDP) are immune-mediated neuropathies characterized by a diverse presentation including muscle weakness and/or sensory deficits. Treatment effect is variable, requiring intensive monitoring to optimize disease management. Tele-neuromonitoring enables to closely track clinical status and the potential to advance treatment decisions.

Methods:
We developed a monitoring app for remote assessment of grip-strength, modified timed-up-& go (TUG) -test and patient reported outcomes. Monitoring frequency, based on disease stability and patient preference, was either weekly or monthly. We evaluated adherence, user-experience, and reliability. The latter was assessed by estimating intra-class correlation coefficients (ICC) and standard errors of the mean (SEM) of the first 8 repeated measurements. Finally, we analyzed longitudinal change in outcome modalities using linear mixed-effects-models.

Results:
In total, 38 patients participated with mean follow-up duration of 11 months (IQR 4.6-19.5 months). Patients graded the app on a 0-10 scale, with a mean user-experience score of 8.35 (minimum 7/10, maximum 10/10). Overall adherence was 93% (95% CI 91.9%- 94.1%). For grip strength 1358/1468 planned remote measurements were reported, and 1343/1430 for modified-TUG. ICC of grip strength and modified-TUG was 0.96 (95% CI respectively: 0.93-0.98 and 0.92-0.99). Average SEM was 8.46% (95% CI: 6.58-10.28) for grip strength and 8.18% (95% CI: 6.12-10.41) for modified-TUG. Furthermore, we found an increase of grip strength over time of 3.1 pounds over 6 months (95% CI 0.61-5.83 p = 0.016).

Conclusions:
Our study shows that tele-neuromonitoring of CIDP and MMN is feasible and reliable. Additional validation with supervised measurements, and standardized clinical outcome measures, such as INCAT and I-RODS, is necessary to determine the exact monitoring potential, as well as further analysis on clinical decision making with remote monitoring. We anticipate that tele-neuromonitoring could serve as a valuable complement to routine clinical follow-up, enabling clinicians to make better informed treatment decisions.

References:
No

Keywords: CIDP, MMN, Monitoring, App, Reliability

Identification of Chronic Inflammatory Demyelinating Polyradiculoneuropathy: Planned Analysis in a Phase 2b Trial of Batoclimab

Poster No:
P 240

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Introduction:
Published reports concerning the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in clinical practice suggest a high rate of overdiagnosis, with one study reporting an overdiagnosis rate of 47%. Clinical trials in CIDP utilize consensus guidelines and expert adjudication committees to ensure appropriate enrollment; however, diagnostic discordance, even among experts, still exists, potentially due to heterogeneity of clinical presentation and complexity of guidelines. The objective of this report is to describe the design of a phase 2b study evaluating an FcRn inhibitor, batoclimab, in patients with CIDP, including a planned retrospective analysis to assess whether a computer-driven algorithm may improve upon expert, guideline-driven adjudication in identifying patients with CIDP.

Methods:
The FcRn inhibitor, batoclimab, is being investigated in a Phase 2b, randomized, placebo-controlled clinical trial in adult patients with active CIDP. CIDP diagnosis and eligibility decisions will be confirmed by a central adjudication committee. Data will also be uploaded into a computerized diagnostic platform, developed by InCircle Review©, that analyzes clinical history, exam features, laboratory values, and electrodiagnostic values against set criteria. The application has been developed to reduce subjectivity, thereby increasing consistency in the diagnosis of study participants. Following trial completion, statistical analyses will be conducted to correlate between the two approaches.

Results:
Details of the Phase 2b trial design and planned analysis will be presented.

Conclusions:
This retrospective analysis could help to establish a standardized, automated approach to patient enrollment in CIDP trials, potentially reducing discordance among adjudicators who currently use guideline-centric methods.

References:
No

Keywords: chronic inflammatory demyelinating polyradiculoneuropathy, diagnosis, batoclimab, clinical trial, FcRn inhibitor

Phase 3 Trial Designs Evaluating Riliprubart, a C1s-Complement Inhibitor, in Chronic Inflammatory Demyelinating Polyneuropathy

Poster No:
P 241

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Introduction:
There is a high unmet need in chronic inflammatory demyelinating polyneuropathy (CIDP). Standard-of-care (SOC) therapies (immunoglobulins/corticosteroids) are burdensome, have variable efficacy, and significant side-effects. Riliprubart, a first-in-class, humanized, IgG4-monoclonal antibody, selectively inhibits activated-C1s within the classical complement pathway, and has convenient low-volume subcutaneous route of administration with a simple autoinjector. Phase 2, open-label trial (NCT04658472) results of riliprubart in CIDP indicated promising clinical benefits with a favorable benefit-risk profile. Here, we present two Phase 3 trial designs which will evaluate riliprubart in two CIDP populations with high unmet needs: patients refractory to SOC therapies and responders to intravenous immunoglobulins (IVIg) with residual disability.

Methods:
Two global, multicenter, randomized, Phase 3 trials are planned: MOBILIZE, a placebo-controlled trial targeting SOC-refractory patients, and VITALIZE, a double-dummy trial targeting IVIg-treated patients with residual disability (i.e., persistent Inflammatory Neuropathy Cause and Treatment [INCAT] score ≥2). Each trial consists of a 24-week double-blinded period (Part-A), then a 24-week open-label period (Part-B). In Part-A, MOBILIZE participants will be randomized (1:1) to receive riliprubart or placebo (N≤140), and VITALIZE participants will be randomized (1:1) to receive riliprubart plus IVIg-placebo or IVIg plus riliprubart-placebo (N≤160). Sample sizes will be re-estimated based on a pre-defined interim analysis during Part-A. Eligible adults with CIDP having INCAT score 2-9 (score 2 exclusively from legs) can be included. CIDP diagnosis will be based on 2021 EAN/PNS guidelines and confirmed by adjudication committee. Primary endpoint is %- participants responding, defined as ≥1 point decrease from baseline in adjusted INCAT score at Week-24 (Part-A). Key secondary endpoints include change from baseline in additional disability/impairment measures (Part-A) and long-term efficacy (Part-B).

Results:
Both trials are expected to begin enrolment in 2024.

Conclusions:
These Phase 3 trials aim to demonstrate efficacy of riliprubart in people with CIDP, including those showing residual disability or refractory disease despite SOC therapies.

References:
No

Grant Support:

Study funded by Sanofi

Keywords: Chronic Inflammatory Demyelinating Polyneuropathy, Riliprubart, Standard-of-care (SOC)-refractory, Intravenous immunoglobulins, Phase 3

Interaction Between Schwann Cells And Myelin-specific T cells In Immune-mediated Neuropathies

Poster No:
P 243

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Introduction:
Immune-mediated neuropathies such as the Guillain-Barré-Syndrome are characterized by infiltration of macrophages and T lymphocytes in nerve biopsies as driver of the clinical damage. An emerging body of evidence indicates that Schwann cells (SCs) may also act as antigen presenting cells and therefore may feature immunocompetence. Here, we aim to examine the interaction between myelin-specific T cells and SCs by using various experimental approaches to investigate the possible immunologically relevant nature of this contact, and to elucidate its potential as therapeutic target.

Methods:
Myelinated co-cultures of murine dorsal root ganglia (DRG) sensory neurons and primary rat SCs were exposed to myelin protein 2 (55-78) peptide specific T cells isolated from immunized Lewis rats after EAN (experimental autoimmune neuritis) induction. Cultures were monitored by live cell bright-field microscopy to identify T cell / SC contact sites. Cultures were analyzed using immunostaining, electron microscopy or calcium imaging. Focused ion beam scanning electron microscopy (FIB/SEM) enabled tracing of SC / T cell-contact in 3D at nanometer-scale resolution.

Results:
Interaction sites between T cells and SCs displayed membrane regions of high electron density indicating recruitment of membrane bound molecules typical for long term immunological contacts. In accordance with that, interaction sites proved accumulation of immunological relevant markers and FIB/SEM 3D models of the spatial size indicates cellular interaction.

Conclusions:
The combination of advanced cell culture techniques and state-of-the-art multimodal imaging approaches offers deep insight into the complex cellular mechanisms underlying myelin destruction seen in immune-mediated neuropathies. The morphological alterations of the T cell, its stable bond to the SC and activated binding site indicate an immunologically relevant interaction. Furthermore, it elucidates the active participation of SCs in the immune-homeostasis during neuritogenic T cell attack in the peripheral nerve. Deciphering the distinct nature of this interaction requires further investigation.

References:
No

Keywords: inflammatory neuropathies, Schwann cell, T cell, electron microscopy, Guillain-Barré-syndrome

OPTIC Trial: Work-related Participation Following Intravenous Methylprednisolone And/Or Immunoglobulin Treatment in Chronic Inflammatory Demyelinating

Poster No:
P 244

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Introduction:
Although participation may be one of the most important predictors for quality of life (QoL) in individuals chronic inflammatory demyelinating polyneuropathy (CIDP), participation in these individuals has not been systematically studied. Therefore, the aim of this analysis is to assess longitudinal outcomes in work-related participation, also in relation to QoL. We hypothesized that 1) individuals with CIDP suffer from residual work-related participation restrictions, despite multimodal immunosuppressant/modulating treatment; and 2) residual work-related participation restrictions are associated with decreased QoL.

Methods:
Secondary outcome analysis of prospectively and longitudinally collected data from a randomized controlled trial on combined intravenous immunoglobulin and corticosteroid induction treatment in individuals with CIDP (OPTIC trial, ISRCTN15893334). Paid and unpaid work-related participation has been assessed by the IMTA Productivity Cost and the iMTA Medical Consumption Questionnaires. QoL has been assessed by the EuroQol questionnaire. All questionnaires have been collected at baseline, after 24, and after 52 weeks.

Results:
Sixty-five study participants have completed the one year follow-up after enrollment so far. Of these, 29 participants (45%) had (un)paid work at baseline, while 18 participants (28%) had (un)paid work at one year follow-up. Of the participants that had (un)paid work at one year follow-up, 10 (56%) worked as many hours as before, while 4 (22%) worked less hours as before due to the disease, and 4 (22%) changed hours due to other reasons. Complete results – including results on demographics/disease characteristics, work related participation, and QoL – will be presented at the conference.

Conclusions:
Our preliminary results suggest that individuals with CIDP may suffer from residual work-related participation restrictions at one-year follow-up, despite multimodal immunosuppressant/modulating treatment.

References:
No

Grant Support:

ZonMW

Sanquin Blood Supply
Spierziekten Nederland

Keywords: chronic inflammatory demyelinating polyneuropathy, participation, quality of life, OPTIC trial

Modulation of motor unit and axonal function in chronic inflammatory demyelinating polyneuropathy (CIDP) induced by immunoglobulin (Ig) therapy

Poster No:
P 245

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Introduction:
High-priced immunoglobulin (Ig) remains first-line treatment for CIDP, yet treatment duration and dosage of Ig vary widely, highlighting the heterogeneous nature of the disease process and variable treatment response. The dynamic background demyelination, remyelination and regeneration processes in CIDP cannot be assessed with conventional nerve conduction studies (NCS) at a single time point. Currently functional scores quantify disease severity but remain imperfect approximations of axonal function and their efficacy in guiding therapeutic decisions in complex CIDP remains limited. The aim was to dissect the action of ongoing Ig-therapy on axonal function in individual CIDP. It is crucial to develop ubiquitous neurophysiological biomarkers for routine clinical use to quantify the ongoing modulation.

Methods:
The degree of motor unit (MU) block or loss is not well reflected in the peak of compound muscle action potentials (CMAP), as CMAP may only decrease when >50% MU are lost. A recent technique MScanFit Motor Unit Number Estimation (MUNE) that has been applied and demonstrated the pattern of axonal loss in multifocal motor neuropathy and amyotrophic lateral sclerosis. MScanFitMUNE was assessed in Abductor Pollicis Brevis (APB) and Tibialis Anterior (TA) muscles innervated by the median and peroneal nerves in CIDP to explore changes in MU properties pre/post Ig immunotherapy.

Results:
Preliminary data of 15 paired (11APB, 4TA) established a significant ($p<0.05$) increase in MScPeak(mV)(0.38±0.17), MSFNUnits(17.93±4.22), MSFNLarge(6.66±2.08) post infusion (7-14 days). Similarly, a significant decrease in MSFMeanUnitAmp, MSFHalfAmpAmp(%), MSFLargestAmp(%) parameters. These findings indicate different percentage block of MU, accompanied by shifts for improvements in axonal thresholds during immediate immunoglobulin therapy period.

Conclusions:
Data from the present series demonstrate significant changes in MU properties immediately pre/post immunoglobulin therapy. These findings provide insight into quantifying and predicting treatment response, and may serve as a guide to monitor disease activity, thereby enabling clinicians to optimize individual treatment regimes, in addition to utility as a clinical trial outcome measures.

References:
Yes

Reference 1: Lin et al., 2011

Reference 2: Bostock et al., 2016

Reference 3: Garg et al., 2017

Reference 4: Jacobsen et al., 2017

Keywords: CIDP, Ig, MScanFit MUNE

Anti-CASPR1 antibodies are associated with HLA-DRB1*03:01 alleles

Poster No:
P 246

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Introduction:
Autoimmune nodopathies (AN) are peripheral neuropathies associated with antibodies targeting the node of Ranvier such as neurofascin 155 (NF155), contactin 1 (CNTN1), contactin-associated protein 1 (Caspr1), and neurofascin 140/186 (NF140/186). Previous studies confirmed a strong association between anti-NF155 AN and the allele DRB1*15 from the human leukocyte antigen (HLA) class II and a mild association between anti-CNTN1 AN and the HLADRB1*11 allele (present in 47% of cases). This study describes the HLA class II allele frequencies in anti-CASPR1+ patients, to assess whether there is any genetic susceptibility factor that could drive the development of the disease.

Methods:
11 anti-CASPR1 positive, 3 double anti-CASPR1 and anti-CNTN1 positive AN patients, and 50 seronegative chronic inflammatory demyelinating polyneuropathy (CIDP) patients were included in the study. HLA-DRB1 and DQB1 genotypes were determined at the four-digit allele levels, and the percentage of individuals carrying each allele was compared with the proportion of the corresponding allele in the general population, obtained from the Allele frequencies database.

Results:
DRB1*03:01 alleles were present in 6 anti-CASPR1+ patients (54,5%), 3 double anti-CASPR1 and anti-CNTN1+ patients (100%) and 11 CIDP patients (22%). In all 3 double anti-CASPR1/CNTN1-positive patients the anti-CNTN1 antibodies disappeared in the chronic phase, remaining the anti-CASPR1 only. As such, we included these patients in the anti-CASPR1 AN group. Overall, DRB1*03:01 alleles appeared in significantly higher proportions in anti-CASPR1+ patients than in CIDP patients (64.3 vs 22%; OR=6.38, CI=1.77 to 22.99, p=0.0068). When comparing the presence of DRB1*03:01 alleles in anti-CASPR1+ patients with the general population, the differences were also statistically significant (64.3 vs 24.2%; OR=5.64, CI=1.876 to 16.96, p=0.0018).

Conclusions:
HLA-DRB1*03:01 alleles associate with the presence of anti-CASPR1 antibodies in AN patients. Further studies should address the functional relevance of this association.

References:
Yes

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Reference 3: Poster n.53: CIDP with antibodies to CNTN1 is associated with HLA-DRB11 haplotype. Journal of Peripheral Nervous System 2019

Grant Support:

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Keywords: HLA, CASPR1, CNTN1, Autoimmune nodopathy

Observational Data As External Control Group To Compare New Treatments For Guillain-Barré Syndrome: A Proof-of-principle

Poster No:
P 247

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Introduction:
Novel immunotherapies and improved trial designs for Guillain-Barré Syndrome (GBS) are urgently needed, as a substantial portion of patients have poor clinical outcome despite current treatment with intravenous immunoglobulins (IVIg) or plasma exchange. This study aimed to assess the potential to construct an external control arm from the observational International GBS Outcome Study (IGOS) that can be used to compare effectiveness of new treatments, tested as proof-of-principle in the Second IVIg Dose (SID)-GBS trial.

Methods:
Patients treated with SID (intervention) were compared with IGOS patients (controls), selected based on the SID-GBS eligibility criteria. Included were European patients with a poor prognosis (modified Erasmus GBS Outcome Score 6-12 at week 1), treated with one course of IVIg 2g/kg in 2-5 days <2 weeks from onset of weakness. A propensity score was calculated based upon age, preceding diarrhea, time between onset of weakness and IVIg initiation, Medical Research Council (MRC) sum-score and GBS disability score (GBS-DS) at week 1. Each SID patient was matched with up to three controls using nearest neighbor matching (caliper <0.2 on the logit of the propensity score), aiming for an adequate balance in all baseline covariates (standardized mean differences <0.1). The primary outcome is the GBS-DS at week 4.

Results:
After applying eligibility criteria, 172/1843 (9%) IGOS patients were available for matching. Before matching, serious imbalances existed for baseline covariates. 46/49 SID patients could be matched to 118 IGOS controls. After matching, adequate balance was achieved for all covariates, including, for example, mean MRC sum-scores of 24 (SID) and 23 (IGOS). The matching procedure will be further optimized and detailed results, including on the comparative analysis for outcome, will be presented.

Conclusions:
This study presents a design to emulate a randomized controlled trial by selecting controls from real-world data, offering promising potential for comparative studies of novel treatments in GBS.

References:
No

Keywords: Guillain-Barré Syndrome, Treatment, Comparative effectiveness research

Real-world Safety Assessment of Treatment of Chronic Inflammatory Demyelinating Polyneuropathy with Subcutaneous IgPro20

Poster No:
P 248

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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare neurological disorder of the peripheral nervous system. This retrospective real-world study evaluated safety outcomes in patients with CIDP treated with subcutaneous IgPro20 (Immune Globulin [Human], 20% Liquid).

Methods:
Adults diagnosed with CIDP that initiated IgPro20 from 2015-2021 (date of initiation termed 'index') were identified by linked medical and pharmacy claims, hospital charge data, and electronic medical records. Eligible patients had a second CIDP diagnosis ≥90 days after initial diagnosis. Thirty safety outcomes, considered relevant from an immunoglobulin and/or infusion process perspective, were evaluated over a 6-month pre-index and available post-index up to 6 months (until first discontinuation, switch, or end of follow-up). Patients were stratified into two cohorts based on prior use of intravenous immunoglobulin (IVIg). Within a cohort, event rate per person-month for each safety outcome was compared between the pre- and post-index using univariate Poisson generalized estimating equation models.

Results:
The final sample comprised 203 patients initiating IgPro20 (mean [SD] age 56.8 [16.4]; 57.6% female). The majority (n=121; 59.6%) had prior IVIg use, and, among those patients, the event rate was statistically similar between the pre- and post-index periods for 26 out of 30 safety outcomes ($p \geq 0.05$). A significant decrease in the event rate was observed for asthenia and hypertension ($p<0.05$). Among patients without prior IVIg use (n=82), the event rate was statistically similar between pre- and post-index for 28 out of 30 safety outcomes. For both cohorts, the event rate increased from pre- to post-index for abdominal/pelvic/neuropathic/back pain and a composite pain outcome (all $p<0.0001$), consistent with the known safety profile referenced in the current IgPro20 product label.

Conclusions:
IgPro20 treatment in patients with CIDP is overwhelmingly associated with stable safety outcomes for both patients switching from IVIg and for those new to immunoglobulin therapy.

References:
No

Grant Support:

CSL Behring

Keywords: Chronic Inflammatory Demyelinating Polyneuropathy, Immunoglobulin, Intravenous immunoglobulin, Subcutaneous immunoglobulin, Safety

Serum proteome in Guillain-Barré syndrome using an aptamer-based proteomics platform

Poster No:
P 249

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Introduction:
Large-scale plasma proteomic technologies are potentially useful to identify clinically-relevant biomarkers and to discover plasmatic molecular signatures associated with disease pathogenesis. Large-scale plasma proteomic data are lacking in Guillain-Barré syndrome (GBS) patients. We aimed to analyze differences in serum proteome at baseline and at follow-up in order to identify disease-associated pathways and individual biomarkers in GBS patients.

Methods:
Twenty GBS patients collected at different Spanish centers and in which clinical data and serum samples at baseline and after one year follow-up were available were selected and compared with 15 healthy controls (HC). We used a multiplex aptamer proteomics platform (Somalogic) for sensitive detection of 7000 serum proteins. Aptamers are single stranded DNA molecules that are modified to mimic protein side chains, which allow selective binding to protein targets of interest. The measurement output is in relative fluorescence units (RFU).

Results:
The Somalogic panel has already been analyzed in all samples. We are currently analyzing the differences in the proteomic profiles between acute and remission phases of GBS and between GBS and HC. Candidate proteins will be selected based on observed fold-change (>0.5 or <-0.5) and adjusted p-value <0.05. We are also performing an enrichment analysis to identify differential relevant pathways and biological processes of the acute phase of GBS.

Conclusions:
This is the first large-scale plasma proteomic analysis in patients with GBS. Final results will be presented at the congress.

References:
No

Grant Support:

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Keywords: GBS, proteomics, Somascan

Ultrasound as a Marker of Disease Activity in Patients with Immune Neuropathies

Poster No:
P 250

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Introduction:
Immune neuropathies including chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN) and anti-MAG neuropathy are characterized by demyelination identified on nerve conduction studies (NCS). Peripheral nerve ultrasound has been increasingly used in patients with demyelinating neuropathy, where abnormally increased cross-sectional nerve area (CSA) can be seen. We aim to investigate the relationship between the increased CSA on ultrasound and demyelinating changes on NCS in patients with chronic immune neuropathies.

Methods:
We prospectively included adult patients diagnosed with immune neuropathies based on clinical assessments and NCS. Patients had electrodiagnostic and ultrasound testing of the following segments: median at the wrist/forearm/arm, ulnar at the wrist/ulnar groove/arm, fibular at the fibular head and tibial at the ankle. Findings on ultrasound were compared to historical, age and gender adjusted controls. We analyzed the association between increased ultrasound CSA and NCS markers of axonal damage and demyelination, including compound motor action potential (CMAP) amplitudes, velocities, distal motor latencies and conduction block.

Results:
Preliminary results from 13 patients (6 CIDP, 4 MMN, 2 anti-MAG and 1 paraprotein-associated neuropathy) showed that 12 had at least one segment with increased CSA, and 9 had more than 4 enlarged segments, with 53% enlargement in the median CSA at the wrist, ulnar groove and fibular head segments. There was increased ultrasound CSA in the segments with NCS conduction blocks ($p=0.024$), but no correlation between increased CSA and distal CMAP amplitude ($p=0.46$), conduction velocity ($p=0.29$) or distal motor latency ($p=0.18$).

Conclusions:
Most of our patients with immune neuropathies show multiple nerve segments with increased CSA on ultrasound. In addition, conduction blocks on NCS were associated with increased CSA, which may serve as a marker of disease activity. Final results (n=40) is expected by the time of the PNS conference.

References:
Yes

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Keywords: Immune neuropathy, Nerve ultrasound, Disease marker

INCbase: the Global CIDP Registry – an Update

Poster No:
P 251

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Introduction:
INCbase is a global web-based registry, with the collective aim of gathering large-scale uniform, high quality prospective data on CIDP patients. Objectives include development of a prognostic model to predict treatment response and discovery of novel biomarkers for diagnosis, disease activity and prognosis, and to elucidate unknown pathophysiological aspects of CIDP.

Methods:
Comprehensive standardized baseline data is collected, with follow-up varying from a minimal dataset each 6 months (core module) to more extensive data collection and extra visits (extended module). Supplementary modules capture data on plasma-exchange and subcutaneous immunoglobulins and the home assessment module enables close monitoring of patients starting treatment withdrawal. Optional biobanking facilitates research into novel biomarkers. The flexible modular nature of the database will allow INCbase to evolve with emerging insights and research interests in the future.

Results:
As of January 2024, 219 patients with clinical suspicion of CIDP are enrolled. Baseline demographics will be presented at the conference. A total of 27 centers from eight countries are operational and around 20-30 additional centers are expected to complete local regulatory procedures in the near future, including facilities in Australia, Belgium, Denmark, Germany, Japan, Spain, the UK and the US.

Conclusions:
Collection of large-scale standardized prospective data on CIDP patients is feasible using INCbase. Future perspectives include incorporation of platform trials infrastructure and crosstalk with other CIDP databases. Further enrollment of centers and patients is anticipated. Centers are invited to contact us for participation. Collected data will be used to answer vital unresolved questions in CIDP. INCbase is supported by the GBS/CIDP foundation, CSL Behring, Grifols, Takeda, Kedrion and Terumo BCT.

References:
No

Keywords: INCbase, cidp, registry, update

Validity and responsiveness of balance measurements using posturography in patients with immune mediated neuropathies

Poster No:
P 252

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Introduction:
Despite that balance is commonly affected in immune mediated neuropathies, validated objective measures are lacking. Posturography is a method to assess a patient's ability to control balance. In this study, we investigated validity and responsiveness of posturography in immune mediated neuropathies.

Methods:
Posturography was performed at multiple timepoints using a force plate. Discriminative validity was investigated by assessing the difference in sway path between patients who did or did not report balance symptoms. Construct validity was investigated by cross-sectionally examining correlations of sway path with disability and impairment measures, including the INCAT disability scale (INCAT-DS), the I-RODS, the MRC sum score (MRC-SS), ataxia scores and the modified INCAT sensory score (mISS), and with the EuroQoL thermometer. Responsiveness was assessed by examining the association of changes in sway path with changes in other outcome measures over time.

Results:
We included 42 CIDP and 14 IgM related polyneuropathy patients. Sway path was higher in patients reporting balance symptoms (CIDP 26% higher ($p=0.02$) and IgM related polyneuropathy 24% higher, $p=0.02$). Moderate correlation was observed between sway path and ataxia scores (CIDP: Spearman's $\rho=0.44$, 95% CI: 0.16 to 0.66; IgM-PNP: Spearman's $\rho= 0.66$, 95% CI: 0.15 to 0.97). Only in subgroup analysis, sway path correlated with the MRC-SS (active CIDP) and the mISS (stable CIDP). Sway path was not correlated with disability as measured by the I-RODS or INCAT-DS, nor with quality of life. Sway path change scores were not correlated with changes in other outcome measures.

Conclusions:
Posturography measurements differ between patients who do or do not report balance symptoms and are mainly correlated with ataxia. Posturography measurements are not correlated to disability or quality of life and responsiveness was relatively poor. Based on these results we cannot recommend the use of posturography in clinical practice or trials in immune mediated neuropathies.

References:
No

Keywords: cidp, posturography, clinimetrics, balance, IgM

Treatment response and refractoriness in patients with chronic inflammatory demyelinating polyneuropathy (INCbase)

Poster No:
P 253

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Introduction:
In some patients with chronic inflammatory demyelinating polyneuropathy (CIDP), response to first-line treatment is unsatisfactory or absent. We explored characteristics and clinimetrics of patients requiring change of treatment in a large cohort of CIDP patients.

Methods:
For this pilot analysis, we included prospective ICOS and INCbase data from patients with clinical suspicion of CIDP starting first-line treatment. We assessed the frequency of treatment change due to insufficient or absent response as judged by treating physician. We analyzed changes in grip strength, MRC sum score, I-RODS and INCAT disability scale, and whether commonly used MCID thresholds were reached. For patients on treatment at inclusion in the registries, treatment history and overall response rates to first-line treatment were reviewed retrospectively.

Results:
We included 131 patients, of whom 65 were untreated at baseline and starting first-line therapy. For four (6%) of these patients, initial treatment was changed (switched, increased or a new treatment added) due to insufficient response after two weeks to six months. Of these patients, three had improved by the minimal clinically important difference (MCID) on at least one outcome measure. Diagnosis remained unchanged during follow-up. Out of 66 patients treated at baseline, 53 had been previously treated, and for 20 (38%) unsatisfactory response to at least one first-line treatment was reported at baseline. Out of 20 patients, 8 (40%) were considered stable on current treatment.

Conclusions:
Treatment changes due to physician-determined treatment failure were rare, but for most of these patients, improvement by the MCID on at least one outcome measure was recorded. These preliminary results illustrate the need for uniform definitions of (in)sufficient treatment response and refractoriness for both clinical care as well as clinical trial design. Additional results for the entire INCbase cohort will be presented at the conference.

References:
No

Keywords: INCbase, cidp, treatment response, refractory

Comparison of Plasma exchange and Immunoadsorption in inflammatory neurological disorders

Poster No:
P 254

Authors:
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Introduction:
Immune-mediated neurological diseases, such as Chronic lnflammatory Demyelinating Polyradiculoneuropathy (CIDP), Guillain-Barre syndrome (GBS) and Multiple Sclerosis (MS) are characterized by immune mediated attack on myelin or axonal structures. Therapeutic apheresis is commonly used to remove pathogenic agents like autoantibodies, inflammatory cytokines or complement from the patient's blood to attenuate the autoimmune response. It is still not clear whether different methods of apheresis, namely plasma exchange (PE) and immunoadsorption (IA), do have distinct impact on different component of the immune system, on protective and destructive serum factors as well as on clinical outcome parameters.

Methods:
Patients with immune mediated neurological conditions (CIDP, GBS, MS; n=75) and controls (n=16) were recruited for the prospective non-interventional study. Blood samples were collected before, during and after apheresis to analyze cytokines, neurotrophic factors, hormones, and vitamins. Immune cell subpopulations were quantified using flow cytometry. Clinical parameters and supplementary diagnostics were collected.

Results:
Both therapies had distinct impact on a variety of soluble and cellular pro/anti-inflammatory and destructive/protective factors. First apheresis effectively eliminates immunogenic plasma factors, with PE being more effective than IA. Hemoglobin and fibrinogen also decrease more with PE than with IA. However, IA compared to PE preserves more vitamins and may even increase serum levels of hepatocyte growth factor and IL-10, considered to be neuroprotective and anti-inflammatory. Blood pressure drops occur with both procedures but are more severe with PE.

Conclusions:
PE eliminates plasma proteins but also neuroprotective factors more unselective and pronounced than IA. Patients with IA had slightly fewer side effects and shorter durations of treatment completion. Better understanding the effects of different apheresis methods may help to improve patient's outcome regarding a specialized therapy dependent on their characteristics. Some may benefit from a more specific removal of destructive factors while others may rely on the preservation of protective and regenerative factors in an acute therapy for inflammatory conditions.

References:
No

Keywords: CIDP, GBS, Apheresis, therapy

Evaluating Janus Kinase (JAK) Inhibition for Treatment of Autoimmune Neuropathy

Poster No:
P 255

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Introduction:
Autoimmune neuropathies (ANs) result in loss of peripheral motor and sensory function and occur spontaneously or following infection or immunization. Recently, interleukin-10 (IL-10), interleukin-21 (IL-21), and interferon-γ (IFN-γ) have been identified as key inflammatory cytokines in the development of AN within multiple mouse models [1]. IFN-γ signaling induces expression of CXCL10 and tumor necrosis factor-α (TNF-α) which recruit immune cells to the peripheral nerve and promote the inflammatory response [2,3]. Despite our improved understanding of AN pathogenesis, there remains a paucity of mechanism-based therapies. Since Janus kinase (JAK)-mediated phosphorylation of STAT1/STAT3 is involved in IL-10, IL-21, and IFN-γ signaling, disruption of this pathway using FDA-approved JAK inhibitors is an attractive treatment strategy for AN [4].

Methods:
Sciatic nerve-infiltrating immune cells from healthy and neuropathic mice were analyzed using single cell RNA-sequencing. Western blotting was used to compare total phosphorylated STAT1/STAT3 within the sciatic nerve of healthy and neuropathic mice. Ex vivo, murine splenocytes were stimulated with IL-10, IL-21, or IFN-γ and a JAK inhibitor and analyzed by flow cytometry and RT-qPCR. JAK inhibitor efficacy in vivo was evaluated using a mouse model of AN and medicated food gels.

Results:
Our analysis of nerve-infiltrating immune cells from mice with AN using single cell RNA-sequencing revealed upregulation of Il10, Il21, Ifng, Jak1, Jak2, Stat1, and Stat3 transcripts as well as gene expression signatures associated with JAK-STAT signaling. Further, western blotting of the sciatic nerve from neuropathic mice showed higher levels of phosphorylated STAT1 and STAT3 relative to healthy controls. Ex vivo, JAK inhibitors effectively blocked phosphorylation of STAT1 and STAT3 which significantly reduced expression of downstream CXCL10 and TNF-α. In a mouse model of AN, we found oral administration of a JAK inhibitor completely protected against development of AN.

Conclusions:
JAK inhibition may be a new, orally available approach for treatment of AN.

References:
Yes

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Grant Support:

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Keywords: JAK inhibition, Autoimmune neuropathy, JAK/STAT signaling

Superior oblique palsy as the initial manifestation of anti-contactin-1 IgG4 autoimmune nodopathy: a case report

Poster No:
P 256

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Introduction:
Autoimmune nodopathies (AN) are autoimmune neuropathies mediated by antibodies targeting the node of Ranvier or paranode. Typically, they present with sensory ataxia, distal weakness, and tremor, often subacutely, resembling distal chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Methods:
This report presents a case of anti-contactin-1 IgG associated AN with an initial manifestation of isolated superior oblique palsy, aiming to broaden the known clinical spectrum of the disease.

Results:
A 68-year-old male with diabetes, hypertension, and hyperlipidemia presented with acute binocular vertical diplopia, which later progressed to include distal paresthesia, sensory ataxia, ageusia, and dysarthria. Concurrent nephrotic syndrome was identified. Nerve conduction studies indicative of demyelination led to a diagnosis of acute-onset CIDP. Despite intravenous methylprednisolone followed by oral prednisolone and mycophenolate, some disability persisted. A flow cytometry assay for AN antibodies later identified anti-contactin-1 IgG, with detectable IgG4 subclass, in his archived serum.

Conclusions:
This case, initially presenting as isolated cranial nerve palsy, expands the clinical spectrum of AN. It underscores the importance of early suspicion and diagnosis in patients with relevant clinical contexts, and suggests that prompt initiation of effective therapies, such as rituximab, could significantly improve patient outcomes.

References:
No

Keywords: Autoimmune nodopathy, Contactin-1, Cranial nerve palsy, Clinical diagnosis

High Test Accuracy in Identifying GQ1b IgG-related Syndromes with New ELISA-based Assay

Poster No:
P 257

Authors:
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Institutions:
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Introduction:
Miller Fisher syndrome (MFS) with GQ1b-IgG was originally described to have acute onset ataxia with ophthalmoparesis. A larger phenotypic spectrum is now recognized all immunotherapy responsive. Diverse clinical phenotypes create a wide differential and highly accurate antibody testing is required. We sought to evaluate a newly developed GQ1b-IgG assay.

Methods:
A new ELISA-based method was developed. Patient sera along with assay controls and a single-point calibrator are diluted and incubated in duplicate wells in a 96-well plate coated with GQ1b antigen. The plate is washed, incubated with anti-human-IgG secondary antibody conjugated with HRP. After a colorimetric reaction optical densities (OD) are read. The OD of patient samples are compared against the calibrator generating a cut-off index (COI). Samples ≥1.0 COI are considered positive. Clinical performance was assessed utilizing chart reviewed patient samples verified to have a suspected GQ1b-related syndrome and prior send-out GQ1b-IgG reference laboratory testing. A second cohort of prospectively identified disease controls and mimics were then tested.

Results:
98 patients met inclusion criteria. Classic MFS was diagnosed in 13 and variant MFS in 2, both with BBE-MFS. The remaining had Guillain-Barre syndrome (n=66), sensory ganglionopathy w/wo Sjögren (n=2), CIDP (n=1), IgG4-nodopathy (n=1), paraneoplastic encephalitis (n=1), CANVAS (n=1), other (n=11). The average positive GQ1b-IgG COI was 3.6 (1.2-4.2). Of those with MFS 87% (13/15) were positive. Both BBE-MFS cases were positive. One GBS case was positive (1/66; 1.5%). A second positive case had a relapsing-remitting form of CIDP. Overall clinical sensitivity and specificity for a GQ1b-related disorder was 87% and 98%, respectively. Qualitative agreement between assays was high (96% overall agreement). However, quantitative titer agreement was modest with a spearmen's coefficient of 0.57. Disease controls were negative (n=180).

Conclusions:
This GQ1b-IgG ELISA test is highly accurate in identification of MFS and its variant forms which is important in distinction of clinical mimics.

References:
No

Keywords: Autoimmune Demyelinating Neuropathy, Miller-Fisher Syndrome, GQ1b, ELISA

Clinical Performance and Post-launch Assessment of a Neurofascin155 (NF155)-IgG4 Flow Cytometry-based CBA

Poster No:
P 258

Authors:
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Introduction:
To determine diagnostic performance of different NF155 antibody assays in suspected autoimmune demyelinating neuropathies reporting the clinical performance of a live-flow-cytometry cell-based-assay (CBA) post-launch in a reference laboratory.

Methods:
Assessment of diagnostic performance of five NF155 antibody assays (two live CBA assays [IgG4 or IgG1 subclass], a line-blot assay [pan-IgG], fixed-CBA [pan-IgG], ELISA [IgG4]) was conducted in suspected autoimmune demyelinating neuropathy patients. The live CBA-IgG4 assay was selected for validation and implemented as a clinical service-line test. Post-launch clinical performance was assessed. Compatibility with autoimmune nodopathy (AN), IVIG-responsiveness and subsequent alternative immunotherapies were recorded.

Results:
A total of 397 patients were tested by the five methodologies. 173 cases were consistent with CIDP/AN and 224 cases had an alternative neuropathy. Of the CIDP/AN cases, the rate of positivity was highest for the live CBA-IgG4 assay and fixed CBA-IgG assay (n=23 each), followed by the line blot-IgG (n=22), ELISA-IgG4 (n=20), and the live CBA-IgG1 assay (n=17). Positivity in the non-CIDP/AN neuropathy cases was highest for the ELISA (n=6), followed by fixed-CBA (n=2), line-blot (n=2), live-CBA (IgG1; n=2), and live-CBA (IgG4; n=0). All live-CBA IgG4 positive cases were compatible with AN. A total of 2119 samples were tested as part of clinical service testing (median age 63.1 years old, 60.6% were male). In total, 77 positives (3.8%; median age 37.6, 50.6% were male) were reported. The rate of positivity was highest in the pediatric population (n=8, 15.3%) and lowest in those >70 years old (n=2, 0.3%). Of positive cases with available clinical information (n=35), 97% had a clinical impression consistent with AN. All but one was inadequately managed with IVIG, of which 28 subsequently received rituximab.

Conclusions:
This study demonstrates that a flow cytometry-based live-CBA NF155 IgG4 assay provides a high degree of diagnostic accuracy and predicts AN with suboptimal IVIG response.

References:
No

Keywords: Autoimmune Nodopathy, CIDP, Neuropathy

Identifying, Characterizing And Evaluating Antibodies In Guillain-Barré Syndrome (GBS)

Poster No:
P 259

Authors:
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Introduction:
Guillain-Barré syndrome (GBS) is a disabling immune-mediated neuropathy which affects ~100,000 people every year. In most cases, the precise underlying immunological mechanism is unknown, and therapeutic approaches have not advanced in over 20 years. In a minority of patients, pathogenic ganglioside antibodies (targeting neuronal surface sialylated glycolipids) arise following infection through a process of molecular mimicry. Although other antibodies undoubtedly exist, their antigenic targets and pathogenic potential are currently undefined. Our project aims to detect and characterize novel GBS-associated antibodies.

Methods:
Using myelinating co-cultures of human induced-pluripotent stem cell (hiPSC)-derived sensory neurons and rat Schwann cells, we have screened over 300 GBS sera from 5 different cohorts, including over 200 samples from the International GBS Outcome Study (IGOS), for IgG peripheral nerve reactivity. Using this platform, between 10-20% (including 34/217 from IGOS) are positive. Reactivity can be seen directed against axons, myelin, non-myelinating Schwann cells and nodal/paranodal structures. In live cultures, myelin reactive IgG can be shown to induce demyelination in the presence of a source of complement.

Results:
In an initial round of immunoprecipitation/mass spectrometry-based proteomics, we have identified a glial membrane protein as a leading candidate for the target of Schwann-cell reactive IgG in one patient. Validation of the mass spectrometry results through Western blot and cell-based assays is ongoing. In future work, we will expand our screening platform to include hiPSC-derived motor neurons and Schwann cells. Further rounds of IP/MS will be performed using sera with the strongest and most specific binding patterns. The frequency of any identified reactivities will be tested in wider GBS cohorts and correlated with clinical features.

Conclusions:
Thus, results to date indicate the presence of peripheral nerve reactive antibodies against novel targets in a substantial proportion of GBS cases. Their antigenic targets and pathogenic relevance remain to be determined.

References:
No

Grant Support:

Medical Research Council

Keywords: Guillain-Barré syndrome, proteomics, antibodies

Moving Toward Translation – Acute Intermittent Hypoxia Priming Significantly Improves Early Regeneration Outcomes In Decompressed Nerves

Poster No:
P 260

Authors:
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Introduction:
Nerve compression injuries, ie. severe carpal tunnel syndrome (sCTS), are frequent, often leading to function loss and debilitating pain states, even after decompression surgery. While the clinical gold standard for improving outcomes is direct median nerve electrical stimulation (ES), the approach is invasive. Our recent discovery that a novel non-invasive therapy called acute intermittent hypoxia (AIH) significantly improves regeneration of co-apted rat tibial nerves in a manner akin to ES, suggests that AIH may also be used to prime/enhance the intrinsic capacity of severely compressed nerves to regenerate following decompression.

Methods:
To transition AIH to the clinics, we developed a reproducible, precise nerve compression and decompression preclinical model in adult male Lewis rats to mimic sCTS pathology, using a mechanical force gauge sensor linked to a data acquisition system. This yields consistent severe sciatic compression injuries with 14g of force on each of 4 constriction sites over 3mm. 14d post-injury, nerves were decompressed, and early regeneration assessed one week later, using histopathological analysis of nerve and/or dorsal root ganglia, and behavioural approaches. Daily AIH treatments consisted of 10 cycles of 5mins 11% oxygen alternating with 5mins 21% oxygen.

Results:
Data support that a single priming AIH treatment (pAIH) 7d prior to decompression is most effective at enhancing the numbers of axons and distance of regeneration relative to Normoxia controls (21% Oxygen) with improvements also observed in response to pAIH+7d daily AIH post-compression or 7d daily AIH post-decompression. Additionally, injury-induced hyposensitivity, improved with all 3 AIH treatment protocols with expression of regeneration-associated markers (HIF1∝, GAP43, BDNF) elevated with AIH treatments in either the nerve and/or DRG. Assessment AIH impact on reinnervation and functional/behavioral outcomes is ongoing.

Conclusions:
Collectively, these findings support a therapeutic role for AIH as a non-invasive means to prime and significantly enhance early regeneration outcomes following decompression of severely compressed peripheral nerves.

References:
No

Grant Support:

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Keywords: Acute Intermittent Hypoxia, Nerve compression Injuries, Severe Carpal Tunnel Syndrome (sCTS), Nerve Regeneration

Outcome measures in Sensory Neuronopathy

Poster No:
P 261

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Introduction:
Sensory neuronopathies demonstrate non-length-dependent, axonal pattern of sensory loss on electrophysiology. This contrasts with CIDP, characterized by demyelinating electrophysiology. While numerous measures have been validated and characterized in CIDP, there is a lack of outcomes-driven guidance of immune-mediated sensory neuronopathies. Management of sensory neuronopathies are also confounded by description of sensory symptoms versus neuropathy severity and disability, necessitating use of objective treatment response.

Methods:
We present 3 patients with possible/probable sensory neuronopathy by Camdessanche diagnostic criteria. Treatment responsiveness is measured via functional measures (RODS, timed up-and-go) and examination (neuropathy impairment score (NIS), grip strength, INCAT-SS).

Results:
Two patients demonstrate clear treatment-responsiveness by multiple outcome measures, whereas one patient did not. Patient 1 showed disease progression by NIS and grip strength over the course of 6 months, which improved after 3 months treatment with IVIG and IV methylprednisolone. Signal of improvement was first seen by grip strength, RODS, and neuropathy impairment scores at 3 months, with sustained improvement through 12-month follow up and guided taper of immunotherapy. Patient 2 developed precipitous onset of non-length-dependent painful sensory neuronopathy due to Sjogren's disease, and demonstrated functional (RODS) and examination (NIS, grip strength) improvement within 1 week of treatment with IV methylprednisolone. Additionally, neurofilament light chain levels normalized after the first initial treatment cycle. Patient 3 demonstrated no significant change in subjective reports or objective outcome measures at 3 and 6 month immunotherapy trials with IVIG or IV methylprednisolone.

Conclusions:
We demonstrate 1) utility of objective outcomes in guiding treatment decisions for sensory neuropathy/neuronopathy, 2) the wide spectrum of rate of recovery that can be seen in treatment-responsive disease, and 3) changes in serum neurofilament light chain correspond with concomitant exam and functional changes, and may be useful as a possible serological biomarker in predicting treatment responsiveness in an axonal process.

References:
No

Keywords: Neuronopathies, Functional measure, Immunotherapy, Neurofilament

Decoding CIDP: Serum Insights via Advanced Mass Spectrometry

Poster No:
P 262

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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) poses a significant challenge within the realm of autoimmune disorders affecting the peripheral nervous system. Our study aims to address the intricate pathophysiology of CIDP and the pressing need for reliable serum biomarkers.

Methods:
The project employs advanced mass spectrometry for a comprehensive analysis of the serum proteome associated with CIDP. With a cohort comprising 100 CIDP cases and 100 age- and sex-matched healthy controls including longitudinal clinical follow-ups, the heightened sensitivity and specificity of this approach enables the identification of distinct protein alterations linked to the disease. Focusing solely on serum samples simplifies biomarker discovery and overcomes logistical challenges linked to cerebrospinal fluid analysis.

Results:
Our primary objective is to identify distinct serum biomarkers crucial for CIDP diagnosis. This approach enhances diagnostic precision, providing a less invasive method for biomarker discovery. By unraveling the intricate molecular signatures associated with CIDP, mass spectrometry offers valuable insights into disease-specific alterations. The project extends its impact to enhance disease monitoring strategies. Validated serum biomarkers hold promise as reliable indicators of CIDP progression. These markers, once identified, could transform monitoring approaches, providing clinicians with more effective tools to assess disease evolution. Furthermore, the study aims to guide treatment decisions in CIDP in the future. The identification and validation of specific serum biomarkers offer a pathway to informed therapeutic interventions.

Conclusions:
By understanding the molecular landscape, clinicians gain insights to tailor treatment strategies, ultimately aiming at improved patient outcomes. In summary, based on advanced mass spectrometry methodologies, this research strives to fill critical knowledge gaps in CIDP. By identifying and validating specific serum biomarkers, the study not only advances diagnostic capabilities but also enhances disease monitoring and treatment strategies, providing a comprehensive approach to address the complexities of CIDP cases.

References:
No

Grant Support:

The project receives support from the Bundesverband Deutsche GBS-Vereinigung e.V.

Keywords: Chronic inflammatory demyelinating polyneuropathy (CIDP), serum biomarkers, mass spectrometry, moleculare signatures, treatment guidance

Prediction of Respiratory Failure and Prolonged Mechanical Ventilation in Guillain-Barré Syndrome: A Prospective Cohort Study

Poster No:
P 263

Authors:
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Introduction:
The Erasmus GBS Respiratory Insufficiency Score (EGRIS) is the most commonly used model to predict the risk of respiratory insufficiency requiring mechanical ventilation (MV) in Guillain-Barré syndrome (GBS). The EGRIS has been developed and validated among Western patients, however model performance is unknown for low- and middle-income countries. We aimed to validate and perform a region-specific adjustment of the EGRIS and identify potential predictors of prolonged MV (PMV) among GBS patients from Bangladesh.

Methods:
We enrolled GBS patients from four prospective observational cohort studies conducted in Dhaka, Bangladesh. The accuracy of the EGRIS to predict the requirement of MV in <7 days of study entry was evaluated. PMV was defined as duration of MV >14 days. Model performance was assessed by discrimination (ability of the model to differentiate between patients who needed MV or not) and calibration (accuracy of absolute risk estimates). Potential predictors for PMV were evaluated by Cox regression analysis.

Results:
594 GBS patients aged ≥6-years-old were enrolled, of whom 541 patients were included in the validation analysis. The EGRIS correctly distinguished patients requiring MV or not in <1 week of study entry in 81% cases (AUC=0.81). Regarding calibration, the EGRIS overestimated the probability of MV compared to the observed probability (41% vs. 20%) which was resolved by updating of the model intercept. Inability to flex the hip at day 7 of start of MV was the strongest predictor for PMV with predicted probabilities of 82%.

Conclusions:
This study validated and developed a region-specific version of the EGRIS and identified predictors of PMV using the largest prospective GBS cohort from Bangladesh. These findings can assist clinicians to identify patients at high risk of developing respiratory failure and requiring PMV to ensure appropriate level of care with timely intubation and tracheostomy of the patients in low resource settings.

References:
Yes

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Reference 3: Doets AY, Walgaard C, Lingsma HF, et al. International Validation of the Erasmus Guillain–Barré Syndrome Respiratory Insufficiency Score. Annals of neurology. 2022;91(4):521-31.

Reference 4: Islam Z, Papri N, Ara G, et al. Risk factors for respiratory failure in Guillain-Barré syndrome in Bangladesh: a prospective study. Annals of Clinical and Translational Neurology. 2019;6(2):324-32.

Keywords: Guillain–Barré Syndrome, EGRIS, Prolonged mechanical ventilation, Bangladesh

Anti-HNK-1 IgM and sNfL levels are potential biomarkers for monitoring disease activity in anti-MAG neuropathy

Poster No:
P 264

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Introduction:
Disease activity biomarkers are needed in anti-MAG neuropathy. Pathogenic anti-MAG IgM targets the human natural killer-1(HNK-1) carbohydrate epitope. Anti-MAG ELISA is valuable for diagnosis, but its correlation with clinical status is uncertain, whereas anti-HNK-1 ELISA appears to show a better correlation. sNfL levels are useful for monitoring disease activity in several neurological disorders, including neuropathies, but their utility in anti-MAG neuropathy is unclear.We aimed to investigate the role of (1)anti-HNK-1 detected by a novel cell-based assay(CBA) and (2)sNfL levels in anti-MAG neuropathy monitoring.

Methods:
Anti-HNK-1 antibodies were tested using a live in-house CBA with HEK293 cells co-transfected with B3GAT1 and CHST10 (enzymes required for HNK-1 biosynthesis).Anti-HNK-1 antibodies were tested in sera from patients with anti-MAG(n=31), other autoimmune neuropathies(n=99), and IgM-MGUS without neuropathy(n=34).Anti-MAG ELISA was used as the gold standard for diagnostic accuracy analysis. Serial sNfL levels were tested by Simoa in 25 anti-MAG patients prospectively followed and in healthy controls(HC). sNfL Z-scores were calculated using Basel sNfL Reference App. Correlations between anti-HNK-1, anti-MAG and sNfL levels were analyzed.

Results:
The HNK-1 CBA had a sensitivity of 100% and a specificity of 99% for anti-MAG neuropathy diagnosis, and correlated with MAG ELISA titers($r=0.6$, $p<0.0001$). sNfL were elevated in anti-MAG patients compared with age-matched HC(median 20.9 vs 12.9pg/ml $p=0.0001$; Z-score 1.15 vs 0 $p=0.0003$). sNfL Z-scores correlated with anti-HNK-1 titers($r=0.33$, $p=0.015$), and a trend was observed with anti-MAG($r=0.26$, $p=0.07$). In individual patients treated with rituximab, sNfL Z-scores decreased after treatment, in parallel to anti-HNK-1 antibodies.

Conclusions:
The HNK-1 CBA displays a diagnostic accuracy comparable to the gold-standard for anti-MAG antibodies. sNfL are elevated in anti-MAG neuropathy patients and correlate with anti-HNK-1 titers, suggesting that antibody titers correlate with active axonal damage. Larger studies, including informative clinical scales, are needed to confirm the role of anti-HNK-1 and sNfL in monitoring anti-MAG neuropathy.

References:
No

Grant Support:

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Keywords: MAG, HNK-1, CBA, sNfL, Biomarkers

Differential Activation of MAPK in PBMC of Patients with Chronic Inflammatory Demyelinating Polyneuropathy and Multifocal Motor Neuropathy

Poster No:
P 265

Authors:
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Institutions:
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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) are immune-mediated peripheral nerve disorders with an incompletely elucidated etiology. Dysregulation of acquired immune responses and loss of tolerance to myelin components are regarded as the primary causes of inflammation, which results in severe disability and poor therapeutic efficacy. Intracellular energy sensor AMP-activated protein kinase (AMPK) as well as mitogen-activated protein kinases (MAPK) play a key role in the regulation of immune cell metabolism (including autophagy), cell survival, and inflammation, representing emerging therapeutic targets in various diseases. To the best of our knowledge, the role of these signaling molecules in CIDP and MMN pathogenesis and disease progression has never been studied so far.

Methods:
Activation status of AMPK, autophagy markers and MAPK were analyzed in peripheral blood mononuclear cells (PBMC) of 17 CIDP patients, 8 MMN patients and 21 age/sex-matched control subjects by immunoblot.

Results:
Results showed that the activation of p38 MAPK was significantly increased in PBMC of both CIDP and MMN patients compared to control subjects. In addition, phosphorylated forms of ERK1/2 were significantly reduced, while phosphorylated forms of JNK1/2 were upregulated in MMN patients compared to control subjects. In contrast, the activation status of these MAPK was not changed in CIDP patients. Moreover, the activation status of AMPK and the levels of autophagy markers (LC3-II and p62/sequestosome 1) were similar in all three groups of subjects.

Conclusions:
In conclusion, the activation of p38 in both CIDP and MMN, as well as the activation of ERK1/2 and JNK1/2 in MMN versus CIDP suggests differential roles of MAPK in pathogenesis and/or progression of these diseases. The significance of these findings needs to be explored in further studies.

References:
No

Grant Support:

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Keywords: Chronic Inflammatory Demyelinating Polyneuropathy, Multifocal Motor Neuropathy, PBMC, MAPK

Development Of A Comprehensive Patient-Reported Outcome Measure (PROM) Set For GBS And CIDP

Poster No:
P 266

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Introduction:
Introduction: Guillain-Barré Syndrome (GBS) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) cause significant physical and mental symptoms and functional impairments that impact patients' daily lives. Patient-Reported Outcomes (PROs) are health outcomes reported directly by the patient and includes symptoms, functioning, mental well-being and other aspects of quality of life. The commonly used Patient-Reported Outcome Measure (PROM), Inflammatory Rasch-built Overall Disability Scale (I-RODS) has a narrow focus on activity limitations and social participation and clinimetric shortcomings. This highlights the need for a PROM set that comprehensively assesses the most important aspects of quality of life in these patient populations. The aim of the study is to develop a standardized and comprehensive PROM set tailored specifically for patients with GBS and CIDP.

Methods:
Methods: The study has a prospective quantitative and qualitative design and consists of multiple sub-studies: (1) Survey study involving an (online) questionnaire containing open-ended questions to identify the most relevant PROs to measure; (2) Focus groups to select most suitable PROMs for measuring the identified PROs; (3) Validation study aimed at validating existing PROMIS domains that measures generally relevant PROs. PROMIS is a set of generic high-quality PROMs designed to assess a wide range of PRO domains that are relevant across health conditions; (4) Delphi study to achieve international consensus among patients and stakeholders regarding PROs and PROMs to be included in the final PROM set. Patients are recruited from prior studies and in collaboration with patient support groups.

Results:
Results: Data collection of the survey study will commence shortly. Results of the survey study and focus groups will be presented at the upcoming PNS meeting.

Conclusions:
Conclusion: This survey study provides important insight into aspects of quality of life that are most important for patients with GBS and CIDP and are crucial to incorporate in a PROM set for use in research and practice.

References:
No

Keywords: Guillain-Barré Syndrome (GBS), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Patient-Reported Outcome Measure (PROM), Patient-Reported Outcomes (PROs)

Subcutaneous Immunoglobulin (IgPro20) Dose Adjustments for Chronic Inflammatory Demyelinating Polyneuropathy Maintenance Therapy in Clinical Practice

Poster No:
P 267

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Introduction:
Subcutaneous immunoglobulin (SCIg), approved for maintenance therapy for chronic inflammatory demyelinating polyneuropathy (CIDP), enables consistent immunoglobulin levels and improved quality of life compared with intravenous immunoglobulin (IVIg). Optimal treatment uses the lowest effective dose tailored to patient needs; however, limited data on the clinical practicalities of individualizing SCIg are available. Here we examine CIDP cases reflecting SCIg dosing in clinical practice.

Methods:
This is a retrospective, non-interventional, anonymized study of 20 patients with CIDP who were initially treated with IVIg then transitioned to maintenance SCIg (IgPro20, CSL Behring). Data (demographics, diagnosis, treatment history, dosing information) were obtained from patient medical records from eight US centers.

Results:
The approved dose for SCIg in CIDP is 0.2 or 0.4 g/kg/week. Of patients with previous IVIg data available (n=17), most (70.1%, n=12) transitioned on a 1:1 IVIg:SCIg ratio (SCIg range: 0.13–0.50 g/kg/week). The five remaining patients either transitioned to lower (n=3) or higher (n=2) SCIg doses relative to prior IVIg. Nine (45%) patients had their SCIg doses adjusted at least once; the other 11 patients (55%) did not require adjusted doses to maintain clinical stability. Of the nine dose-adjusting patients, five, who were on stable transitioned doses, relapsed and required increased doses to regain stability. The remaining four dose-adjusting patients underwent reductions. Two patients, one of whom reduced their dose due to pregnancy, successfully maintained stable disease at lower doses. The other two patients who had dose reductions, demonstrated signs of relapse and were returned to higher doses for disease stabilization; one returned to their baseline dose, while the other underwent a series of adjustments and was eventually maintained on a dose slightly higher than baseline.

Conclusions:
These cases demonstrate the flexibility of SCIg treatment in patients with CIDP, highlighting the importance of continued patient-physician discussions to individualize SCIg therapy and achieve optimal clinical outcomes.

References:
No

Keywords: Chronic Inflammatory Demyelinating Polyneuropathy, subcutaneous immunoglobulin, individualized treatment, dose adjustments

Validation of Serum Albumin as Early Predictor of Disease Course and Outcome in Guillain-Barré Syndrome

Poster No:
P 268

Authors:
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Introduction:
Biomarkers are pivotal to improve prediction of the highly variable disease course in Guillain-Barré syndrome (GBS). With global affordability and accessibility, serum albumin represents a potentially impactful biomarker, previously correlated with GBS severity. Our study aimed to validate albumin as an early predictor of disease course and clinical outcome.

Methods:
We employed clinical data and biosamples collected in the Second Immunoglobulin Dose (SID-GBS) trial. In this multicenter randomized controlled trial, patients received standard Intravenous Immunoglobulin (IVIg) treatment on day1-5. On day7-9, patients with poor prognosis (modified Erasmus GBS Outcome Score ≥6) were randomized to SID or placebo (1.6g/kg albumin); patients with better prognosis received standard care. Hypoalbuminemia (<3.5g/dL) at baseline and week1, 2, 4 was related to clinical severity and outcome during a 26-week follow-up, using age-adjusted logistic and ordinal regression analyses.

Results:
We included 283 patients. Incidence of hypoalbuminemia was 11% (n=25/222) at baseline and 29% (n=74/252) at week1, and for SID-randomized, placebo(albumin)-randomized and non-randomized patients, respectively, 73% (n=30/41), 23% (n=7/30), 14% (n=19/137) at week2, and 60% (n=25/42), 32% (n=11/34), 3% (n=5/158) at week4. Hypoalbuminemia was associated with increased risk of mechanical ventilation (hypoalbuminemia at baseline: OR 4.7, 95%CI 1.9-11.8). Patients with hypoalbuminemia had higher GBS disability score at week4 (baseline: OR 2.5, 95%CI 1.6-4.1; week1: OR 2.7, 95%CI 2.0-3.7; week2: OR 2.9, 95%CI 2.0-4.2) and risk of not regaining independent walking at week26 (baseline: OR 3.4, 95%CI 1.0-10.1; week1: OR 3.4, 95%CI 1.4-8.5; week2: OR 5.0, 95%CI 2.0-13.7). The added value of serum albumin to existing prognostic models will be presented at the conference.

Conclusions:
Hypoalbuminemia at baseline, week1 and 2 is associated with severe disease course and poor outcome in GBS. Albumin may prove a simple, low-cost biomarker to enhance prognostic models, enabling development of more personalized treatment strategies. Unraveling the exact role of albumin in GBS requires additional research.

References:
No

Keywords: Guillain-Barré syndrome, Albumin, Biomarker, Prognosis, Therapeutic Target

Phase 2 Trial of Riliprubart in CIDP: Effect on Complement Biomarkers and Neurofilament Light Chain

Poster No:
P 269

Authors:
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Introduction:
Riliprubart, a first-in-class, humanized IgG4-monoclonal antibody, selectively inhibits activated-C1s within the classical-complement pathway. Phase-2, open-label trial (NCT04658472) data demonstrated positive clinical effects of riliprubart in chronic inflammatory demyelinating polyneuropathy (CIDP). Here, we present preliminary results of biomarker changes related to target-engagement (complement) and neuroaxonal damage [neurofilament light-chain (NfL)].

Methods:
Global, multicenter, open-label, Phase-2 trial evaluating riliprubart across three subgroups: Standard-of-Care (SOC)-Treated, SOC-Refractory, and SOC-Naïve. Participants undergo 24-week treatment (Part-A), followed by optional treatment-extension (Part-B: 52-weeks, Part-C: until end-of-study). In Part-A, changes from baseline in total hemolytic-complement (CH50) and plasma-NfL levels were measured by in-vitro liposomal immunoassay and Quanterix Simoa®, respectively. Post-hoc analyses for complement-biomarkers (Ba/Bb/C3a/C4a/C5a/sC5b9/C1q, intact-C2/C3/C4/C5, factors-H/I/D/P) were performed using multiplex-ELISA. Samples (Weeks-1 and 24) were mapped to treatment-response and correlated with complement-biomarker analysis.

Results:
As of Oct-2023, available interim data from 49 participants were analyzed, 29 of whom were SOC-Treated, 12 SOC-Refractory, and 8 SOC-Naïve. Reduction in complement activation, informed by CH50, was rapidly achieved and sustained through Week-24 in all participants. Overall, mean±SEM NfL level at baseline was 26.4±2.6 pg/mL. NfL change from baseline was: -6.7±2.6 (N=29), -6.2±2.6 (N=12), and -2.7±4.5 (N=7) in SOC-Treated, SOC-Refractory, and SOC-Naïve subgroups, respectively. All participants had complement-biomarker levels largely within normal range at baseline. Upon treatment, C4a-levels decreased at Week-24, with concurrent increase in C4-levels, indicating effective inhibition of C1s-mediated C4-cleavage. Decreased C5a/C3a/C3-levels were observed, suggesting reduced downstream-pathway activation and inflammation. Associations between biomarkers and clinical outcomes were examined within the SOC-treated subgroup which had the largest available samples. Responders (vs non-responders) showed a greater reduction in C5a (-28.8% vs 21.1%), C3a (-45.0% vs -31.4%), and C3 (-32.9% vs -9.4%), along with an increase in C4 (34.0% vs -5.7%) levels.

Conclusions:
Phase-2 results to date indicate that riliprubart robustly inhibits the classical-complement pathway and may reduce NfL levels associated with neuroaxonal damage in CIDP.

References:
No

Grant Support:

Study funded by Sanofi

Keywords: Biomarkers, Chronic inflammatory demyelinating polyneuropathy, Complement, Neurofilament-light chain, Riliprubart

Characteristics of Chronic Inflammatory Demyelinating Polyneuropathy subtypes: Results from a Multinational, Real-World Survey

Poster No:
P 270

Authors:
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Institutions:
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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare, chronic, neurological condition characterised by progressive muscle weakness and impaired sensory function. Patients are diagnosed with typical CIDP or a variant: distal, multifocal, focal, motor, or sensory CIDP. The aim of this study was to characterise patients with the various clinical presentations of CIDP.

Methods:
Analysis was conducted using data from the Adelphi CIDP Disease Specific Programme™, a cross-sectional survey of neurologists from China, France, Germany, Italy, Japan, Spain, UK, and USA (September 2022 - April 2023), treating at least two CIDP patients per typical month. This real-world data is limited by participating physicians' confirmation of the included patient's CIDP diagnosis.

Results:
164 physicians provided data for 1056 CIDP patients (typical CIDP: 69.2%, distal: 6.8%; multifocal: 8.4%; focal: 2.9%; motor: 7.3%; sensory: 5.3%). Mean (SD) age of typical CIDP patients was 53.2 (12.9) years (subtypes: distal: 58.3 (13.6); multifocal: 56.3(13.3); focal: 53.8(10.4); motor: 53.2(12.6), sensory: 56.1(13.3)). 62.2% of typical patients were male (distal: 51.4%; multifocal: 68.5%; focal: 58.1%; motor: 64.9%; sensory 58.9%). 35.6% of patients with typical CIDP were initially misdiagnosed with another condition (distal: 42.9%; multifocal: 44.0%; focal: 36.8%; motor: 36.5%; sensory 42.9%). Peripheral numbness was the most frequently reported symptom among typical (82.5%), focal (58.1%) and sensory (82.1%) patients, distal muscle weakness among multifocal (82.0%) and motor (62.3%), and peripheral tingling among distal (76.4%). Maintenance therapy was prescribed for 85.2% of typical CIDP patients (distal: 75.0%; multifocal: 83.1%; focal: 67.7%; motor: 74.0%; sensory: 58.9%). Of typical CIDP patients prescribed a maintenance therapy, 53.0% were prescribed intravenous/subcutaneous immunoglobulin (distal: 61.1%; multifocal: 56.8%; focal: 57.1%; motor: 71.9%; sensory: 66.7%).

Conclusions:
Variable patient characteristics and treatment patterns were observed across CIDP variants. Further research is required to ensure the needs of patients with different variants are adequately identified and managed.

References:
No

Grant Support:

Data collection was undertaken by Adelphi Real World as part of an independent survey, entitled the Adelphi Real World CIDP Disease Specific Programme. Johnson & Johnson Innovative Medicine were one of multiple subscribers to the dataset. The study described here was funded by Johnson & Johnson Innovative Medicine .

Keywords: Chronic Inflammatory Demyelinating Polyneuropathy, typical CIDP, CIDP variants, Real-World Survey, Characteristics

Immune checkpoint inhibitors related peripheral nerve disorders: clinical and electrophysiological particularities

Poster No:
P 271

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Introduction:
The immune-checkpoint inhibitors (ICIs) related peripheral nerve disorders are insufficiently known, highly heterogeneous and profoundly debilitating.

Methods:
We reviewed the clinical and electrodiagnostic features of a retrospective multicentre French cohort of patients with a diagnostic of ICI-related neuropathy between 2016 and 2023. Inclusion criteria were (i) neurological onset < 3 months after last ICI perfusion, and (ii) exclusion of alternative diagnosis. We applied the 2021 EFNS criteria for demyelinating neuropathy and we researched the clinical and electrophysiological outcome.

Results:
We included 39 patients: men:women=1:1, median age 61 years (31-72) treated by anti-PD1 monotherapy (76%) or antiCTLA4-antiPD1 combination (24%). Median delay from ICIs initiation to neuropathy symptoms was 58,5 days (4 cycles), lower in the combination group (median 33,5 days vs 81,5 days in monotherapy p=0,02). Half of the patients presented a systemic irAE. CSF was inflammatory in 56% of cases with proteins 1 g/dL (0.3-3.11), pleocytosis median 4 cells/ml (0-23), and median IL-6 4 pg/mL (0-19). Cranial nerve involvement was exceptional (5%), the most frequent electrical phenotype was demyelinating neuropathy fulfilling EFNS 2021 criteria (74%). Nerve conduction studies (NCS) longitudinal follow-up was available in 16 patients (41%), median follow-up was 3 months (2-12). Dissociated clinic-electrical evolution was seen in 31% of patients (stable/worsening NCS and clinical improvement). ICIs treatment was stopped, and steroids were the first line of treatment for all patients. However, 74% of patients received additional intravenous immunoglobulin (IvIg). Supplementary immunomodulation (cyclophosphamide, tocilizumab) was required in 5 cases. Seventy-seven percent of patients improved within a median of 4.5 months, median decrease in mRS of 2 points. Noteworthy, the antiPD1 rechallenge was proposed in 7 patients with a single clinical relapse.

Conclusions:
Our series expands the knowledge on ICIs-related peripheral neuropathy, an acute-subacute entity presenting most commonly with a demyelinating electrical phenotype. Our findings argue for the benefit of adding IvIg to steroids as a first line treatment.

References:

No

Grant Support:

No grant support

Keywords: Immune checkpoint inhibitors, demyelinating neuropathy, Tocilizumab, outcome

Clinical Features And Treatment Outcome Of Pediatric Neurofascin 155 IgG4 Autoimmune Nodopathy

Poster No:
P 272

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Introduction:
To study clinical features and outcomes of children with neurofascin-155 IgG4 autoimmune nodopathy (NF155 AN).

Methods:
Pediatric and adult patients with NF155 AN were identified through the Neuroimmunology laboratory.

Results:
10 NF155 AN pediatric and 25 NF-155 IgG4 adult patients. Clinical information of pediatric patients was available in 7. Median age of onset (years): pediatric patients 9 (4 to 15), and adults 49 (21 to 72). A significantly higher percentage of pediatric patients were diagnosed initially with GBS compared to adults (43% vs 12%, p=0.03). However, most pediatric patients developed functional progression of symptoms over 2 months (5/7, 71%). All pediatric patients had distal predominant weakness (100%), which was present in 64% of adults (p=0.03). The majority of pediatric patients (86%) needed walking aids at disease nadir. Cranial neuropathy, sensory ataxia, and dysautonomia were reported more frequently in adults. Three pediatric patients had tremors and one had cerebellar ataxia. Electrodiagnostic testing demonstrated demyelinating polyradiculoneuropathy in all pediatric patients. CSF revealed elevated protein (5/5, 100%), median 206 mg/dl (107 to 274 mg/dl). Most common immunotherapies in pediatric patients: IVIG (86%), corticosteroid (71%), and rituximab (57%). Most pediatric patients (71%) responded to corticosteroids and rituximab. Median INCAT at nadir and last follow up were 5 (1 to 8) and 1 (0 to 5), respectively. Following immunotherapy, 3 pediatric patients were able to ambulate independently, but one required waking aids (contractures) despite improvement.

Conclusions:
Pediatric cases appear to have more aggressive onset compared to adults, often requiring gait aid at disease nadir. Presenting features such as sensory ataxia, dysautonomia, and cranial neuropathy appears to be less common compared to adults. Most of the patients respond favorably to rituximab.

References:
No

Keywords: NF155, nodopathy, demyelinating neuropathy, pediatric, immunotherapy

Long-Term Outcomes in Seropositive Autoimmune Autonomic Ganglionopathy

Poster No:
P 273

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Institutions:
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Introduction:
Outcomes in autoimmune autonomic ganglionopathy (AAG) are heterogeneous, with monophasic, relapsing and progressive courses described. No controlled trials exist to guide immunotherapy choice, duration or expected response. Additional data is needed to help counsel patients on prognosis and long-term immunosuppression requirements. We aimed to assess the treatments used and clinical course in ganglionic acetylcholine receptor (gAChR) antibody positive AAG.

Methods:
We conducted a single-center retrospective review of seropositive AAG patients. We included adult patients who had: (1) a clinical presentation consistent with autonomic ganglionopathy; (2) detectable abnormalities on standardized autonomic testing completed between 2000 and 2023; (3) positive gAChR antibody titer ≥0.2 nmol/L; and (4) follow up at minimum 3 months from the initial assessment.

Results:
Among the 27 patients included, median Composite Autonomic Scoring Scale (CASS) score at presentation was 8 (1-10) and positively correlated with antibody titers. Twenty-three patients received immunotherapy, and median time from onset to treatment initiation was 13 months (3-144 months). Of those treated, all received at least one course of induction, most commonly intravenous immunoglobulins. Nineteen were treated with maintenance immunotherapy, 10 of which required alternative trials or combinations of multiple agents. Duration of maintenance treatment ranged between 1 and 15 years, and 7 patients had ongoing immunotherapy after their last follow-up. Partial symptomatic improvement was reported in 16 of the treated patients, 7 reported stabilization, and none reached clinical remission. Among untreated patients, 2 slowly progressed and 2 remained stable. Comparing initial and last available autonomic testing (completed a median of 7 years from onset), 11 patients had modestly improved CASS scores, 8 were unchanged and 7 were worse. CASS change did not relate to subjective recovery.

Conclusions:
Immunotherapy led to subjective symptomatic improvement in most seropositive AAG patients; however, none achieved remission, objective improvement on autonomic testing was not pronounced, and most required chronic maintenance treatment.

References:
No

Keywords: autoimmune autonomic ganglionopathy, autonomic nervous system, immunotherapy, inflammatory neuropathy

Blood-Nerve Permeability in Inflammatory Neuropathies

Poster No:
P 274

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Introduction:
Dynamic contrast-enhanced-MRI (DCE-MRI) has shown promise in assessment of peripheral neuropathies.1,2 The plasma extravascular volume transfer constant (Ktrans) is the most frequently used parameter to assess blood-nerve permeability.3-5 The objective of this study was to use blood-nerve permeability parameters – Ktrans and extravascular fluid /nerve blood volume (nBV) to differentiate inflammatory neuropathies from controls.

Methods:
DCE-MRI with gadolinium of the lumbosacral spine was performed in patients with Guillain Barre Syndrome (GBS) and new / relapsed Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) and controls (patients with genetic neuropathies or post lumbar discectomy).

Results:
37 nerve segments from controls (N=9) and 57 nerve segments from patients (N=11) were analyzed. The Ktrans ratio of the mixed spinal nerve to motor root was higher in patients vs. controls ($p<0.05$). Higher Ktrans values tended to have worse clinical and functional scores

Conclusions:
Ktrans at the mixed spinal nerve (MSN) relative to the motor root may help identify patients with inflammatory neuropathies. There is a trend of worse clinical and functional outcome measures in patients with higher blood-nerve permeability.

References:
Yes

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Reference 2: Zochodne DW. Local blood flow in peripheral nerves and their ganglia: Resurrecting key ideas around its measurement and significance. Muscle and Nerve. 2018;57(6):884-95.

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Grant Support:

Australian Brain Foundation Grant

Keywords: Inflammatory Neuropathies, MRI Imaging, CIDP

Presence Of Reflexes May Not Exclude A Diagnosis of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

Poster No:
P 275

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Introduction:
The European Academy of Neurology / Peripheral Nerve Society (EAN/PNS) 2021 revision of the diagnostic criteria for CIDP advocate a stepwise approach to the diagnosis of CIDP which requires clinical criteria including absence or reduced reflexes before the application of electrodiagnostic criteria.1

Methods:
We applied the 2021 EAN/PNS criteria to our cohort of 40 patients receiving intravenous immunoglobulin (IVIG) for CIDP and 51 controls. We compared clinical characteristics and electrodiagnostic findings between those patients who met criteria for CIDP or possible CIDP to those who did not meet criteria.

Results:
The sensitivity of the EAN/PNS 2021 criteria was 42.5% and the specificity was 55% in our cohort of 91 patients. Of the patients being treated for CIDP who did not meet criteria, 11/23 (47.8%) of patients did in fact satisfy electrodiagnostic criteria. 6 patients had preserved reflexes, an additional 3 patients did not have weakness and 2 patients did not have sensory loss, with respect to the clinical phenotype. Other than a shorter disease duration there were no significant differences in patients who meet electrodiagnostic criteria but were not classifiable as definite or possible CIDP (EDX1CIDP0) and patients with CIDP/ Possible CIDP. More electrodiagnostic parameters in the EDX1CIDP0 group were significantly different to controls compared to patients with CIDP or possible CIDP.

Conclusions:
The sensitivity and specificity of the EAN/PNS 2021 criteria for the diagnosis CIDP or possible CIDP were low in our cohort compared to other studies.2,3 Many of the patients who could not be classified as CIDP or possible CIDP due to clinical features especially the presence of reflexes. Clinical phenotypes help classify patients with CIDP but may disadvantage patients who may not meet clinical criteria ascribed to the phenotype. Electromyography is an extension of the physical examination and should be used to define the phenotype rather than being secondary to clinical examination findings.

References:
Yes

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Grant Support:

N/A

Keywords: EAN/PNS 2021 Diagnostic criteria, CIDP

Regulation of Neurofascin secretion by ADAM cleavage

Poster No:
P 276

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Introduction:
Cell adhesion molecules (CAM) play important role in myelin and node formation. Members of the a-disintegrin and metalloproteinase (ADAM) family are also key regulator of myelin formation. ADAMs cleave membrane-anchored proteins such as growth factors, but also CAMs. Recently, ADAMs have been shown to cleave and regulate members of the L1-CAM family (L1 and NrCAM). Neurofascin-155 (Nfasc155), Neurofascin-186 (Nfasc186) and contactin-1 (CNTN1) are also members of the L1-CAM family. These proteins are the targets of autoantibodies in autoimmune nodopathy (AN) and protein degradation seems to be responsible for paranode alterations in Nfasc155-AN. We thus wondered whether Nfasc155 is a target of ADAMs, and whether ADAM cleavage participate to the establishment and maintenance of the nodes of Ranvier.

Methods:
see other sections

Results:
We found that both ADAM10 and ADAM17 are expressed by Schwann cells, but only ADAM10 was found in the paranodal area at adult age. Our developmental study indicated that ADAM10 appears early at the node of the Ranvier. At P2, ADAM10 is first expressed along the myelin segment, then at P8-P10 it transiently accumulates at the nodal and paranodal areas. Then as myelination maturate, ADAMs progressively disappeared from the paranodal area, and became mostly constrained to the node. We next wondered whether Nfasc155 is also a target of ADAM10. Using HEK cells, we have shown that Nfasc155 is readily cleaved and secreted in the media. The inhibition of ADAM10/17 using selective blockers or by deleting the ADAM binding site on Nfasc155, completely abolished Nfasc155 secretion. By contrast, inhibition of others proteases such as, furin, thrombin, or γ-secretase did not affect Nfasc155 secretion. Our data indicate that Nfasc155 might be secreted from glial cell in an ADAM-dependent manner.

Conclusions:
In conclusion, Nfasc155 is another member of L1-CAM family that is cleaved by ADAM10/17. The physiologic and pathologic implications of this cleavage need to further investigated.

References:
No

Grant Support:

AFM telethon is supporting this work

Keywords: neurofascin, autoimmune nodopathy, ADAM10, Schwann cell

Peripheral nervous system involvement in sacoidosis: results from an ambispective study on 550 consecutive patients.

Poster No:
P 277

Authors:
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Introduction:
Sarcoidosis is a systemic inflammatory disease of unknown etiology that involves mainly skin, lungs and lymph nodes. Neurological involvement is reported in 5-15% of cases, occurring usually at onset or within the first two years of disease.

Methods:
We performed a cohort ambispective study on 550 consecutive patients with sarcoidosis followed at three Center for Rare Diseases in Italy from January 2018 to January 2023. Diagnosis of neurosarcoidosis was achieved in 10.36% (n=57) of our sample, including 27 patients (47.37%) with peripheral nervous system (PNS) involvement. Three hundred and thirty-four consecutive patients with the diagnosis of chronic sarcoidosis were enrolled as control group for data comparison.

Results:
In patients with PNS involvement, neurological involvement was often the presenting symptom (59%; 16/27). Cranial neuropathies were the most frequent manifestation (20/27, 74%), specifically facial nerve palsy (12/20), although multiple cranial nerves involvement is not rare (10/20). Twelve patients (44%) also presented with peripheral neuropathy and/or radiculopathy. PNS involvement is usually associated with central nervous system involvement (20/27, 74%). Cerebrospinal fluid analysis was performed in 22 PNS patients, showing hyperproteinorrachia and/or pleocytosis (19/22). No differences in main demographic and clinical data were found between PNS sarcoidosis patients and control group. Focusing on organ involvement, PNS patients showed less frequent intrathoracic involvement (thoracic lymph node involvement, $p= 0.05$; lung, $p= 0.02$) and a tendency towards more frequent extrathoracic lymph node involvement ($p= 0.06$). Twenty-five patients with PNS involvement underwent brain magnetic resonance with gadolinium and 19/27 also 18-fluorodeoxyglucose positron emission tomography (18FDG-PET). PNS patients were treated with steroid therapy at onset symptoms ($p < 0.01$), yet one third (9/27) had at least one neurological relapse during follow-up.

Conclusions:
In conclusion, although rare, neurosarcoidosis deserves consideration in the presence of any obscure inflammatory neurological manifestation and an early diagnosis is crucial for timely therapy and better outcome.

References:
No

Keywords: neurosarcoidosis

Patient Experiences and Perspectives of Chronic Inflammatory Demyelinating Polyneuropathy: Development of a Conceptual Model

Poster No:
P 278

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Introduction:
CIDP is a rare, chronic neurological disorder characterized by progressive muscle weakness and impaired sensory function. Patient experiences are heterogenous so understanding the disease burden from the patient perspective is key to informing patient-focused drug development (PFDD). The purpose of this research was to develop a conceptual model that characterizes the patient experience of living with chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods:
A targeted literature review (TLR) was conducted using Ovid (Embase, MEDLINE, PsycINFO) and handsearching to identify references that described the patient experience of CIDP. Virtual, 45-minute, semi-structured concept elicitation interviews were conducted with patients from the United States who had a confirmed CIDP diagnosis. Interviews were recorded, transcribed verbatim, and analyzed according to qualitative content analysis principles.

Results:
A preliminary CIDP conceptual was developed based on the TLR sources. Data from n=12 interviews (age 33-77 years, n=7 male, n=6 non-Hispanic White) refined the model. The conceptual model comprised symptom experiences, impacts of CIDP, and treatment experiences (including unmet needs). Patients most frequently reported experiencing muscle weakness (n=12), neuropathic sensations (e.g., pins and needles, tingling) (n=12), numbness (n=10), fatigue (n=10), difficulties with balance (n=8), and pain (n=6). Patients reported they were most bothered by muscle weakness, which was also identified as the most important symptom to treat by the majority of the sample. CIDP most commonly negatively impacted mobility (n=12), activities of daily living (n=12), emotional wellbeing (n=11), work (n=9), hobbies/leisure (n=9), and fine motor skills (n=8). Findings indicated patients would benefit from less burdensome treatment options that better address their core CIDP symptoms.

Conclusions:
Muscle weakness is a debilitating symptom of CIDP which impacts patient functioning across numerous aspects of life. The conceptual model represents important aspects of the CIDP disease experience from the patient perspective and can inform PFDD. Further research is planned to refine outcomes of priority for CIDP patients.

References:
No

Keywords: CIDP, Outcomes Research, Patient Experience Data

Electrophysiological diagnosis of Guillan-Barre syndrome: features of new criteria

Poster No:
P 279

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Introduction:
The electrodiagnosis of Guillain-Barré syndrome (GBS) can be typically divided into demyelinating or acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN). Although serial electrophysiology has considered as the most reliable way for accurate diagnosis of GBS subtype, recently two new diagnostic criteria, which use single or second study, have been proposed. We aimed to verify the usefulness of each criteria.

Methods:
We reviewed records of 33 patients who joined Japanese Eculizumab trial for GBS (JET-GBS). The nerve conduction studies at onset, 4, 13 and 26 week from onset were analysed using four criteria (Ho et al., 1995; Hadden et al., 1998; Rajabally et al., 2015; Uncini et al., 2017). Sereal studies were used for diagnosis with Ho's and Hadden's criteria.

Results:
With Ho's criteria, 45% of patients were diagnosed as AIDP, 45% as AMAN and 9% as equivocal form. With Hadden's criteria, 61% of patients were diagnosed as AIDP, 15% as AMAN and 24% as equivocal form. The rate of patients who diagnosed with AIDP was higher than Ho's criteria. About new criteria, 12% of patients were diagnosed as AIDP, 61% as AMAN and 21% as equivocal form with Rajabally's and 64% as AIDP, 30% as AMAN and 6% as equivocal form with Uncini's criteria. Compared with Ho's criteria, patients with AIDP were increase with Hadden's and Uncini's criteria and patients with AMAN were increase with Rajabally's. The patients of equivocal form were decreased Uncini's criteria.

Conclusions:
It is necessary to pay attention to the characteristics of each criteria.

References:
No

Keywords: Guillan-Barre syndrome, Acute motor axonal neuropathy, Acute inflammatory demyelinating polyneuropathy, Nerve conduction study, eculizumab

Alternative rituximab dosing regimen for subacute onset and refractory chronic immune mediated demyelinating polyradiculoneuropathy

Poster No:
P 280

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Introduction:
The optimal rituximab dosing regimen in subacute onset and refractory chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is unknown. We report two cases of subacute onset CIDP where rituximab every 3 months for 1 year was used to wean steroids and maintain stability in CIDP.

Methods:
Case 1: 55-year-old woman presented with 2 weeks with gait instability. Exam showed proximal > distal leg weakness, distal vibratory loss, and areflexia. EMG/NCS showed an acquired demyelinating neuropathy. CSF showed WBC 4, protein 255, glucose 59. She received IVIg but progressed over 8 weeks and developed a facial palsy. Plasma exchange (PLEX) and dexamethasone were started with stabilization in exam. PET scan, VEGF, SPEP/IFE were normal. Neurofascin 155 antibodies were negative. With steroid wean, Jamar grip and Rasch-build Overall Disability Scale (R-ODS) worsened. She received rituximab 1g IV induction dosing (Day 1, Day 15) with repeat dosing of 1g IV every 3 months for 1 year. She stopped dexamethasone completely 1 year after rituximab. Her Jamar is 45lbs and R-ODS is 47/48.

Results:
Case 2: 36-year-old man presented with 1 week of distal foot > hand weakness and numbness. Exam showed distal limb weakness, absent vibration, and areflexia. CSF showed WBC 0, protein 465, glucose 66. He improved with IVIg, later progressed over 3 months despite additional IVIg and developed a facial palsy. EMG/NCS showed an acquired demyelinating neuropathy. SPEP/IFE, VEGF, and neurofascin and contactin antibodies were negative. PLEX and IV methylprednisolone were started. While weaning IV methylprednisolone, he worsened. He received rituximab induction dosing followed by 1g IV every 3 months for 1 year. Eighteen months after initiating rituximab, he stopped steroids. Jamar is 150lbs in his right hand. R-ODS is 37/48.

Conclusions:
These cases illustrate alternative dosing regimen for rituximab in subacute onset CIDP which appeared safe, allowed for successful weaning of steroids, and maintained exam stability for CIDP.

References:
Yes

Reference 1: Hu J, Sun C, Lu J, Zhao C, Lin J. Efficacy of rituximab treatment in chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review and meta-analysis. J Neurol. 2022 Mar;269(3):1250-1263. doi: 10.1007/s00415-021-10646-y. Epub 2021 Jun 12. PMID: 34120208.

Reference 2: Shimizu S, Iijima M, Fukami Y, Tamura N, Nakatochi M, Ando M, Nishi R, Koike H, Kaida K, Koga M, Kanda T, Ogata H, Kira JI, Mori M, Kuwabara S, Katsuno M. Efficacy and Safety of Rituximab in Refractory CIDP With or Without IgG4 Autoantibodies (RECIPE): Protocol for a Double-Blind, Randomized, Placebo-Controlled Clinical Trial. JMIR Res Protoc. 2020 Apr 1;9(4):e17117. doi: 10.2196/17117. PMID: 32234705; PMCID: PMC7160709.

Keywords: CIDP, Rituximab, inflammatory neuropathy

TIMP-1 exhibits a novel myelin membrane isoform and sex-specific interactions in peripheral nerve

Poster No:
P 281

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Introduction:
In peripheral nerve, myelin insulation of large-diameter neurons enables rapid saltatory impulse conduction across long distances. To leverage myelin repair after nerve injury, Schwann cells activate an extensive regulatory molecular machinery. We aimed to assess the role of tissue inhibitor of metalloproteinases (TIMP)-1 as an X chromosome-encoded gene in Schwann cell survival signaling and remyelination.

Methods:
TIMP-1 expression in male and female rat sciatic nerve was comparatively assessed over the course of chronic constriction injury (CCI). The nerve's whole lysates and sucrose fractions were analyzed. TIMP-1-based affinity capture followed by LC-MS/MS proteomics and bioinformatics analyses were employed to identify sex-specific and universal TIMP-1 interactors in uninjured and CCI nerves. Recombinant (r)TIMP-1 protein was administered by intraneural injection to test its effect on myelination and cell survival post-CCI using methylene blue/azure II, FluoroMyelin™ and myelin protein zero (P0) and pAKT immunoblotting.

Results:
A novel myelin membrane (mm)TIMP-1 isoform here emerged in buoyant lipid raft-enriched nerve fractions post-CCI. mmTIMP-1 was observed in both sexes at days 1 and 7 post-CCI. TIMP-1-based affinity capture and LC-MS/MS proteomics identified female-specific networks related to exosomes in CCI but not normal nerves. Interactors involved in extracellular matrix structure organization were observed in normal and CCI nerves of both sexes. Myelination (FluoroMyelin, P0) and pAKT were enhanced in CCI nerves after rTIMP-1 compared to vehicle treatment.

Conclusions:
A novel myelin membrane and the classical TIMP-1 isoforms exist in the damaged nervous system. TIMP-1 may engage in sex-specific exocytosis post-injury. TIMP-1 replacement may enhance remyelination and/or decrease demyelination of the damaged peripheral nerve.

References:
No

Grant Support:

NIH and US Department of VA

Keywords: TIMP-1, glia, Schwann cell, myelin, sex-specific

Vasculitis associated with leprosy: what are the histopathological findings?

Poster No:
P 282

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Introduction:
Peripheral nerve infection by Mycobacterium leprae can cause a variety of neuropathies and lesions, including vasculitis. This study aimed to describe the common histopathological characteristics in cases of vasculitis associated with leprosy.

Methods:
We performed a retrospective analysis of the nerve biopsy database over the last 25 years and an individual review of selected medical records.

Results:
Six cases out of more than 840 nerve biopsies (0.7%) showed pathologically definite vasculitis correlated with leprosy. On microscopic examination, in addition to the presence of inflammatory cells in the vessel wall, disruption of endothelium/fragmentation of internal elastic lamina, or acute thrombosis, was also found. Foci of inflammatory infiltrate outside the vessel wall were observed, simultaneously affecting the epineurium, perineurium, and endoneurium in five biopsies, as epithelioid granuloma without caseous necrosis. In sections stained with Wade, the bacilloscopic index ranged from 2+ to 4+/6+, with granular bacilli. Semithin sections demonstrated significant decreases in the number of large and small nerve fibers. The initial clinical condition of these patients was typical of a type 2 leprosy reaction, with systemic inflammatory findings (fever, joint pain, and elevated laboratory tests of inflammatory activity such as ESR and C-reactive protein), leading to the indication of nerve biopsy. Furthermore, they presented asymmetrical sensory changes (paresthesia, neuropathic pain). We classified the patients into the following clinical forms of leprosy: three relapses, one pure neural type, and one reactive neuritis type.

Conclusions:
Although marked distortion of the wall of capillaries and small vessels due to inflammation in leprosy is common, pathologically definite vasculitis can also be found. We did not find a specific histopathological pattern for leprosy vasculitis, but nerve biopsy was the gold standard for diagnosis in these patients. Infection with the leprosy bacillus is a definitive cause of secondary systemic vasculitis.

References:
Yes

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Keywords: Vasculitis, Leprosy, Sural nerve, Biopsy

Neuritis x Reactional neuritis in leprosy: Histopathological findings

Poster No:
P 283

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Introduction:
Neuritis is a nerve inflammation secondary to injury or infection (which can be viral or bacterial). This study aimed to describe the findings of histopathologically defined neuritis associated with leprosy in the clinical form of reactional neuritis (with nerve thickening and pain on palpation).

Methods:
We performed a retrospective analysis of the database of nerve biopsies between 1998 and 2023 and an individual review of selected medical records.

Results:
Fifty-seven peripheral nerve biopsy exams were selected (6.7% of the total). The patients presented a clinical condition of reactive neuritis (thickened nerve and pain upon manipulation) with neuritis (inflammatory infiltrate in the epineurium, perineurium, or endoneurium, either around fascicles or close to vessels). In the microscopic aspect, the mononuclear inflammatory infiltrate predominated in the endoneurium and was, on average, of a moderate degree. Although leprosy can be described as a granulomatous disease, epithelioid granuloma was present in only 16 cases and vacuolated macrophages in approximately 52% of cases. The following histopathological findings: fibrosis in any nerve area, decreased number of neural fibers in the semithin sections, and subperineural edema were not coincident in all cases. However, perineurium and endoneurium fibrosis were the most common alterations (mild to moderate fibrosis on average). There were signs of pathologically definite vasculitis in six cases. In addition to the histopathological examination, the PCR test was positive in 36 cases.

Conclusions:
The areas of the peripheral nerve most altered in these cases were the perineurium and endoneurium. There were not histopathological changes considered common to all cases. Mononuclear inflammatory infiltrate may be present in all regions of the peripheral nerve, but vasculitis is uncommon. Nerve thickening on physical examination was not always correlated with the degree of fibrosis or edema.

References:
No

Keywords: Neuritis, Sural nerve, Biopsy, Leprosy

Optimizing Value-Based Outcome Measures in Inflammatory Neuropathy: Patient Perspective Regarding Timing, Rationale, and Data Sharing

Poster No:
P 284

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Introduction:
Chronic Inflammatory Neuropathies are a group of disabling autoimmune neuromuscular disorders. Outcome measures can be used to monitor patients and their response to treatment. It is important to involve patients in determining effective methods for collecting and sharing outcome measure data. The purpose of this study was to understand how outcome measures, when integrated within a value-based framework, affect patients' care experiences and to elicit their input on timing and display of data to optimize shared decision-making.

Methods:
25 participants with a diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy or multifocal motor neuropathy completed an online questionnaire after participating in a 1-year prospective study exploring outcome measure use in clinical settings. The outcome measures panel included patient-reported outcome measures (PROMs) such as I-RODS and EQ-5D-5L and functional measures including MRCss and grip strength. Participants used scales and free-text fields to describe their experience with the measures.

Results:
All participants reported the measures were helpful to them and their care providers in making treatment decisions. 78% specified outcome measures allowed them to track their disease state over time. 83% reported reviewing the outcome results over time with their physician made them feel more heard or understood. The majority of participants preferred functional measures to be administered annually and PROMs every 6 months. Graphic representations of outcome data were considered easy to follow with 71% preferring bar graphs for each measure over composite graphs.

Conclusions:
Outcome measures are useful tools in shared decision-making. PROMs improve care experiences and better capture psychosocial aspects of health. For outcome measures to be effective, it is important to administer validated measures in a manner consistent with patient preferences, including when and what tests to administer, as well as how to display data in a way that is meaningful to patients. These results were used to develop our clinic's assessment pathway.

References:
No

Grant Support:

Supported by the Mahon Family Foundation.

Keywords: Chronic Inflammatory Neuropathy, Outcome Measure, Value-based Healthcare, Chronic inflammatory demyelinating polyradiculoneuropathy, Multifocal Motor Neuropathy

Prognostic Biomarkers in Guillain-Barre Syndrome: Lymphocyte-Based Ratio and Albumin Level

Poster No:
P 285

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Introduction:
Guillain-Barre syndrome (GBS) is an immune-mediated polyneuropathy with variable outcome. Biomarkers for mechanical ventilation and prognosis in the early stage are crucial for the management of GBS. Recently, serum albumin level, C-reactive protein (CRP)-albumin ratio (CAR), and lymphocyte-based ratio have been reported as biomarkers for poor prognosis in GBS. We conducted this study to assess the prognostic value of albumin level, CAR, and lymphocyte-based ratio in GBS at a center of South Korea.

Methods:
The electronic data of patients diagnosed with GBS, who visited * hospital from January 2012 to January 2023, were retrospectively analyzed. Baseline blood samples, drawn within 24 hours after admission, were evaluated for baseline albumin level, CRP, neutrophil count, lymphocyte count, and monocyte count. Neutrophil-lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR) were calculated. Serum albumin levels at 2 weeks after treatment with IVIg were collected if available. Respiratory failure was defined if patients required intubation. Patients with GBS disability score at nadir higher than 3 were classified as having severe disease. A poor outcome was designated if the patient could not walk independently more than 3 months later.

Results:
Ninety-three patients were enrolled (mean age 53.3±16.6, men: women = 1.7:1). Thirteen out of 93 (14%) required intubation, 66 (71.0%) patients had severe disease, and 15 (16/1%) patients were designated as having a poor outcome. Lower serum albumin levels at admission and 2 weeks after, along with higher NLR and MLR, were significantly associated with respiratory failure and poor outcomes.

Conclusions:
Both the lymphocyte-based ratio at admission and serum albumin level may represent prognostic factors for respiratory failure and poor outcomes in GBS.

References:
No

Keywords: Guillain barre syndrome, biomarker, prognosis

Observational Study to Assess Individualized Criteria for IVIG Therapy in Patients with Chronic Immune-Mediated Neuropathies

Poster No:
P 286

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Introduction:
EAN/PNS guidelines for CIDP diagnosis and treatment were updated in 2021, whereas EFNS/PNS guidelines for MMN date from 2010. For both disorders intravenous immunoglobulin (IVIg) is considered first-line treatment and individualization of IVIg therapy recommended during therapy. However, there is considerable uncertainty in individualized dosing and infusion frequencies in real-world practice.

Methods:
I-GUIDE study is an ongoing non-interventional, multicenter, longitudinal study designed to determine the patterns of use of 10% IVIg (Gamunex® 10%, Grifols) in real-world clinical practice and to identify factors driving physician's treatment decisions for CIDP and MMN patients. Data is collected at baseline, and at each infusion cycle (as scheduled within routine care, approximately every 4 weeks), for up to 18 months. At baseline, patient demographics, medical and disease history, and treatment are assessed. At each visit, decision making criteria regarding continuation and individualization of Gamunex 10% treatment (dosing, intervals, co-medication) are recorded.

Results:
14 German hospital-based (9; 64%) and office-based (5; 36%) neurologists participated in the study. From April 2021 to October 2022, 85 adult patients were recruited. The gender ratio was 1.6:1 (61% male:39% female) with a mean age of 63 years (range: 28-88). CIDP was diagnosed in 76 patients with 88% being typical CIDP (67 patients) and 12% CIDP variants (9 patients). The study cohort comprised 9 patients with MMN. Following symptom onset, neuropathy diagnosis was made in the first year in 49% (42/85), within 2 years in 79% (67/85), and within ≥3 years in 21% (18/85) of the patients.

Conclusions:
Considerable variability regarding daily management of IVIg treatment for CIDP and MMN and regarding decision making criteria was seen in the preliminary data analysis. To gain further insights on concepts of individualizing IVIg therapy during long-term treatment in real-world practice the observational I-GUIDE study is currently ongoing.

References:
No

Keywords: chronic immune-mediated neuropathies, intravenous immunoglobulin, real-world practice, Non-interventional study, outcome measures

The short-term treatment of Efgartigimod in CIDP：a single center real-world experience in China

Poster No:
P 287

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Introduction:
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a type of autoimmune neuropathy presenting significant treatment challenges due to limitations in standard of care therapies. Efgartigimod, an FcRn antagonist, has shown promise in treating antibody-mediated disorders and is explored in this study for its efficacy and safety in CIDP patients.

Methods:
This single-center study in China evaluated the short-term efficacy and safety of Efgartigimod in five CIDP patients. Dosing was tailored to individual patient needs, with clinical effectiveness assessed using various scales including INCAT, iRODS, MRC sum score, grip strength, NIS, and TUG. Safety was evaluated by monitoring adverse events and measuring plasma IgG concentrations.

Results:
All five patients responded to Efgartigimod treatment, with four (80%) meeting predefined effectiveness criteria. Significant improvements were observed across clinical scales, with varied responses among patients. The reduction rate in total IgG levels averaged 43%. Adverse events were minimal, with one patient experiencing transient diarrhea, and no aggravation of pre-existing conditions was noted.

Conclusions:
Efgartigimod demonstrates promising efficacy and safety in the short-term treatment of CIDP, offering a potential alternative therapy for patients with limited response to standard treatments. This study provides valuable insights into the real-world application of Efgartigimod in CIDP, warranting further research.

References:
No

Keywords: Chronic Inflammatory Demyelinating Polyradiculoneuropathy, Efgartigimod, Treatment, Real-world study

A Statistical Model Facilitates Accurate Chronic Inflammatory Demyelinating Polyradiculoneuropathy Diagnosis Combined with Laboratory Testing

Poster No:
P 288

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Introduction:
CIDP misdiagnosis leads to inappropriate treatment with economic and patient burden. Consensus guidelines assist diagnosis but are underutilized based on complexity. We sought to determine if a probabilistic statistical model calculator could simplify accurate diagnosis.

Methods:
2021-EAN/PNS guidelines were used for CIDP diagnosis with twenty-six clinical and 217 nerve-conduction variables chosen based on these criteria and publications addressing mimics. 110 CIDP and 309 mimics (IgG4-nodopathies, paraneoplastic, POEMS, anti-MAG, diabetic radiculoplexus neuropathies (DRPN), MMN, inherited, eight others) underwent data extraction. Univariate and multivariate regression analysis identified the most informative variables, validated in a CIDP subset cohort.

Results:
10,946 clinical and 94,223 electrophysiological datapoints were extracted. Univariate analysis identified 11/26 clinical variables with significant odds-ratios, including progression over 8-weeks (OR 52.47 $p<0.0001$), proximal upper-lower limb weakness (OR 3.03 $p=0.0005$), reduced-absent tendon reflexes in all limbs (4.62 $p=0.0001$), absent autonomic involvement (OR 5.5 $p=0.02$), and absent muscle atrophy (OR 16.67 $p=0.0002$). Parsimonious multivariate-regression analysis identified these five variables in combination could predict CIDP (92% area-under-curve, 95% CI 87.6-94.4). Univariate analysis of all electrophysiologic variables identified ulnar conduction velocity slowing <35.7m/s (OR 3.98 $p<0.001$) and presence of ulnar motor conduction block (OR 16, $p<0.0001$) most informative for the model (93% area-under-curve, 95% CI 90.8-95.2). EAN/PNS electrodiagnostic criteria did not enhance the model (92% area-under-curve, 95% CI 88.6-94.8). At 98% probability cut-off, sensitivity is 96% and specificity 74%; all but four CIDP patients among original and validation cohorts were identified, along with 13/17 IgG4-nodopathies, 18/24 paraneoplastic, 10/39 MMN, 9/24 POEMS, 7/21 anti-MAG, 5/36 DRPN, 1/43 inherited, 17/105 others. Lab testing for NF155/Contactin1-IgG4, paraneoplastic, VEGF-gammopathy, MAG-gammopathy and inherited gene panel increase specificity to 90%, eliminating 60% (48/80) of false-positives.

Conclusions:
A CIDP calculator with limited clinical-nerve-conduction variables facilitates accurate CIDP diagnosis. Specificity is enhanced by revisiting the clinical phenotype and considering individualized serum laboratory testing.

References:
No

Grant Support:

N/A

Keywords: Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Inflammatory Neuropathy, EAN/PNS criteria

Blockade Of CD1d-restricted Lipid Antigen Presentation Ameliorates Experimental Autoimmune Neuritis

Poster No:
P 289

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Introduction:
Inflammatory neuropathies such as the Guillain-Barré-Syndrome (GBS) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) present as clinically heterogeneous disease entity affecting the peripheral nerves and nerve roots. The contribution of MHC-mediated peptide antigen presentation driving cytotoxic and helper T cell activation and expansion is a well-established aspect of the underlying immunopathology. Although presumably relevant, the role of CD1d mediated lipid antigen presentation, modulating the effector functions of invariant Natural Killer T cells (NKT), has not been elucidated so far. Here, we propose that lipid constituents of cellular and myelin debris released during inflammatory nerve damage may serve as CD1d ligands, further propagating the inflammatory response through NKT cell activation and contribute to clinical disability.

Methods:
We induced experimental autoimmune neuritis (EAN) in female Lewis rats by inoculation of myelin protein 2 peptide (P255–78). Animals received an anti-CD1d blocking antibody via intraperitoneal injection twice a week, starting in parallel to immunization with P2 peptide. The analyses were based on clinical testing and electroneurography, micro bead arrays, immunohistochemistry, and morphometric assessment of myelination.

Results:
Under treatment with the anti-CD1d antibody, animals displayed a significant improvement in clinical scores beginning at the peak of disease from day 16 onwards. This clinical improvement was paralleled by a significant elevation of nerve conduction velocity and increased myelin thickness at the end of the experiment on day 28. Immunohistochemistry of sciatic nerves obtained on day 21 pointed at a significant reduction in T-lymphocytes, NK cells and NKT cells and was suitable to demonstrate effective blockade of CD1d. Cytokine secretion analysis from splenocytes by microbead array indicated a marked reduction in several pro-inflammatory cytokines including IFN-gamma, IL-2 and IL-17.

Conclusions:
Collectively, these findings highlight CD1d mediated lipid antigen presentation as relevant pathway aggravating peripheral nerve inflammation in EAN. Thus, CD1d blockade is a potential novel therapeutic target in inflammatory neuropathies.

References:
No

Keywords: experimental autoimmune neuritis, inflammatory neuropathy, Natural Killer T cell, CD1d, lipid antigen

Early electrophysiological abnormalities in the setting of Guillain Barré syndrome

Poster No:
P 290

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Introduction:
The diagnosis of Guillain Barré syndrome (GBS), the most common form of acute polyradiculopathies, is mainly clinical. Nerve conduction study (NCS) play a key role in GBS diagnosis and its classification. Nevertheless, at early stages, patients may not meet neurophysiological criteria and serial NCS are necessary for more accurate diagnosis of subtypes. The aim of our work is to identify early NCS in GBS and follow their dynamic over time.

Methods:
We retrospectively reviewed patients admitted to our clinical neurophysiology department with suspected GBS over the period from January 2014 to December 2021. We have selected patients fulfilling clinical criteria for GBS with NCS performed within 14 days of clinical onset. They were subdivised to 3 subgoups: group A ≤ 4 days, group B: 5-9 days et groupe C: 10-14 days. We have analyzed their clinical, electrophysiological and ancillary testing.

Results:
50 patients were included; 9 in group A, 21 in group B and 20 in group C. Early NCS confirmed the diagnosis of GBS in 77,8% of cases before day 4 from onset. The most frequent abnormalities encountered in group A were prolonged distal motor latency, reduced dCMAP amplitude and conduction block. Reduced motor nerve conduction velocity (MNCV) and abnormal F responses are more frequent after 5 days from onset. Sural-sparing pattern and Abnormal sensory nerve action potential are involved after day 10 from onset.

Conclusions:
Along with other studies, we confirmed that, in early electrodiagnostic evaluation of GBS, MNCV is often in normal range or slightly reduced. Hence, the evaluation of other parameters such as prolonged DML and conduction block (the most frequently found demyelinating parameters in our study) may provide crucial information regarding demyelination and aid early diagnosis and treatment. Alternatively, because of severe distal demyelinating process, reduced dCMAP amplitude can mimic axonal neuropathy and serial NCS are required to identify the electrophysiologic subtype.

References:
No

Keywords: GBS, electrodiagnostic findings, early stage

Clinical Features of Anti-Contactin-Associated Protein 1 Autoimmune Nodopathy in Japan

Poster No:
P 291

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Introduction:
We aimed to elucidate the clinical features of anti-contactin-associated protein 1 (Caspr1) autoimmune nodopathy (AN) in Japan.

Methods:
We enrolled patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) seronegative for autoantibodies against neurofascin-155 and contactin-1, fulfilling the definite EFNS/PNS electrodiagnostic criteria as nationwide consecutive samples referred to our department for antibody testing since 2015, with cerebrospinal fluid (CSF) protein levels ≥ 100 mg/dL (Cohort 1) and consecutive patients in our department since 2000 (Cohort 2). Anti-Caspr1 antibodies were detected by enzyme-linked immunosorbent assay with recombinant human Caspr1 protein and validated by immunohistochemistry and western blotting. We compared the clinical features of patients with anti-Caspr1 antibodies (anti-Caspr1 AN group), including one additional case previously reported in Japan, with those of seronegative CIDP patients in Cohort 2.

Results:
Fifteen cases with anti-Caspr1 antibodies (male: female = 10: 5) were identified (Cohort 1: 13/325, Cohort 2: 1/51) and the main subclass of the antibody was IgG4 in 13 (87%). Anti-Caspr1 AN group demonstrated older onset (median: 64 vs 44 years), and higher proportions of gait disturbance (100% vs 54%), tremor (60% vs 16%), sensory ataxia (80% vs 22%), and elevated CSF protein levels (242 vs 83 mg/dL) than seronegative CIDP with statistical significance. Nerve conduction studies showed more prolonged F-wave and distal motor latencies and reduced conduction velocities in all of the nerves tested in anti-Caspr1 AN than in seronegative CIDP. Electron microscopic evaluation of the sural nerve biopsy demonstrated axo-glial detachment. Poor responders to intravenous immunoglobulin and corticosteroids were 7/14 (50%) and 3/12 (25%), respectively. In six patients with serum availability, the antibody titers decreased with clinical improvement.

Conclusions:
Elderly onset, gait disturbance with sensory ataxia, severe conduction delay, and high CSF protein levels would be the keys for early diagnosis of anti-Caspr1 AN.

References:
Yes

Reference 1: Koga M, Maeda T, Shimizu F, et al. Autoantibodies against contactin-associated protein 1 and complexes of paranode-specific proteins in chronic inflammatory demyelinating polyradiculoneuropathy. Clin Exp Neuroimmunol 2023; 14: 116-121.

Keywords: Caspr1, autoimmune nodopathy, chronic inflammatory demyelinating polyradiculoneuropathy

Longitudinal Gait Assessment Using a Wearable System Detects Clinically Significant Changes In Patients With Peripheral Neuropathies

Poster No:
P 292

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Introduction:
Wearable sensors (WS) are useful to study gait patterns and quantify gait parameters in patients with peripheral neuropathies.We have previously shown that WS are able to capture differences between gait patterns in patients with steppage or ataxia.They could also potentially be useful to quantify impairment and monitor response to treatment over time.The aim for this study is to analyze clinically-relevant longitudinal changes in gait patterns in a cohort of patients with peripheral neuropathies.

Methods:
We performed a longitudinal study analysing multiple gait parameters in patients with peripheral neuropathies using a novel WS system that simultaneously registers and integrates data from wearable inertial,surface EMG and plantar pressure sensors positioned at gait-relevant anatomical sites during 2-minute walking test performance.Patients were monitored every 6 months.Longitudinal changes in kinematics,muscle activity,spatio-temporal parameters and plantar pressure were analysed in patients with clinically significant changes defined as a change of 2 points in MRC or 4 absolute points in R-ODS.

Results:
We included 41(119 observations) CIDP patients, 20(54 observations) IgM-MGUS-associated neuropathies, 11(16 observations)CMT and 24(45 observations) healthy controls.Wilcoxon test and linear mixed-effects models (LME) were used to capture significant longitudinal changes using data from 2-minute walking test.After correction for multiple comparisons, significant differences were observed in 17 biomechanical features when selecting the best and the worst clinical assessments in which there was a difference of,at least, 2 points on the MRC sumscore.When using all available longitudinal assessments, LME analysis identified 8 different biomechanical features correlating with clinical changes.Finally, in patients showing a clinical change of 4 points on R-ODS, 18 biomechanical features correlated with the clinical change using LME.

Conclusions:
This longitudinal study suggests that WS are able to capture clinically significant changes in diverse biomechanical parameters, and therefore supports the potential of these systems as a quantifiable and objective tool to monitor disease status in patients with peripheral neuropathies.

References:
No

Grant Support:

Instituto Carlos III (Spain), Fondo Investigaciones Sanitarias (FIS) PI22/00387 and GBS-CIDP Foundation.

Keywords: Wearable sensors, Peripheral neuropathies, CIDP, Longitudinal gait assessment

Preceding Infection Serology Titers Are Associated With Clinical Features In Guillain-Barré Syndrome

Poster No:
P 293

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Introduction:
Guillain-Barré syndrome (GBS) is a postinfectious disease, in which preceding infections elicit the production of antibodies that cross-react with gangliosides on peripheral nerves. Positive serology of associated microbes (Campylobacter jejuni [CJ], Mycoplasma pneumoniae [MP], Cytomegalovirus [CMV], Epstein-Barr virus [EBV], and Hepatitis E virus [HEV]) has been linked to clinical phenotypes in GBS. However, it is unknown whether serology titer heights affect these associations. In this study, we aim to determine serology parameters of associated preceding infections in relation to clinical features in GBS.

Methods:
All patients included in the International GBS Outcome Study with an available serum sample from study entry or week 1 were included (n=1461). Serum samples were tested for IgM and IgG against CJ, MP, CMV, EBV, and HEV and IgA against CJ. Acquired data were analyzed in relation to clinical features in GBS.

Results:
Of tested patients, 444/1454 (30.5%) were tested positive for CJ, 144/1450 (9.9%) for MP, 55/1445 (3.8%) for CMV, 32/1450 (2.2%) for HEV, 12/1448 (0.8%) for EBV, and 85/1438 (5.9%) for more than one microbe. Anti-CJ titers correlated most prominently with anti-GA1 and -GalNAc-GD1a, and –GM1 complex antibodies, anti-MP with anti-GalC complexes, and anti-CMV and anti-EBV with anti-GM2 complexes. In CJ-positive patients, higher anti-CJ titers were associated with higher frequencies of preceding diarrhea, pure motor GBS, Miller Fisher syndrome, axonal pathology, lower Medical Research Council sum scores during follow-up, and poor outcome at 26 weeks. IgA anti-CJ was an independent predictor of the time required to regain the ability to walk unaided.

Conclusions:
Preceding infection serology parameters correlate with anti-ganglioside antibodies and are associated with clinical features in GBS, suggesting that the magnitude of the immune response against preceding infections may affect the extent of cross-reactivity and consequent nerve damage. Further clinical analyses, including associations with the other microbes, will be presented at the Annual Meeting.

References:
No

Keywords: Guillain-Barré syndrome, Preceding infections, Serology, Antibodies, Clinical associations

Exploring the Clinical and Laboratory Characteristics of POEMS Syndrome in a Brazilian cohort

Poster No:
P 294

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Introduction:
Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) encompass a rare paraneoplastic syndrome. Diagnosing it may be highly challenging, as the full syndrome may not be evident in early stages. Additionally, developing countries may lack ancillary tests for its confirmation. We sought to describe the clinical and laboratory features of a cohort of Brazilian patients with POEMS syndrome.

Methods:
Patients diagnosed with POEMS syndrome at seven different referral centres in Brazil were included. Clinical, laboratory and neurophysiological data were obtained from clinical notes using a standardized proforma. All included patients met the current criteria for POEMS syndrome.

Results:
Thirty-four out of 42 patients were male (80%). The mean age at onset was 52 years old (ranging from 22 to 83), and the mean time for diagnosis was 10,6 months (ranging from 2 to 108). The most common neurophysiological pattern is demyelinating sensorimotor neuropathy, but with axonal loss present in 61% of cases, being more frequent in the lower limbs. Eleven patients underwent nerve biopsy, and 3 had inflammatory infiltrate. Papilledema was present in 9/30 patients (30%). Twenty seven out of 29 (92%) had albumin cytological dissociation. A monoclonal lambda component was detected in the serum of most cases, but clonal plasma cells on bone marrow biopsy were found in 15/29 cases (51%). Bone lesions was found in 24/34 (70%). Sixteen (84%) had typical skin changes. Endocrinopathy was present in 26/30 cases (86,6%), lymphadenomegaly in 21/37 (56,7%), splenomegaly in 66%, hepatomegaly in 38 and four cases had Castleman's disease.

Conclusions:
POEMS syndrome is a rare condition, and its true prevalence in Brazil needs to be determined. Our data suggest that the prevalence of endocrinopathy and bone lesions is higher than reported in the literature. Additional patients are being recruited to better define and evaluate whether this percentage could be related to the time taken for diagnosis

References:
No

Keywords: POEMS syndrome, inflammatory polyneuropathy, Monoclonal Gammopathy

Anti-ganglioside antibodies and neurological disorders after SARS-CoV-2 infection

Poster No:
P 295

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Introduction:
Background SARS-CoV-2 infection is a systemic disorder presenting typically with respiratory symptoms but various neurological manifestations such as Guillain-Barré syndrome (GBS), acute cerebrovascular diseases and encephalitis were reported. Objective Antibodies against gangliosides were measured in cases with neurological symptoms after SARS-CoV-2 infection, and the relationship between antibodies and clinical symptoms was investigated.

Methods:
Patients and Methods / Material and Methods We examined 31 patients with neurological symptoms associated with SARS-CoV-2 infection from July 2020 to April 2022. Serum IgG and IgM class antibodies against various gangliosides （GM1, GD1a, GD1b, GM3, GT1b, GQ1b, asialo-GM1,GM2, GD3,GD2, GT1a, GalNAc-GD1a） were measured by ELISA and compared with clinical symptoms.

Results:
GBS was diagnosed in 24 of 31 cases. Other cases included spinal cord disorder/cerebellar ataxia in 1 case, cerebellitis in 1 case, meningitis urinary retention syndrome in 1 case, bilateral facial nerve paralysis in 3 cases, and lower limb muscle weakness in 1 case. The average age of onset was 57.8 years. There were 25 cases in men and 6 cases in women. Among the 31 cases, 9 cases were positive for ganglioside antibodies. Regarding the types of ganglioside antibodies, 5 cases were positive for GM3 antibody, 3 cases were positive for asialo-GM1 antibody, 2 cases were positive for GT1a antibody, and 1 case was positive for GalNAc-GD1a antibody.

Conclusions:
In this study, some kind of ganglioside antibodies were detected in about one-third of the cases. In particular, IgG GM3 antibodies were detected in five cases. It has been reported that GM3 levels in plasma lipidomes and exosomes increase after COVID-19 infection, are involved in virus replication, and are associated with severity. It was considered that GM3 antibodies are produced in association with GM3 concentrated in plasma lipidomes and exosomes, which may affect the appearance of neurological symptoms.

References:
No

Keywords: Anti-ganglioside antibodies, SARS-CoV-2 infection

The Role Of Complement Activation In IgM M-Protein Associated Neuropathies

Poster No:
P 296

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Introduction:
Polyneuropathy associated with an IgM monoclonal gammopathy (IgM-PNP) is a slowly progressive, predominantly distal sensorimotor neuropathy, often characterized by sensory ataxia and by demyelinating features on nerve conduction studies. Anti-MAG IgM antibodies are found in up to 70% of cases. Complement activation is considered an important part of the pathophysiology of IgM-PNP and anti-MAG neuropathy. Whether anti-MAG titer and its complement-activating properties correlate with IgM-PNP disease severity has not been studied in detail. We studied the correlation of anti-MAG antibody titer and its complement-activating properties with IgM PNP disease severity.

Methods:
We used serum samples from 101 IgM-PNP patients enrolled in the Dutch arm of the IMAGiNe cohort study to assess anti-MAG titers by ELISA and IgM binding and complement (C3) deposition (expressed as C3 deposition relative to the negative control, i.e., C3/EDTA ratio) using a primate peripheral nerve model. We studied correlations of C3/EDTA with anti-MAG ELISA titer and clinical characteristics, including iRODS score, INCAT modified sensory sum score and ataxia score.

Results:
Complement deposition correlated significantly with anti-MAG antibody titer (Spearman's rho 0,80; $p < 0.0001$), but not with any clinical characteristic.

Conclusions:
Complement activation is an important part of IgM-PNP pathophysiology, but complement deposition only correlates significantly with anti-MAG antibody titer and not with any clinical characteristic.

References:
No

Keywords: IgM M-protein, Polyneuropathy, Gammopathy, Complement, Anti-MAG

Development of a prediction tool to guide clinical decision making on performing nerve conduction studies in chronic polyneuropathy

Poster No:
P 297

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Introduction:
Nerve conduction studies (NCS) are often performed to categorize polyneuropathies into axonal or demyelinating. The distinction is important as immune-mediated demyelinating polyneuropathies are potentially treatable, but these represent only a small proportion (about 5%) of chronic polyneuropathies. Recommendations on when to perform NCS vary from in every patient with suspected polyneuropathy to only in selected cases, and the evidence for these recommendations is low. This study aimed to develop a prediction tool to guide and improve clinical decision making on NCS in chronic polyneuropathy.

Methods:
In this prospective observational multi-center study, we included 1200 patients referred to a neurology outpatient clinic with suspicion of chronic polyneuropathy. From the electronic medical records we retrieved information regarding patient characteristics, disease characteristics, neurological examination, medical history and family history.

Results:
Using regression analysis we will model a clinical prediction tool that estimates the probability of an electrodiagnosis of demyelinating polyneuropathy. The modeling will be based on the data of a subset of 1000 patients and we will validate the prediction tool with the data of the subset of the remaining 200 patients. Data collection and analysis is ongoing, and results will be presented.

Conclusions:
This study will generate evidence-based results to support recommendations regarding NCS in patients with suspected chronic polyneuropathy.

References:
No

Keywords: NCS, prediction model

Conduction Block based on CMAP Area reduction May Improve Chronic Inflammatory Demyelinating Polyradiculopathy Diagnosis

Poster No:
P 299

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Introduction:
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) diagnosis relies heavily on nerve conduction studies (NCS). A key indicator supportive of demyelination is a conduction block (CB), which indicates a cessation of impulse propagation due to myelin sheath disruption, manifesting as a reduction in compound muscle action potential (CMAP) size during nerve stimulation. Differentiating CB from effects of increased temporal dispersion, including effects of axonal loss and collateral reinnervation, can be challenging. The EAN/PNS CIDP 2021 consensus guideline defines CB by amplitude reduction, although CMAP area reduction may better reflect a CB. This study evaluates the effect of area- and amplitude-based CB and its impact on CIDP classification.

Methods:
As reference standard, patients from three tertiary hospitals meeting the 2021 EAN/PNS criteria for CIDP were included, alongside patients who did not meet the criteria but CIDP was a presumptive diagnosis based on clinical and supportive criteria including treatment response. Patient-controls were included who underwent extensive NCS based on suspicion of having an inflammatory neuropathy, but received an alternative diagnosis. NCS, including CMAP amplitude, area, and duration for the median, ulnar, radial, musculocutaneous and peroneal nerves, were reassessed. Sensitivity and specificity were calculated using the EAN/PNS electrodiagnostic criteria with amplitude-based and area-based CB.

Results:
Data entry is complete for 228/323 patients and all 339 controls. Conduction blocks (CBs) based on amplitude reduction was observed in 24.6% (384/1564) of motor nerves in patients and 4.3% (144/3329) in controls. Using area reduction, CBs were found in 18.0% in patients and 2.0% in controls. When classifying according to the electrodiagnostic criteria of the EAN/PNS guideline and separating weakly and strongly supportive of demyelination from not supportive, specificity was 66.1% for CMAP amplitude reduction and improved to 73.2% with CMAP area reduction, while sensitivity remained similar (88.2% vs. 89.5%).

Conclusions:
Preliminary results suggest that area reduction-based CB identification may improve CIDP diagnostic specificity without affecting sensitivity.

References:
No

Keywords: Chronic inflammatory demyelinating polyneuropathy, Nerve conduction study, Conduction block, Diagnosis, Area

Phase 2 Trial of Riliprubart in Chronic Inflammatory Demyelinating Polyneuropathy: Quality-of-life and Fatigue

Poster No:
P 300

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Introduction:
People with chronic inflammatory demyelinating polyneuropathy (CIDP) often experience fatigue in conjunction with weakness and sensory abnormalities. This adversely affects the ability to walk and perform daily activities, impacting quality-of-life (QoL). Evidence suggests that complement activation is likely involved in the pathogenesis of CIDP. Riliprubart, a first-in-class, humanized, IgG4 monoclonal antibody, selectively inhibits activated-C1s in the classical complement pathway. A Phase 2, open-label trial (NCT04658472) indicates favorable efficacy and safety of riliprubart, along with improved function in participants with CIDP, as measured by the Inflammatory Neuropathy Cause and Treatment (INCAT) disability score, Inflammatory Rasch-built Overall Disability Scale (I-RODS), and grip strength. Here, we assess the effects of riliprubart on fatigue and QoL in people with CIDP in the ongoing Phase 2 trial.

Methods:
This is a global, multicenter, open-label trial evaluating riliprubart across three subgroups: Standard-of-Care (SOC)-Treated, SOC-Refractory, and SOC-Naïve. Participants underwent a 24-week treatment period (Part-A), followed by optional treatment-extension (Part-B: 52-weeks, Part-C: until end-of-study). During Part-A, changes from baseline in fatigue and health-related QoL were descriptively analysed using Modified Rasch-built Fatigue Severity Scale (R-FSS; range 0-21, higher score indicates worse outcomes) and EuroQol Visual Analogue Scale (EQ-VAS; range 0-100, higher score indicates better outcomes), respectively.

Results:
As of Oct-2023, 77 participants were treated with riliprubart, of whom N=29/47 SOC-Treated, N=14/18 SOC-Refractory, and N=8/12 SOC-Naïve were analyzed at Week-24 (Part-A). The mean [SD] change from baseline in R-FSS at Week-24 showed reduction in fatigue in all participants treated with riliprubart across all subgroups (SOC-Treated: -3.79 [7.39], SOC-Refractory: -3.50 [8.75], and SOC-Naïve: -6.63 [4.14]). Similarly, the mean [SD] change from baseline in EQ-VAS at Week-24 showed improvement in QoL across all subgroups (SOC-Treated: 9.59 [21.59], SOC-Refractory: 12.21 [19.56], and SOC-Naïve: 10.50 [15.92]).

Conclusions:
These findings suggest that riliprubart decreases fatigue severity and improves QoL in people with CIDP, in addition to clinical improvement.

References:
No

Grant Support:

Study funded by Sanofi

Keywords: Chronic inflammatory demyelinating polyneuropathy, Fatigue, Quality-of-life, Riliprubart, Patient-reported outcomes

Genetic variation in the FCGR2/3 locus in Guillain-Barré syndrome

Poster No:
P 301

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Introduction:
Fc-gamma receptors (FcγRs) are important for effector functions of immunoglobulin G (IgG) and are therefore expected to play a role in the pathophysiology of the Guillain-Barre syndrome (GBS). The FCGR2/3 locus, encoding low-to-medium-affinity FcγRs, contains extensive genetic variation. We hypothesized that genetic variation in the FCGR2/3 locus influences GBS susceptibility, disease severity, and the pharmacokinetics of intravenous immunoglobulin (IVIg).

Methods:
Copy number variation and single nucleotide polymorphisms in the FCGR2/3 locus were studied using multiplex ligation-dependent probe amplification (MLPA). The study cohort consisted of 467 GBS patients and 919 healthy controls of European descent. Severe disease was defined as MRC sum score < 40 at nadir. The increase in serum IgG one or two weeks after the start of IVIg treatment was determined.

Results:
No significant associations were observed between genetic variation in FCGR2/3 locus and predisposition for GBS. However, in patients with an antecedent Campylobacter jejuni infection, a higher frequency of three or more FCGR3A copies was observed compared with healthy controls (Fisher exact test; $p = 0.022$). FCGR3A copy numbers were also associated with more severe disease (OR = 2.02; 95% CI = 1.00 – 4.12), but not when groups were stratified for C. jejuni infection. No association was found between FCGR2/3 variants and the ability to walk unaided in time-to-event analysis. In addition the pharmacokinetics of IVIg was not affected by genetic variation in the FCGR2/3 locus.

Conclusions:
Our study suggests that copy number variation in the FCGR2/3 locus influences the susceptibility to develop C. jejuni related GBS and therefore indirectly associates with severe disease in GBS.

References:
No

Grant Support:

The project is sponsored by the Prinses Beatrix Spierfonds (W.OR19-24)

Keywords: Genetic variation, Fc-gamma receptors, GBS

Does Ultrasonography Of The Sural Nerve Contribute To Differentiate Various Demyelinating Neuropathies ?

Poster No:
P 302

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Introduction:
The aims of this study were to [1] describe sural nerve cross-sectional area (CSA) measures in demyelinating neuropathies using high resolution ultrasonography [2] identify sonographic pattern of sural nerve involvement that can help to differentiate various demyelinating neuropathies.

Methods:
Between July 2021 and May 2023, we enrolled 50 patients (17 with immune-mediated neuropathy, 17 with inherited neuropathy and 16 with suspected immune-mediated or inherited neuropathy). Of the 17 patients with immune-mediated neuropathy, 7 had typical chronic inflammatory demyelinating polyneuropathy ('typical CIDP') and 6 were 'CIDP variants'. Of the 17 patients with inherited neuropathy, 8 had demyelinating Charcot-Marie-Tooth disease type 1 (CMT1). Ultrasound of peripheral nerves was performed using broad frequency (5-18 MHz) transducer. CSA was assessed at pre-determined sites of median nerve (wrist, mid-forearm, mid-arm), ulnar nerve (wrist, mid-forearm, 5cm distal to elbow, elbow groove, 5cm proximal to elbow), radial nerve (spiral groove), sciatic nerve (thigh), tibial nerve (popliteal fossa, ankle), peroneal nerve (popliteal fossa, fibular head), and sural nerve (ankle).

Results:
All 7 patients with 'typical CIDP' showed normal CSA of sural nerve with multifocal or regional or diffuse enlargement in other nerves. Of the 6 'CIDP variants', 4 showed normal and 2 showed high CSA of sural nerve with multifocal or regional or diffuse enlargement in other nerves. Of the 8 CMT1 patients, 2 had normal CSA and 6 showed high CSA of sural nerve with diffuse or regional or multifocal enlargement in other nerves.

Conclusions:
Our observational study showed multifocal or regional or diffuse enlargement of peripheral nerves with sparing of sural nerve (sural sparing pattern) in all patients with 'typical CIDP'. Limitations of this study are small sample size and heterogeneity of patient characteristics. The detailed analysis is ongoing.

References:
No

Keywords: Ultrasonography of peripheral nerves, Nerve ultrasound, CIDP, CMT, Sural nerve

Does Mycophenolate Mofetil Facilitate IGIV Withdrawal in CIDP? Mycopid Study : Multicentric Randomized, Double-blind, Placebo-controlled trial

Poster No:
P 303

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Introduction:
Introduction: IVIG, corticosteroids and plasma exchange are effective in CIDP patients. When patients are switched between these different treatments, the response rate reaches 80%. However, 40% of responders relapse if treatment is interrupted. Treatment dependency is defined as relapse if treatment is stopped or decreased. Immunomodulatory drugs could prevent relapses and facilitate the withdrawal of IVIG, but controlled studies are missing. Objective: to determine whether mycophenolate mofetil (MM) could help reduce IGIV dependency and facilitate IGIV withdrawal.

Methods:
Methods : Multicentric randomized, double-blind, placebo-controlled trial Inclusion criteria: patients with definite/ probable CIDP (2010 EFNS/PNS criteria) or atypical CIDP (clinical criteria and at least two supportive criteria) and who respond to IVIG. Patients were randomized to receive IGIV + placebo or IGIV + MM. 3 courses of IVIG (2g/kg) were initially administered every 4 weeks, followed by a progressive withdrawal strategy, increasing the interval between IVIG administrations by 1 week, unless relapse was observed. IVIG was stopped out once a 10-week interval was achieved. If three consecutive attempts to increase IVIG intervals failed, the last well-tolerated interval was maintained. Primary outcome: proportion of relapse during the tapering period or after the withdrawal. Main secondary outcomes: proportion of patients having undergone successful withdrawal, changes in disability and score at end of the study (24 month), adverse events.

Results:
Main Results: • 17 (45.9%) placebo patients and 20 (54.1%) MM patients included. • Proportion of relapses: 12 (71%) placebo patients, 12 (60%) MM patients (p=0.55). • IGIV-weaned patients: 2 placebo patients (12%) and 10 (50.0%) MM patients, (p=0.013). • -1 point ONLS in MM group vs ONLS stable in placebo group at end of the study

Conclusions:
Conclusion. MM does not decrease relapse during the tapering period but significantly increases the likelihood of being able to stop treatment as compared to placebo

References:
No

Keywords: CIDP, mycophenolate mofetil, IGIV withdrawal

Early Nerve Conduction Findings Predict Treatment Outcomes in Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Poster No:
P 304

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Introduction:
Nerve conductions aid chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) diagnosis but their role in therapy monitoring is less commonly utilized in clinical practice. Whether early changes in any nerve conduction variables can predict treatment outcomes is addressed.

Methods:
Utilizing 2021 EAN/PNS criteria, newly diagnosed CIDP patients were identified (January 1996-October 2023). Baseline and follow-up electrodiagnostic studies (27 variables) of each patient were uniformly compared with serial neuropathy impairment scores (NIS) over time.

Results:
The study included 39 patients (61.5% male, mean age 52.2 years, median follow-up 39.5 months with IQR 2.7-91.8). All participants received at least one first-line treatment, mostly IVIG (92%). Changes in nerve conductions at the first follow-up visit (median 4.9 months, IQR 3.2–7.9) were compared with longitudinal NIS changes, identifying 26 responders and 13 non-responders (worsening or no improvement). Median baseline NIS changes for responders versus non-responders were -28.0 versus 4.0 ($p<0.001$) at first follow-up and -34.5 versus 12.0 ($p<0.001$) at last follow-up. Responders showed significant improvements over non-responders in median changes of ulnar CMAPs (1.0 mV vs -0.4 mV, $p=0.036$), fibular CMAPs (0.3 mV vs -0.3 mV, $p=0.003$), summated CMAPs (1.7 mV vs -1.5 mV, $p=0.005$), and fibular conduction velocity (3 m/s vs -1 m/s, $p=0.034$). Correlation coefficients were calculated for 27 nerve conduction variables, comparing baseline changes at the first follow-up visit to longitudinal NIS changes. Only fibular CMAP change negatively correlated with NIS throughout the entire follow-up period (6 to >60 months, R-value -0.6 to -0.8, $p<0.003$). Three patients had no fibular response at baseline and during follow-up despite improved NIS, while all had present ulnar and summated CMAP responses.

Conclusions:
Early nerve conduction changes predict clinical outcomes in CIDP and allow distinction of responders from non-responders initially and long-term. Small fibular CMAP improvements often accompany dramatic NIS improvements. Ulnar and summated CMAP improvements are viable secondary indicators when fibular response is absent.

References:
Yes

Reference 1: Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force-Second revision. Eur J Neurol 2021;28:3556-3583.

Keywords: CIDP, Nerve conduction study, Clinical outcomes, Inflammatory neuropathy, NIS

Development of a Framework to Compare Outcomes Between Diverse GBS Populations

Poster No:
P 305

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Introduction:
Guillain-Barré Syndrome (GBS) is a polyradiculopathy caused by antibody- and complement-mediated nerve damage. Despite treatment with intravenous immunoglobulin and/or plasma exchange, approximately 20% of patients remain unable to walk without assistance after 6 months, and many experience persistent residual disability. ANX005, an investigational drug, inhibits C1q and the classical complement pathway. A phase 3 randomized controlled trial (GBS-02) is ongoing in Bangladesh (BD) and the Philippines (PH) to investigate the efficacy of ANX005 versus placebo. The current study (ANX005-GBS-04) aims to compare characteristics of the GBS-02 population to non-BD patients from the International GBS Outcome Study (IGOS).

Methods:
IGOS contains prospectively collected data from 2000 GBS patients from 21 countries. The GBS-02 eligibility criteria will be applied to non-BD patients in the IGOS study. Using validated clinical prognostic factors for GBS, including muscle strength, age, preceding diarrhea, electrophysiology, and serum neurofilament light chain, we will calculate a propensity score for each patient representing the probability of being a member of the GBS-02 study. Based on the propensity scores, each GBS-02 patient will be matched to up to four non-BD IGOS controls to establish an external comparator cohort.

Results:
Matching will be based on the baseline characteristics of the 241 patients enrolled in the ongoing GBS-02 study. Comparability of GBS-02 and non-BD IGOS cohorts will be assessed before and after matching approaches.

Conclusions:
This study will provide a format for comparison of diverse populations of patients with GBS and for future comparative effectiveness studies.

References:
No

Grant Support:

Supported by Annexon Bioscience

Keywords: Guillain-Barré Syndrome, ANX005, Clinical trials

Update on the International Guillain-Barré Syndrome Outcome Study

Poster No:
P 306

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Introduction:
The International GBS Outcome Study (IGOS) aims to define the determinants and predictors of the clinical course of GBS to provide a basis to personalize treatment and identify best practices. In this abstract, we provide an update of IGOS.

Methods:
IGOS is a observational prospective cohort study conducted in 21 countries across 5 continents. All patients within the diagnostic spectrum of GBS are included irrespective of age, disease severity and treatment, within two weeks from onset of weakness. Data is collected at standard time points during follow-up of 1 to 3 years, including clinical symptoms and signs and the ability to walk. In addition, nerve conduction studies and biomaterials are collected for future biomarker studies.

Results:
Until May 2021, the IGOS has enrolled 2000 patients worldwide, with the most recently included participants still under follow-up until May 2024. The majority of patients (n=1110, 60%) were male and the median age was 52 (IQR: 34-65, total number of children n=155, 8.4%). The sensorimotor variant was the most frequently reported variant (n=1046, 60%). IVIg was provided to 1319 patients (72%), while 203 (13%) received plasma exchange. At six months, 82% of patients (n=1172) were able to walk. To date, the IGOS consortium has published 16 manuscripts, with currently 22 additional studies still in progress, including a paper describing the IGOS-2000 cohort. In spring 2024, we will launch a procedure enabling scientists to submit proposals for conducting research using IGOS data. Data will be shared using a safe Digital Research Environment.

Conclusions:
To date, IGOS is the largest GBS database including clinical, electrophysiological and serological data. Ongoing and future studies will leverage these insights to compare the effectiveness of treatments and ultimately improve outcome for GBS patients.

References:
Yes

Reference 1: Jacobs BC, van den Berg B, Verboon C, Chavada G, Cornblath DR, Gorson KC, Harbo T, Hartung HP, Hughes RAC, Kusunoki S, van Doorn PA, Willison HJ; IGOS Consortium. International Guillain-Barré Syndrome Outcome Study: protocol of a prospective observational cohort study on clinical and biological predictors of disease course and outcome in Guillain-Barré syndrome. J Peripher Nerv Syst. 2017 Jun;22(2):68-76. doi: 10.1111/jns.12209. PMID: 28406555.

Grant Support:

BCJ reports grants for research from Baxalta, Grifols, CSL-Behring, Annexon, Hansa Biopharma, Roche, Prinses Beatrix Spierfonds, GBS-CIDP Foundation International and Horizon 2020, and consultancy fees from Roche and Annexon, and he is chair of the Steering Committee of Internation GBS Outcome Study (IGOS) and member of the Steering Committee of International CIDP Outcome Study (ICOS) and INCbase.

Keywords: Guillain-Barré Syndrome, Real-World Data, Outcome

Early disease course after treatment in patients with Guillain-Barré Syndrome: a prospective observational cohort study

Poster No:
P 307

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Introduction:
Guillain-Barré Syndrome (GBS) has a variable disease course and outcome. Some patients do not improve or even deteriorate shortly after treatment with Intravenous Immunoglobulin (IVIg) or Plasma Exchange (PE), although factors contributing to this poor response are unknown. Our aim is to study the early disease course after treatment in patients with GBS from the International GBS Outcome Study (IGOS).

Methods:
IGOS is a prospective cohort study conducted in 20 countries across 5 continents, including patients with GBS within two weeks from onset of weakness. For this study, we included patients initially treated with IVIg or PE within fourteen days of study entry. We defined failure-to-improve as worsening or failure to improve by at least one grade on the GBS Disability Scale (GBS-DS) from entry to week 2/4, excluding patients with treatment-related fluctuations. Sensitivity analyses will be performed to assess failure-to-improve using the Medical Research Council sum score (MRC-ss). Using multivariable logistic regression analyses, we studied the association of selected determinants with failure-to-improve at week 4.

Results:
Of 1076 treated patients, IVIg was provided to 905 (84%) and 171 (16%) received PE. In 440/721 (61%) IVIg-treated patients and in 90/154 (59%) PE-treated patients, no improvement was observed at week 2. At week 4, 310/717 (43%) patients had not improved after IVIg and 73/153 (48%) had not improved after PE. At entry, higher age (OR per 10 years:1.27, 95%CI:1.17-1.39), lower MRC-ss (OR:0.93, 95%CI:0.91-0.94), cranial nerve involvement (OR:1.46, 95% CI:1.05-1.94), time from weakness to admission (OR per day:0.94, 95%CI:0.89-0.98) and higher GBS-DS at entry (OR:0.43, 95%CI:0.35-0.53) were associated with increased risk of not improving within 4 weeks after treatment.

Conclusions:
Early deteriorations or lack of improvement after treatment is common in patients with GBS. Future research should focus on how identified risk factors for failure to early improve could be leveraged to further personalize treatment.

References:
Yes

Reference 1: Jacobs BC, van den Berg B, Verboon C, Chavada G, Cornblath DR, Gorson KC, Harbo T, Hartung HP, Hughes RAC, Kusunoki S, van Doorn PA, Willison HJ; IGOS Consortium. International Guillain-Barré Syndrome Outcome Study: protocol of a prospective observational cohort study on clinical and biological predictors of disease course and outcome in Guillain-Barré syndrome. J Peripher Nerv Syst. 2017 Jun;22(2):68-76. doi: 10.1111/jns.12209. PMID: 28406555.

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Keywords: Guillain-Barré Syndrome, Early disease course, Treatment response

CLINICAL AND IMMUNOLOGICAL STUDY ON EARLY DIFFERENTIATION OF ACUTE-ONSET CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY AND GUILLAIN-BARRÉ

Poster No:
P 308

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Introduction:
Currently, there are no definitive clinical or electrophysiological markers that make distinguishing between acute-onset chronic inflammatory demyelinating polyradiculoneuropathy (A-CIDP) and acute inflammatory demyelinating polyneuropathy (AIDP), a demyelinating variant of Guillain-Barré syndrome (GBS). The purpose of this study is to identify early points of differentiation between A-CIDP and AIDP.

Methods:
Six patients with A-CIDP who received immunotherapy as GBS within 2 weeks after the onset of weakness were clinically and electrophysiologically compared with AIDP (n=16). We retrospectively examined cerebrospinal fluid (CSF) interleukin-8 (IL-8) in the acute phase from patients with A-CIDP (n=4) AIDP (n=13), or acute motor axonal neuropathy (AMAN) (n=11).

Results:
In A-CIDP group, the average time from onset to hospitalization was 8.7 days, and the mean time to first relapse was 88.2 days. Four patients were unable to walk independently at the peak of the disease, and two had cranial nerve damage and none required mechanical ventilation. In AIDP group, twelve patients had cranial nerve damage and six required mechanical ventilation. Initial nerve conduction studies (NCS) in A-CIDP group revealed a sural-sparing pattern (SSP) in two patients, whereas NCS at the time of relapse no SSP. Average CSF IL-8 in AIDP group was higher than in A-CIDP ($p < 0.005$). The AUC of the ROC curve was 0.77, and the cutoff value for CSF IL-8 was 87.9 pg/ml. It was also significantly higher in AIDP than in AMAN ($p = 0.028$).

Conclusions:
The absence of cranial nerve damage, no need for mechanical ventilation, and no SSP in the early stage NCS suggest A-CIDP. As shown recently, high levels of initial CSF IL-8 are a promising marker to distinguish between AIDP and A-CIDP. Initial CSF IL-8 levels are also be useful in differentiating AMAN from AIDP.

References:
No

Keywords: acute-onset chronic inflammatory demyelinating polyradiculoneuropathy, Guillain-Barré syndrome, acute inflammatory demyelinating polyneuropathy, sural-sparing pattern, cerebrospinal fluid interleukin-8

Insights into Refractory Chronic Inflammatory Demyelinating Polyneuropathy: A Comprehensive Real-World Study

Poster No:
P 309

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Introduction:
Refractory chronic inflammatory demyelinating polyneuropathy (CIDP) is a challenging subset of CIDP. It does not respond well to immune therapy and causes substantial disability. A comprehensive understanding of its clinical profile, electrophysiological characteristics and potential risk factors associated with refractoriness remains unknown

Methods:
Data in this cross-sectional study was collected and reviewed from the Huashan Peripheral Neuropathy Database (HSPN). Included patients were categorized into refractory CIDP and non-refractory CIDP groups based on treatment response. The clinical and electrophysiological characteristics were compared between refractory and non-refractory CIDP groups. Potential risk factors associated with refractory CIDP were explored

Results:
Fifty-eight patients with CIDP were included. Four disease course patterns of refractory CIDP are described: a relapsing-remitting form, a stable form, a secondary progressive form and a primary progressive form. Compared to non-refractory CIDP patients, refractory CIDP exhibited a longer disease duration (48.96 ± 33.72 vs 28.33 ± 13.72 months, p=0.038) and worse functional impairment (MRC sum score, 46.08 ± 12.69 vs 52.81 ± 7.34, p=0.018; mRS, 2.76 ± 0.93 vs 2.33 ± 0.99, p=0.082; INCAT, 3.68 ± 1.76 vs 3.03 ± 2.28, p=0.056, respectively). Electrophysiological studies further revealed greater axonal impairment (4.15 ± 2.0 vs 5.94 ± 2.77 mv, p=0.011, ulnar CMAP) and more severe demyelination (5.56 ± 2.86 vs 4.18 ± 3.71 ms, p=0.008, ulnar distal latency; 7.94 ± 5.62 vs 6.52 ± 6.64 ms, p=0.035, median distal latency; 30.21 ± 12.59 vs 37.48 ± 12.44 m/s, p=0.035, median conduction velocity; 58.66 ± 25.73 vs 42.30 ± 13.77 ms, p=0.033, median F-wave latency), compared to non-refractory CIDP. Disease duration was shown to be an independent risk factor for refractory CIDP (p<0.05, 95%CI [0.007, 0.076]).

Conclusions:
Conclusion: This study provided a comprehensive description of refractory CIDP, addressing its clinical features, classification of clinical course, electrophysiological characteristics, and prognostic factors, effectively elucidating its various aspects.

References:
No

Grant Support:

No grant support for this study.

Keywords: Chronic Inflammatory Demyelinating Polyneuropathy, Disease course pattern, Refractory, Prognosis, Electrophysiological characteristics

Estimated Prevalence Of Diagnosed Chronic Inflammatory Demyelinating Polyradiculoneuropathy And Clinical Subtypes In Nine Countries

Poster No:
P 310

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Introduction:
This study synthesized available literature and estimated diagnosed prevalence of adults with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Methods:
A review of published epidemiological literature (Pubmed, Web of Science core collection and Scientific Electronic Library Online) was performed, supplemented by manual searches of rare disease registries and other sources. After exclusions based on title/abstract screening, duplicates, representativeness or relevance, studies underwent full text review. Diagnosed CIDP cases were defined using the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 criteria and classified as typical or atypical/variant CIDP. Although updated European Academy of Neurology (EAN)/PNS 2021 criteria are available, no prevalence studies using these criteria were identified and no direct quantifying factor to adjust 2010 estimates was found. If CIDP subtypes were incomplete or unavailable, reported estimates were adjusted according to the literature. Prevalence estimates were projected over 2020–2030 for nine countries (USA, France, Germany, Italy, Spain, United Kingdom, Canada, Argentina, Brazil). Where country-specific prevalence data were unavailable, results from studies of comparable populations were used.

Results:
Overall, 1234 studies were identified; 30 underwent full-text review, and three were included in the final analysis. Two hospital-based studies, conducted in Ireland and Chile, contributed diagnosed prevalence data; the latter also reported CIPD subtype proportions. A German prospective study reported proportions of definite/probable/possible CIDP cases and of disease subtypes, which were used to adjust case proportions from the other two studies. According to these data, estimated diagnosed prevalence was 7.08 per 100,000 persons across all included countries except Brazil and Argentina (3.05 per 100,000 persons); typical CIDP cases accounted for 51%.

Conclusions:
Data allowing estimation of diagnosed prevalent CIDP cases are scarce. This study provides a synthesis of available CIDP epidemiology across several countries. Country-specific studies, particularly using updated EAN/PNS 2021 criteria, are needed.
Study/writing support funder: Takeda Development Center Americas, Inc./Takeda Pharmaceuticals International AG.

References:
No

Keywords: chronic inflammatory demyelinating polyradiculoneuropathy, epidemiology, prevalence, disease subtypes, literature review

PERIPHERAL NERVE SOCIETY

Non-SIG Related Abstracts

P 311 - 365

LOW INTENSITY ULTRASOUND PROMOTES AXONAL REGENERATION AND FUNCTIONAL RECOVERY

Poster No:
P 311

Authors:
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Introduction:
Peripheral nerve injuries are common conditions that can arise from trauma (e.g., compression, severance) and can lead to neuropathic pain as well as motor and sensory deficits. Although much knowledge exists on the mechanisms of injury and nerve regeneration, treatments that ensure functional recovery following peripheral nerve injury are limited. Peripheral nerve regeneration is reliant on many signals from the biomechanical microenvironment, including trophic support from repair Schwann cells (SCs) and extracellular matrix (ECM) dependent signaling, which will induce downstream pathways crucial for axonal regrowth and remyelination. Low intensity ultrasound (LIU) has become a promising, non-invasive therapeutic to improve peripheral nerve regeneration in preclinical models. Given the LIU mechanism is unknown, we investigated the molecular and functional impact of LIU post peripheral nerve injury.

Methods:
We performed a daily LIU application of 0.3W/cm2 on a mouse sciatic nerve crush model. Through comprehensive evaluation of cross-validated functional, morphological, electron microscopy, and molecular assays at 7-, 20-, 60- days post injury, we assessed the effect of LIU on neurotrophic factors, axonal regrowth and remyelination, ECM-dependent signaling, and peripheral nerve function. In vitro assays were used to distinguish cell-specific effects of LIU.

Results:
Here we show that LIU specifically stimulates neurotrophic factor expression, and support the significant increase of regenerating and myelinated axons in the distal injured nerve. Furthermore, ECM-dependent signaling appears to be modulated by LIU treatment to further promote pro-survival pathways. Importantly, we also observe beneficial effects on peripheral nerve sensory and motor functions.

Conclusions:
Our results suggest that a daily LIU treatment post injury promotes neurotrophic factor expression to further facilitate axonal regeneration and remyelination, along with functional recovery. We discuss future investigation to isolate the cell-specific activated receptors and other possible downstream factors activated with LIU to uncover unique mechanobiological signals involved in peripheral nerve regeneration.

References:
No

Keywords: ultrasound, regeneration, neurotrophic factor, myelin

Development and characterization of an in vitro model of human peripheral nerve degeneration

Poster No:
P 312

Authors:
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Institutions:
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Introduction:
Schwann cells, (SCs) are activated upon nerve injury to acquire a repair phenotype able to promote axon regrowth. However, most available information of the cellular responses to nerve tissue damage was obtained primarily using animal models. The goal of this project was to use a model of nerve degeneration in vitro to study injury-associated changes in SCs from human tissues.

Methods:
An in vitro model of human nerve degeneration was established by culturing whole nerve segments in medium supportive of SC growth. Nerve segments cultured for 5 and 15 days were compared with donor-matched intact (control) tissues. Immunohistochemistry was performed to characterize the cellular composition of the nerves on the basis of key markers of mature and repair SCs. Proliferation and apoptosis markers were used to determine the viability of the cells before and after culture.

Results:
In vitro degenerated nerves increased the expression of NGFR in repair SCs, endoneurial fibroblasts, perineurial, and epineurial cells. Curiously, fascicles closer to the periphery of the nerve contained lower levels of NGFR and higher levels of Sox10, a SC-specific transcription factor, when compared to those fascicles in the center of the nerve. Sox2 expression (a repair SC marker) was increased with degeneration in SCs from outer areas, while expression of S100B, (a general SC marker) was maintained regardless of the relative location of the SCs within the nerves. Importantly, myelin phagocytosis, and axon degeneration were incomplete in degenerated nerves in vitro. Cell proliferation was detected only in a subset of endoneurial cells; however, signs of cell death were not observed.

Conclusions:
Overall, in vitro degeneration partially recapitulates human SC responses to injury, including myelin degradation and the conversion of mature SCs into a repair-like phenotype. This model may prove useful to investigate the complex molecular organization of human peripheral nerve cells in homeostasis and after injury.

References:
Yes

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Reference 2: Monje PV. The properties of human Schwann cells: Lessons from in vitro culture and transplantation studies. Glia. 2020;68(4):797-810. doi:10.1002/glia.23793

Grant Support:

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NEU STAR, Department of Neurosurgery (University of Kentucky)
Indiana State Department of Health (ITSCBIRF, Indiana)

Keywords: Peripheral nerve, Schwann cells, Human tissues, In vitro degeneration

Hedgehog Pathway Induction Following Facial Nerve Injury in Mice

Poster No:
P 313

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Institutions:
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Introduction:
Motor nerve injury is a common clinical problem and may result in significant disability for affected patients. Understanding the cellular and molecular events that follow motor nerve injury in mice may aid in the discovery and development of new treatments. To identify potential therapeutic candidates, we employed a mouse model of facial nerve transection injury that permits analysis of the injured facial nerve at various time points post-injury.

Methods:
A mouse model of facial nerve transection injury and tissue recovery was used. We first used bulk RNA sequencing to compare pooled uninjured and injured murine facial nerves 7 days post injury. In situ hybridization and immunohistochemistry were used to characterize Sonic hedgehog-expressing cells at several time points after injury. We then tested the effect of a potent Smoothened agonist on nerve regeneration, administering agonist intraperitoneally before and after injury. Immunohistochemistry quantified Schwann and immune cells. Rat Schwann cell cultures were used for further interrogation of the effect of the Smoothened agonist on Schwann cells.

Results:
Sonic hedgehog (Shh) was the highest differentially upregulated gene 7 days post-injury and Schwann cells were the predominant cell that expressed Shh. Gli1, a readout of Hedgehog Pathway activation, was expressed broadly in the injured nerve, with Gli1+ cells found in a "bridge" of early nerve tissue regeneration across the injury zone. Treatment with the Smoothened agonist both pre- and post-injury resulted in an increased number of Schwann cells (SOX10+) and immune cells (CD45+) within the injured nerve 5-, 7-, 14-, and 21-days post-injury.

Conclusions:
Induction of the Hedgehog pathway appears to modulate Schwann and immune cell infiltration in the injured nerve. Enhancing this signal may have therapeutic benefit.

References:
No

Keywords: Sonic Hedgehog, Smoothened Agonist, Facial Nerve Injury, Schwann Cell, Immune Cell

Utility of a point of care, electronic medical record (EMR) imbedded, neuropathy impairment scale

Poster No:
P 314

Authors:
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Institutions:
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Introduction:
Evaluate the performance of an EMR imbedded neuropathy impairment scale (NSNIS) in a community-based polyneuropathy cohort.

Methods:
We developed a structured clinical documentation support (SCDS) toolkit that collects data on patient reported outcomes, type and severity of symptoms, a timed 25-foot walk, modified Rankin score for degree of disability, toxic exposure assessment, and the use and efficacy of both symptomatic and disease modifying agents, physical rehabilitation measures, and alternative treatments. Within this toolkit, we developed a point-of-care, easy to use, neuropathy impairment scale (NSNIS). It has a maximum normal score of 322 and scores motor (250), sensory (32) and reflex (40) impairments individually.

Results:
Among 1,055 patients, 327 had a predominantly somatic polyneuropathy. In this population, NSNIS scores were negatively correlated with 25-foot walk times ($r=-0.31$, $p<0.001$) and total fatigue-scale scores ($r=-0.16$, $p=0.005$). In 102 and 155 patients with idiopathic and acquired polyneuropathy etiologies, respectively, NSNIS scores were negatively correlated with modified Rankin scale ($\rho=-0.23$, $p=0.022$; $\rho=-0.56$, $p<0.001$) and severity of global symptoms ($\rho=-0.21$, $p=0.040$; $\rho=-0.17$, $p=0.035$). Negative correlations with the modified Rankin and global symptoms scales did not reach significance for 32 patients having hereditary etiologies. Patients having idiopathic etiologies and an abnormal electromyography (EMG) result had lower baseline NSNIS scores than patients with normal EMG results ($p = 0.029$). The NSNIS was able to quantify polyneuropathy severity in patients with a range of sensorimotor symptoms and anatomical distributions. Patients with sensorimotor symptoms ($p = 0.015$), weakness ($p<0.001$), or loss-of-balance ($p=0.004$) had lower NSNIS scores than patients without these symptoms. The efficacies of response to modifying and symptomatic therapies were independent of baseline NSNIS scores.

Conclusions:
Our novel EMR imbedded, point-of-care neuropathy impairment scale is well suited to characterize features of polyneuropathy related to clinical signs and symptoms, severity of deficit, EMG findings and disability.

References:
No

Grant Support:

Funding support from the Agency for Healthcare Research and Quality
RO1HS024024057

Keywords: Neuropathy impairment scale, Polyneuropathy, Clinical documentation support toolkit (SCDS)

Long-read whole-genome sequencing in peripheral neurodegeneration: challenges, insights, and paths forward

Poster No:
P 316

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Introduction:
Inherited peripheral neuropathies are clinically and genetically heterogeneous disorders that still present a significant diagnostic challenge. It is tempting to suggest that there are novel causative genes, and perhaps 'non-conventional' mutational mechanisms yet to be identified. Using long-read sequencing to bridge this heritability gap seems promising, as it allows identification of variants that were previously intractable with next-generation technologies.

Methods:
We selected 15 families presenting with peripheral neuropathy that had undergone extensive analyses using short-read sequencers but remained genetically undiagnosed to date. Nanopore whole-genome sequencing was performed on 32 individuals from these families on a PromethION device using R10.4.1 flow cells. Downstream data analyses were conducted using a pipeline established in-house.

Results:
Challenges surfaced across multiple layers of the pipeline, from quality control and library preparation to downstream bioinformatic analyses, data filtering and validation of candidate disease-causing variants. These included issues related to the high-quality sample requirements of long-read sequencers from "historical" cases and the quality control process. Additionally, selecting parameters for accurate base-calling proved critical, along with combining structural variants (SVs) shared among different individuals of the same family due to ambiguous breakpoints. Our experience also highlighted the need for comprehensive SV databases for reliably downsizing the list of candidate variants. Furthermore, verification of candidate variants proved difficult, requiring tailoring of different techniques for each variant of interest.

Conclusions:
Long-read sequencing is poised to become the next paradigm-shifting tool in human genetics and will help us bridge the many heritability gaps in genetic diseases. As technologies rapidly evolve, researchers embarking on such studies face numerous challenges. Sharing experiences and knowledge among early-stage users of these tools will greatly facilitate advancement in the field, benefiting patients and researchers.

References:
No

Grant Support:

Marie Sklodowska-Curie Actions Postdoctoral Fellowship (STRIPE)
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AFM-Telethon Trampoline Grant 2023 (24894)
ABMM-Telethon Project Grant

Keywords: long-read WGS, nanopore sequencing, peripheral neurodegeneration

Efficacy of dilunisal versus tafamidis on transthyretin familial amyloid polyneuropathy and cardiomyopathy

Poster No:
P 317

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Introduction:
Transthyretin related familial amyloidosis is a lethal disease frequently complicated with polyneuropathy (FAP) and cardiomyopathy (FAC). Diflunisal is a generic nonsteroidal anti-inflammatory drug. Similar to tafamidis, it can kinetically stabilize circulating transthyretin and inhibit amyloidogenesis. However, the long-term efficacy of diflunisal on FAP and FAC, especially those with non-V30M genotypes, has not been investigated and compared with tafamidis.

Methods:
We followed up the Taiwanese FAP patients with predominant A97S mutation who regularly received diflunisal or tafamidis. Progression of polyneuropathy was evaluated by FAP stages and nerve conduction study (NCS), while progression of cardiomyopathy was assessed by 99mTc-PYP SPECT imaging, echocardiography and blood pro B-type natriuretic peptide (pro-BNP).

Results:
Thirty-five FAP patients, aged 65.0±6.0 years, receiving diflunisal and 22 patients, aged 63.1±5.9 years, receiving tafamidis were enrolled for analysis. Diflunisal significantly delayed the transition of FAP stage I to II (hazard ratio=0.43, p=0.007) and FAP stage II to III (hazard ratio=0.18; 95% confidence interval [CI], 0.08-0.43; p<0.001), and significantly decreased the reduction of ulnar compound muscle action potential amplitude (p<0.001) and the slowing of ulnar motor nerve conduction velocity in the ulnar nerves (p=0.027) compared to the historic patients without treatment. There was no obvious difference in the progression of FAP stage and NCS parameters between patients treated by diflunisal and tafamidis. Both diflunisal and tafamidis significantly decreased the volumetric heart-to-contralateral lung ratio on the 99mTc-PYP SPECT (p=0.010 and 0.007), and stabilized the interventricular septum and left ventricle posterior wall thickness on echocardiography and pro-BNP level in blood during the treatment. There were no significant adverse events during the treatment of diflunisal and tafamidis.

Conclusions:
The diflunisal treatment was effective in suppressing the progression of FAP and FAC, and was not inferior to the efficacy of tafamidis. Diflunisal may become an available, cost-effective and safe alternative treatment for late-onset FAP and FAC.

References:
No

Grant Support:

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Keywords: diflunisal, familial amyloid polyneuropathy, familial amyloid cardiomyopathy, tafamidis, transthyretin

Neuropathy Impairment and Nutritional Status With Eplontersen in Patients With Hereditary Transthyretin-Mediated Amyloidosis

Poster No:
P 319

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Introduction:
Eplontersen improved neuropathy impairment and quality of life (QoL) versus historical placebo (placebo) in patients with hereditary transthyretin amyloidosis with polyneuropathy in the NEURO-TTRansform trial. Whether these benefits were observed in patients with worsening nutritional status (modified body mass index [mBMI]) is unknown, and the subject of this secondary analysis.

Methods:
Patients from NEURO-TTRansform were categorized by treatment, by change from baseline in mBMI at Week 66 (>10% decrease; <2.5 to 10% decrease; -2.5 to +2.5% change; >2.5 to 10%; >10% increase). Change in modified Neuropathy Impairment Score+7 (mNIS+7, composite score), and Norfolk QoL-Diabetic Neuropathy (Norfolk QoL-DN) total score was evaluated.

Results:
Patients (eplontersen n=144; placebo n=60) were of mean (standard deviation [SD]) age, 54.9 (15.0) years, and 69% were male. Overall distribution of mBMI trended towards improvement for eplontersen and worsening for placebo. Across mBMI categories, eplontersen demonstrated consistent benefit on neuropathy impairment and QoL versus placebo. Mean (95% CI) differences (Week 66) in mNIS+7 scores for eplontersen versus placebo were -29.5 ([-45.5, -13.5]; mBMI >10% decrease), -17.8 ([-30.1, -5.5]; <2.5 to 10% decrease), -17.1 ([-30.8, -3.4]; -2.5 to +2.5% change), and -8.8 ([-22.9, 5.3]; >2.5 to 10% increase). For Norfolk-QoL-DN; -24.3 ([-38.4, -10.2]; mBMI >10% decrease), -14.9 ([-29.1, -0.8]; <2.5 to 10% decrease), -15.6 ([-30.8, -0.5]; -2.5 to +2.5 % change), and -2.1 ([-13.5, 9.2]; >2.5 to 10% increase).

Conclusions:
Benefits in neuropathy impairment and QoL were observed with eplontersen versus placebo, regardless of degree of mBMI change from baseline, including in patients with worsening nutritional status.

References:
No

Keywords: amyloid, ATTRv, eplontersen, polyneuropathy, transthyretin amyloidosis

Switching From Inotersen To Eplontersen In Patients With Hereditary Transthyretin Amyloidosis Polyneuropathy

Poster No:
P 320

Authors:
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Introduction:
Inotersen, a modified antisense oligonucleotide (ASO) TTR gene silencer, is approved in multiple countries for treatment of adults with hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN). The phase 3 NEURO-TTRansform study (NCT04136184/EudraCT 2019-001698-10) demonstrated that eplontersen, an investigational ligand-conjugated modified ASO TTR gene silencer, was effective and well tolerated with an acceptable safety profile in adults with ATTRv-PN treated to Week 66. We report safety and efficacy in the subset of patients in NEURO-TTRansform who switched from inotersen to eplontersen.

Methods:
NEURO-TTRansform enrolled 168 patients with ATTRv-PN. A subset of patients (n=24) received subcutaneous inotersen 300 mg weekly during Weeks 1–34 and subcutaneous eplontersen 45 mg every 4 weeks during Weeks 37–81. Safety and efficacy analyses were performed at Week 85.

Results:
Of the 24 patients randomized to inotersen, 20 (83%) switched to eplontersen at Week 37 and 19 (79%) patients remained in the study through Week 85. More adverse events were reported while receiving inotersen than following switching to eplontersen. Mean platelet counts decreased from baseline during inotersen treatment and, following the switch to eplontersen, increased to baseline levels. Mean percentage change from baseline (decrease) in serum transthyretin concentration was greater during eplontersen treatment (−81%; measured at Week 85, after switch) than inotersen treatment (−74%; measured at Week 35, before switch).

Conclusions:
In NEURO-TTRansform, patients with ATTRv-PN first treated with inotersen experienced a decrease in the incidence of adverse events, reversal of reduced platelet count, and a further reduction in serum transthyretin concentration after switching to eplontersen.

References:
No

Keywords: amyloidosis, treatment efficacy, treatment safety, antisense oligonucleotide, transthyretin

Neuropathy in V122I Hereditary Transthyretin Amyloidosis: a Brazilian Multicenter Cross-Sectional Study

Poster No:
P 321

Authors:
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Introduction:
The TTR V122I variant is classically associated to cardiomyopathy. Nerve involvement is typically considered a minor manifestation. The aim of this study: characterize a Brazilian population with the V122I.

Methods:
A national, multicenter (10 reference centers), observational, cross-sectional study. For clinical and electroneuromyographic analysis we excluded compound heterozygous carriers and individuals with comorbidities or factors that could cause neuropathy. Homozygous were analyzed separately.

Results:
We found 246 TTR V122I carriers from 84 families: 240 heterozygous, 4 homozygous, and 2 compound heterozygous (V30M/V122I and I107V/V122I). Gender distribution was similar. Age: 19 to 89 years, mean 53.4. Race: 26.7% white, 17.3% black and 56% mixed. 126 carriers were submitted to clinical and electrophysiological analysis: 122 heterozygous; 4 homozygous. Considering the heterozygous, 42.6% were symptomatic. CTS preceded by 5,3 years the onset of polyneuropathy and/or cardiomyopathy in 69,2%. Onset manifestation excluding CTS: cardiomyopathy (52,9%), polyneuropathy (37,3%) and mixt (9,8%). Mean age of disease onset: 64.8 years, 2.1 years earlier in homozygous. Follow-up: 14/27 cardiological patients developed polyneuropathy and 8/19 neurological patients developed cardiomyopathy. The mixed phenotype increased to 52.9%. Polyneuropathy: 62,2% had a sensory/sensory-motor polyneuropathy, 32,4% small fiber neuropathy and 5,4% isolated dysautonomia. Coutinho stage: 92.3% stage1 ; 7,7% stage2. Sensory symptoms-91,7%, weakness-44,4%, dysautonomia-14.3% to 54.3%, neuropathic pain-52,8%. EMG was abnormal in 50%: CTS(82%), cubital tunnel syndrome(9,8%), sensory axonal polyneuropathy(11,5%), sensory-motor axonal polyneuropathy(29,5%), CIDP-like(1,6%), multiple mononeuropathy(3,3%), radiculopathy(13,1%). CTS was bilateral in 95.8%. SSR response was absent in 17.6%, never as an isolately.

Conclusions:
The V122I variant was found in whites, blacks and mixed individuals. Neuropathy is frequent at onset, and the only manifestation in 21,6% after follow-up. CTS was the most frequent EMG finding. Cubital tunnel syndrome should be searched regularly. An axonal length-dependent symmetrical polyneuropathy predominates, although atypical patterns were seen. Greater understanding of the manifestations associated to TTR V122I is critical for earlier diagnosis and treatment.

References:
No

Keywords: amyloidosis, TTR, V122I, polyneuropathy, electroneuromyography

Peripheral Nervous System involvement in Amyotrophic Lateral Sclerosis: from diagnosis to disease understanding

Poster No:
P 322

Authors:
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Introduction:
TAR DNA-binding protein-43 (TDP-43)-positive inclusions in the brain and spinal cord are the neuropathological hallmark of amyotrophic lateral sclerosis (ALS), found in >95% of patients. The mechanism by which TDP-43 causes neurodegeneration is still unknown, with evidence supporting both a nuclear loss-of-function and a cytoplasmic toxic gain-of-function. TDP-43 positive aggregates have been recently reported in motor nerve biopsies of ALS patients. Their appearance occurs before axonal degeneration, and a relevant proportion of ALS patients displays TDP-43 aggregates not only in the axon, but also in myelinating Schwann cells (SC), suggesting the possible contribution of non-cell autonomous effects.

Methods:
To evaluate this hypothesis, we generated two new mouse models carrying an extra-copy of the wt or the A382T mutant TDP-43 inserted in the Rosa26 locus to allow conditional tissues-specific over-expression. Specific expression in SCs or motoneurons (MNs) has been obtained through the crossing with P0-Cre or ChAT-Cre mice, respectively. Mice have been analyzed from a behavioral, neurophysiological and pathological point of view at different time points.

Results:
P0-Cre/TDP43A382T mice show moderate overexpression of human TDP43 transcript in peripheral nerves. These transgenic mice display a mild progressive morphologic phenotype characterized by altered myelination, paranodal alterations and axonal degeneration, starting by 6 months of age. We did not detect behavioral and neurophysiological alterations up to 12 months. In ChAT-Cre/ TDP43A382T signs of motoneuron degeneration are visible starting at 6-months of age, accompanied by motor defects such as hindlimb clasping.

Conclusions:
Our data indicate that we have generated a new model to study the cell-autonomous role of TDP43 inclusion and that Schwann cell specific expression of a mutant form of TDP43 may contribute to axonal pathology via a non-cell autonomous mechanism.

References:
No

Keywords: Schwann cell, neurodegeneration, ALS, motoneuron

Successful Simulation of Infusion Pump Use for IgPro20 Prefilled Syringes

Poster No:
P 323

Authors:
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Introduction:
IgPro20 (Hizentra®) is a subcutaneous human immunoglobulin approved for primary immunodeficiency (PID) and chronic inflammatory demyelinating polyneuropathy (CIDP). This summative human factor evaluation study assessed the usability of IgPro20 in pre-filled syringes (PFS) using an infusion pump.

Methods:
After patients and lay caregivers received one training session, all users were asked to administer an infusion into a pad, following three scenarios: 1. Infusion of 50 ml directly from the 50 ml PFS 2. Infusion of 40 ml after transfer from a 50 ml PFS into a transfer syringe 3. Infusion of 60 ml after pooling a 50 ml and 10 ml PFS into a transfer syringe

Results:
A total of 81 users, including 17 healthcare professionals, 19 caregivers, 15 patients with CIDP, 30 patients with PID were included (caregivers/patients: n=39 experienced users, n=25 naïve users). Most of the users (n=80/81; 99%), successfully simulated the infusion with 50mL PFS; one patient (CIDP) terminated the infusion early (thinking it was complete) resulting in underdosing. Other usability-related errors (not resulting in a deviation ≥10% of the planned dose) included failure to visually check the content of the PFS (6%;n=5), incorrect attachment of the infusion tubing to the PFS (1%;n=1), incorrect insertion and securing of the PFS in the pump (10%;n=8), and errors with needle insertion (8%;n=7). The 40 ml and 60 ml transfer and infusion were successfully completed by n=71/78 (91%) of participants and n=73/78 (94%), respectively. The most observed errors were overdosing (40 ml) and underdosing (60 ml). Overall, three adverse events (needle sticks) occurred.

Conclusions:
This study shows that users can successfully administer IgPro20 in PFS using an infusion pump. Lay users, including patients with CIDP, were able to correctly administer a dose of 40 to 60 ml. Difficulties seen in the study can be addressed by providing appropriate training.

References:
No

Grant Support:

N/A

Keywords: chronic inflammatory demyelinating polyneuropathy, prefilled syringes, subcutaneous immunoglobulin

The Prevalence Of Polyneuropathy In A Community-Based Sample of Older Adults In Zambia

Poster No:
P 324

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Institutions:
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Introduction:
Polyneuropathy can be due to metabolic, nutritional, toxic, and infectious causes. In sub-Saharan Africa, where HIV prevalence is still high, non-communicable diseases are increasingly common and may be contributing to polyneuropathy. However, there is limited data regarding polyneuropathy prevalence and contributors. Therefore, we are conducting a community-based cohort study to estimate the prevalence of polyneuropathy and contributors among older Zambians.

Methods:
Adults age >55 are being enrolled from randomly selected households in two high-density communities. During household interviews by community health workers, demographics, medical history, diet, anthropomorphic measurements, HIV, and glucose testing are collected. The Single Question Neuropathy Screen, validated against the Brief Peripheral Neuropathy Screen in Zambia, is used to assess sensory polyneuropathy symptoms. All participants are then invited for examination by a neurologist to assess polyneuropathy signs. Polyneuropathy is defined as at least one distal bilateral symptom and one or more distal bilateral sign (decreased vibratory or pinprick sensation).

Results:
To date, 184 Zambians (mean age 67 yrs; 66% female, mean education 5.7 yrs) have enrolled. Mean household income was ZMW 1339 ($52/month). Fifty percent endorsed food insecurity in the past 30 days, whereas 25% drank alcohol. Twenty-four (13%) participants were HIV-positive and 9% reported tuberculosis treatment. Eight (4%) had diabetes, and an additional 14 (8%) warranted diabetes testing based on glucose fingerstick. Fifty-four (29%) had central obesity. Forty-nine (26%) endorsed polyneuropathy symptoms. Of the 50 participants that have undergone examination so far, 23 (48%) had absent/diminished Achilles reflexes, 12 (24%) had decreased distal vibration, and 7 (14%) had diminished pinprick. Ten (20%) met criteria for polyneuropathy.

Conclusions:
Polyneuropathy is common in this Zambian cohort of older adults. Characterizing the disease burden and contributors in these individuals is essential to improve our understanding of polyneuropathy risk factors in resource-limited settings and to develop context-specific preventative interventions to reduce morbidity.

References:
No

Grant Support:

NIH NIA 5P30-AG066582-03, University of Michigan African Studies Center, University of Michigan Global REACH Partnership Development Grant, American Neurologic Association- Neurologic Association of Zambia Early Career Research Grant

Keywords: epidemiology, neuropathy, diabetes, resource-limited setting, sub-Saharan Africa

Late Onset Krabbe Disease Presenting With Vocal Cord Paralysis And Non-Uniform Demyelinating Neuropathy

Poster No:
P 325

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Introduction:
Krabbe disease is an inherited autosomal recessive disease caused by deficiency of the lysosomal enzyme galactocerebrosidase. It results in progressive buildup of unmetabolized lipids that adversely affect the myelin sheath of the central and peripheral nervous system. It mainly manifests as an infantile phenotype (<12 months of age), but may also present a late onset phenotype (> 12 months of age to as late as the seventh decade of life), whose phenotype is highly variable. In this paper we report a patient whose initial manifestations were Vocal cord paralysis and an asymmetrical demyelinating neuropathy.

Methods:
We reviewed the clinical presentation, electroneuromyography (ENMG), whole exome sequencing (WES), brain and spine magnetic resonance imaging (MRI), nerve biopsy, biochemical and serological tests.

Results:
A 46-year-old woman presented at age of 32 vocal cord paresis, that was soon accompanied by progressive sensory and motor manifestations, worse at the upper limbs. The disease was progressive and in a few years the patient was wheelchair bound and gastrostomized. There was no family history, no consanguinity and no comorbidity. Nerve conduction studies showed asymmetric and severe demyelinating sensorimotor polyradiculoneuropathy with associated axonal loss. An initial panel for inherited demyelinated neuropathies was normal, and she was treated with corticosteroids and IVIg. In the absence of a response, we reinvestigated. A nerve biopsy demonstrated the presence of globoid cells. WES revealed a single nucleotide polymorphism on the GALC gene that was classified as a VUS, but an enzymatic assay of the Galactocerebrosidase activity showed reduced activity, and a new Brain MRI revealed a periventricular symmetric leukoencephalopathy, with no contrast enhancement.

Conclusions:
This patient presented atypical manifestations of the late onset Crab disease. The reverse phenotyping contributed to better characterize the spectrum of this subtype of the disease.

References:
Yes

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Keywords: Krabbe Disease, polyradiculoneuropathy, Reverse phenotyping

Leptin Signaling from Adipocytes to Schwann Cells Guides Glial Metabolic Adaptation to Enhance Regeneration Following Acute Nerve Injury.

Poster No:
P 326

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Introduction:
Nerve regeneration after acute injury can be remarkably efficient, but full functional recovery is rare for reasons that are not entirely understood. Nerve repair critically depends on Schwann cells that orchestrate break down and resynthesis of myelin and, at the same time, support axonal regrowth. How Schwann cells meet the high metabolic demand required for regeneration remains poorly understood and adequate glial metabolic adaptation may be key for successful nerve repair.

Methods:
We employ experimental nerve crush in mice to investigate the metabolic dynamics in the course of nerve de- and regeneration. In a series of conditional mutagenesis approaches we then investigate the functional relevance of leptin signaling for glial metabolic adaptation after acute nerve injury and its role for nerve repair. In detail, we abolish either leptin receptor function from Schwann cells, or leptin secretion in adult adipocytes, to study adipo-glial communication in nerve regeneration.

Results:
We found that acute nerve injury entails a strong oxidative shift in the energy metabolism of Schwann cells in the course of nerve repair. We thereby identified the adipokine leptin as an upstream regulator of glial metabolic adaptation in nerve regeneration. The integration of leptin signals by leptin receptors in Schwann cells establishes a link between injury-specific catabolic processes in regenerating nerves, including myelin autophagy and mitochondrial respiration.

Conclusions:
Our findings propose a model according to which acute nerve injury initiates a therapeutically targetable intercellular crosstalk between Schwann cells and adipocytes. This dynamic interaction modulates glial metabolism, ensuring the provision of ample energy for optimal nerve repair.

References:
Yes

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Grant Support:

DFG Emmy Noether (FL1025-1-1)

Keywords: Schwann cell, acute nerve injury, adipocyte, energy metabolism, regeneration

Eplontersen Improves Autonomic Neuropathy Symptoms in Hereditary ATTR: An Analysis From NEURO-TTRansform

Poster No:
P 327

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Introduction:
Hereditary transthyretin-mediated amyloidosis (ATTRv) with polyneuropathy (PN) commonly affects the autonomic nervous system, leading to gastrointestinal dysfunction, cachexia, and orthostasis. The NEURO-TTRansform trial demonstrated that, after 65 weeks of treatment, eplontersen significantly reduced PN impairment and improved quality of life compared with external placebo in patients with ATTRv-PN. We evaluated the degree of autonomic impairment in patients with ATTRv-PN in NEURO-TTRansform, and the impact of eplontersen on progression of autonomic impairment after 84 weeks.

Methods:
Primary endpoints included change in modified Neuropathy Impairment Score +7 (mNIS+7) composite score and Norfolk Quality of Life Diabetic Neuropathy (Norfolk QOL-DN) total score with eplontersen versus external placebo after 65 weeks of treatment. Here, a questionnaire of autonomic symptoms (COMPASS-31), nutritional status (modified body mass index; mBMI), and autonomic components of mNIS+7 and Norfolk QOL-DN were evaluated in patients treated with eplontersen 45 mg every 4 weeks, using mean (SD) at baseline and Week 81/85.

Results:
At baseline, mean (SD) [quartiles] COMPASS-31 score was 19.4 (11.3) [Q1=12.0; Q3=25.5]. In patients treated with eplontersen (n=141), at Week 81, mean (SE) COMPASS-31 score decreased by –2.6 (0.7), indicating benefit. There was an improvement in individual orthostatic intolerance (−0.6 [0.2]) and gastrointestinal (−1.2 [0.3]) domains of COMPASS-31. At Week 85, there was an increase in mean (SE) mBMI (1.3 [8.9]), and improvements in autonomic impairment components of mNIS+7 (heart rate with deep breathing: −0.2 [0.1]), and Norfolk QOL-DN (autonomic neuropathy domain: −0.3 [0.2]).

Conclusions:
Autonomic impairment was pronounced at baseline in patients with ATTRv-PN in NEURO-TTRansform. Eplontersen demonstrated benefit across multiple measures of autonomic impairment, which are known to progress rapidly without treatment and negatively impact quality of life.

References:
No

Keywords: hereditary amyloidosis, transthyretin, eplontersen, autonomic neuropathy

Neurofilament Light Chain in ATTR Amyloidosis with Cardiomyopathy: Analysis from the Phase 3 APOLLO-B study

Poster No:
P 328

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Introduction:
Transthyretin (ATTR) amyloidosis is a rapidly progressive, fatal disease, often presenting with a mixed phenotype of polyneuropathy and cardiomyopathy. Neurofilament light chain (NfL) is a biomarker of neuroaxonal damage. We assessed NfL as a potential biomarker for polyneuropathy in patients with ATTR amyloidosis with cardiomyopathy from APOLLO-B, and the effect of patisiran on NfL levels.

Methods:
APOLLO-B was a Phase 3 randomized, double-blind, placebo-controlled study of patisiran in patients with wild-type/hereditary (ATTRwt/ATTRv) amyloidosis with cardiomyopathy (NCT03997383). NfL was measured post-hoc at baseline and 12 months. Patients with PND>II were excluded. Baseline NfL was compared with age- and sex-matched healthy controls and two sets of reference values (Mayo Clinic and University of Basel). Baseline and 12-month NfL levels are presented for placebo- and patisiran-treated patients with baseline NfL greater than Mayo Clinic normal range or above 95th percentile vs University of Basel database.

Results:
236 patients had baseline NfL data and no other self-reported cause of polyneuropathy. Mean baseline NfL was significantly higher than matched healthy controls (32.0 vs 17.2 pg/mL; $P<0.05$) and similar to levels in the Phase 2 open-label extension of patisiran in ATTRv amyloidosis with polyneuropathy (NCT01961921). A substantial percentage of patients had elevated NfL vs Mayo Clinic (13.1% [ATTRwt], 46.7% [ATTRv]) and University of Basel (38.2% [ATTRwt], 60.0% [ATTRv]) reference values. Patients with elevated baseline NfL showed a trend toward numerical decrease, or less of an increase in NfL vs placebo when treated with patisiran for 12 months.

Conclusions:
Baseline NfL was elevated in patients with ATTRwt/ATTRv amyloidosis with cardiomyopathy, suggesting the potential presence of peripheral neurologic involvement. A trend toward impact on NfL was documented following patisiran treatment. As NfL can be affected by factors including renal dysfunction or concomitant conditions causing nerve damage, additional studies and extended-term data are necessary to validate these findings.

References:
No

Grant Support:

This study was funded by Alnylam Pharmaceuticals

Keywords: ATTR amyloidosis, neurofilament light chain, polyneuropathy, patisiran, APOLLO-B

Multiparametric Evaluation of the Upper Limbs in hereditary transthyretin Amyloidosis patients (the EULA multicenter project)

Poster No:
P 329

Authors:
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Institutions:
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Introduction:
Hereditary transthyretin amyloidosis with polyneuropathy (hATTR) is one of the most severe, disabling hereditary neuropathies. The project aims to collect multiparametric data regarding hand functionality using standard measurements and the engineered glove [Hand Test System (HTS)] which allows objective and quantitative evaluation of finger movements, at baseline and after 6 (T1) and 12 (T2) months in 70 patients at different stages of the disease and healthy controls (HC).

Methods:
To date, we analyzed the baseline data from forty-nine patients (F: 21; M: 28; age: 62.16±12.65) and thirty HC (F: 17; M: 13; age: 49.50± 16.80). Multiparametric evaluation is based on: HTS with 2 tasks and eyes closed [Finger-Tapping (FT) and Index-Middle-Ring- Little (IMRL) sequence]; 9-hole peg test (9-HPT); dynamometry (handgrip and tripod pinch); clinical scales [Disability of the Arm, Shoulder and Hand (DASH), Norfolk Quality of Life (Norfolk QoL) and Neuropathy Impairment Score (NIS)].

Results:
The FT and IMRL sequences showed were significantly different in patients at various disease stage and HC (FT: $P<0.01$ and IMRL: $P<0.0001$). Interestingly, the difference between stage 1 and HC in the dominant hand in finger tapping is significant ($P<0.05$), but no significant difference was observed between stages 0 and 1. Hand grip showed a statistically significant difference between the groups only in dominant hand $p<0.05$ (stage 0 and HC p=ns; stage 1 and HC $p<0.05$; stage 2 and HC $p<0.05$; stage 0 and stage 1 p=ns). The parameters of HTS significantly correlate with 9-HPT, DASH, Norfolk QoL and NIS.

Conclusions:
The results of this study support the hypothesis that HTS tests provide an accurate measurement of upper limb function in hATTR and are more sensitive to detect changes in the disease stage than standard techniques. The project is ongoing and more complete results in terms of longitudinal evaluation and follow-up are being collected.

References:
Yes

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Reference 4: Bove, Marco et al. “The effects of rate and sequence complexity on repetitive finger movements.” Brain research vol. 1153 (2007): 84-91.

Grant Support:

This work is supported by Akcea Therapeutics, Inc., a wholly-owned subsidiary of Ionis Pharmaceuticals, Inc” a Delaware corporation having an office at 2855 Gazelle Court, Carlsbad, CA 92010.

Keywords: hereditary transthyretin amyloidosis, Evaluation, quantitative measurement, accurate measurement, upper limb

Peripheral nerve injuries repair using a tissue-engineered nerve conduit in a rabbit model

Poster No:
P 330

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Introduction:
Peripheral nerve injuries are a significant concern in the medical field, due to their potential to cause long-term disability. The autograft is considered the best surgical intervention for peripheral nerve repair. However, it causes morbidity at the donor site and recovery from larger gap injuries remains challenging. The alternative is to use nerve conduits to guide axonal migration, but these have several clinical limitations. Aim : Our study aims to create a living tissue-engineered nerve tube in which a capillary network will be developed in vitro by seeding endothelial cells. Such a nerve tube will be able to quickly connect to the host's vasculature and accelerate the graft vascularization, which is crucial in supporting axonal migration over long distances.

Methods:
The nerve conduit is made of a living rolled fibroblast sheet that can be seeded with endothelial cells to stimulate the creation of a network including capillary-like structures. Nerve conduits were transplanted for 1 year into immunodeficient New Zealand rabbits to bridge a 4 cm peroneal nerve defect. Electrophysiologic studies were performed in all animals to evaluate the nerve conduction and the muscular activity. The Toe spread reflex (TSI) was used as an indicator of onset of motor recovery in the peroneal nerve-dependent muscles.

Results:
The nerve conduction analysis in the tibialis anterior muscle revealed that nerve recovery had started around the 18th week. The electromyogram showed a return of muscle activity around the 24th week for the autografts. By 36 weeks, an improvement in TSI indicated partial recovery of motor function in rabbits with autografts ($p<0.05$). An onset recovery was also observed in the nerve conduit group.

Conclusions:
Our approach to developing a pre-vascularized living nerve conduit that could significantly accelerate graft vascularization could be a promising new clinical option for repairing major injuries (> 3 cm).

References:
Yes

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Keywords: Peripheral nerve injuries, tissue engineering, peripheral nerve repair, nerve conduit

Fibrin-based Delivery of Hedgehog Pathway Modulators During Nerve Repair in Mouse Models of Nerve Injury

Poster No:
P 331

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Institutions:
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Introduction:
Fibrin gel is a hydrogel composed of fibrinogen and thrombin, and several formulations are approved by the FDA as hemostatic agents. Fibrin gels are commonly used during surgical nerve repair as a reinforcing adhesive. In addition to hydrogels, fibrin may potentially serve as a substrate for 3D bioprinted nerve conduits for nerve gap repair. Thus, fibrin is a versatile biomaterial that may be used either as a hydrogel or as a substrate for 3D printed conduits. The Hedgehog (Hh) signaling pathway is known to play a critical role in peripheral nerve injury and regeneration, with Sonic hedgehog expression marking injury-responsive Schwann cells after nerve injury and Hh pathway agonists inducing the repair phenotype in cultured Schwann cells. However, as a powerful morphogen, the broad biological functions of Hh signaling make systemic Hh pathway activation unattractive as a therapeutic strategy.

Methods:
We have previously discovered that a potent Hh pathway agonist binds to fibrinogen and can be released from fibrin gel in vitro and in vivo. In addition to fibrin gel, we also developed a preliminary gelatin methacryloyl (GelMA)-fibrin conduit that can be used for repair of a sciatic nerve gap injury in mice.

Results:
Thus, we can deliver Hh pathway agonists via several methods and employ fibrin-based drug delivery in different degrees of peripheral nerve injury.

Conclusions:
We describe the in vivo and in vitro effects of fibrin-based Hh-pathway agonist delivery using both a hydrogel and a preliminary 3D printed GelMA-fibrin conduit.

References:
No

Keywords: peripheral nerve injury, Hedgehog pathway, fibrin-based drug delivery, 3D bioprint

Neurophysiological study of the maturation of the peripheral nervous system of Wistar rats

Poster No:
P 332

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Introduction:
Background: Peripheral nerve conduction studies are frequently used in experimental animal models and clinical evaluations of humans. Standardization of nerve conduction parameters during maturation is of great importance in experimental studies of early-onset neuropathies and in experiments involving myelin/myelination.

Methods:
Objective: To study the maturation of nerve conduction of tail and sural nerves of Wistar rats. 20 Wistar rats (20 grams – 300 grams) were studied from the second week of life (10 days). Nerve conduction studies were performed with a commercial equipment. Latency was measured from the stimulus artifact to the initial negative deflection, while amplitude was measured from the baseline to the negative peak.

Results:
Result: The study showed that conduction velocity of the sural and caudal sensory nerves increased progressively from the initial study (14.01±2.68 m/s and 17.91±3.67 m/s), tending to stabilize around the 11th week of age, with a mean and standard deviation of 46.7± 3.46 for the sural nerve and 44.42±3.13 for the caudal nerve.

Conclusions:
Conclusion: According to our findings, sensory nerve conduction of wistar rats is completely stablished at the age of 11 weeks, suggesting myelination has been competed at this age.

References:
Yes

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Keywords: MYELINATION ONSET, NERVE CONDUTION STUDY, WISTAR RAT

PMP2 Regulates Myelin Thickening and ATP Production During Remyelination

Poster No:
P 333

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Introduction:
It is well established that axonal Neuregulin 1 type 3 (NRG1t3) regulates developmental myelin formation as well as EGR2-dependent gene activation and lipid synthesis. However, in peripheral neuropathy disease context, elevated axonal NRG1t3 improves remyelination and myelin sheath thickness without increasing Egr2 expression or activity, and without affecting the transcriptional activity of canonical myelination genes. Surprisingly, Pmp2, encoding for a myelin fatty acid binding protein, is the only gene whose expression increases in Schwann cells following overexpression of axonal NRG1t3. The purpose of this study is to clarify the function of PMP2 upregulation downstream of NRG1t3-mediated hypermyelination during development and remyelination.

Methods:
We generated mice overexpressing NRG1t3 and knocked out for Pmp2 (Pmp2-/-;NRG1t3OE). We utilized nerve crush surgery as a remyelination model, and measured mouse sciatic nerve morphology, electrophysiology, and molecular pathways during development and remyelination. We also used a fluorescent fatty acid analogue to quantify fatty acid uptake, and a Seahorse analyzer to measure ATP production in the Pmp2-/-;NRG1t3OE mouse sciatic nerves during development and remyelination.

Results:
Here, we demonstrate PMP2 expression is directly regulated by NRG1t3 active form, following proteolytic cleavage. Then, using the Pmp2-/-;NRG1t3OE mouse model, we demonstrate that PMP2 is required for NRG1t3-mediated remyelination. We demonstrate that the sustained expression of Pmp2 in NRG1t3OE mice enhances the fatty acid uptake in sciatic nerve fibers and the mitochondrial ATP production in Schwann cells.

Conclusions:
In sum, our findings demonstrate that PMP2 is a direct downstream mediator of NRG1t3 and that the modulation of PMP2 downstream NRG1t3 activation has distinct effects on Schwann cell function during developmental myelination and remyelination.

References:
No

Grant Support:

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Keywords: NRG1t3, PMP2, FABP8, Schwann cell, Myelin

The role of the redox environment in wound-induced axon degeneration.

Poster No:
P 334

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Introduction:
In the United States, millions of people suffer from axon degeneration due to injury or disease. Restorative treatments are not available yet and the identification of new molecular pathways for therapeutics development will be critical. Axon degeneration in the CNS has been linked to the production of reactive oxygen and nitrogen species (ROS/RNS) in damaged neurons. Here we hypothesized that ROS/RNS also induce the degeneration of peripheral cutaneous sensory axons following tissue injury, and that ROS/RNS inhibition delays axon degeneration.

Methods:
We used zebrafish for pharmacological and genetic manipulations in combination with in vivo time-lapse imaging.

Results:
We show that the ROS, superoxide, but not hydrogen peroxide, promotes axon degeneration following injury. To assess whether superoxide is contributes to RNS formation, we treated fish with the nitric oxide synthase inhibitor, L-NAME, and this delayed degeneration, indicating that RNS are critical. To further establish the source of superoxide, we analyzed axon degeneration in cyba-/-. These mutants lack the functional NADPH oxidase subunit, P22phox, which delayed axon degeneration upon injury. This mutant also has NADPH accumulation, we further elevated NADPH level in injured zebrafish and it displayed delayed axon degeneration, suggesting that NADPH can serve as a ROS scavenger to delay axon degeneration.

Conclusions:
Our study employing zebrafish, pharmacological interventions, and genetic manipulations, reveals a pivotal role of ROS, specifically superoxide, in promoting axon degeneration post-injury. By inhibiting nitric oxide synthase with L-NAME, we established the significance of RNS in degeneration. The investigation of cyba-/- mutants lacking the P22phox subunit of NADPH oxidase corroborated the involvement of superoxide and NADPH. Elevating NADPH levels in injured zebrafish delayed axon degeneration. This study provides insights into the intricate mechanisms underlying axon degeneration and NADPH may be a valuable therapeutic for neurodegenerative diseases.

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Yes

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Keywords: axon degeneration, ROS/RNS, NADPH oxidase

Efficacy and safety of patisiran for ATTR-PN: a systematic review and meta-analysis

Poster No:
P 335

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Introduction:
Transthyretin amyloid polyneuropathy (ATTR-PN) is a rare, progressive and fatal autosomal dominant disorder. Therapies such as liver transplantation and TTR stabilizations have limitations. Patisiran is a small interfering RNA (siRNA), offering potential as a genetic-level therapy for ATTR-PN. However, evidence on patisiran's efficacy and safety for ATTR-PN remains limited.This study aimed to further clarify patisiran's efficacy and safety for ATTR-PN by meta-analysis.

Methods:
After literature searches in PubMed, Ovid MEDLINE, Embase, JBI EBP, Cochrane and ClinicalTrials.gov databases on June 7, 2023, 10 studies with 463 patients were included and clinical data were extracted.

Results:
Results showed an 89% (95% CI 82–96%) pooled responsiveness rate. The standardized mean difference (SMD) of mNIS+7 scores was -0.18 (95% CI -0.32 – -0.03, p-value 0.018) and Norfolk QOL-DN was -0.23 (95% CI -0.38 – -0.09, p-value 0.001). 404 adverse events (AEs) (90.4%), 152 serious AEs (SAEs) (34.0%) and 33 deaths (7.4%) were recorded. Most of AEs were mild to moderate. No deaths were attributed to patisiran.

Conclusions:
In conclusion, patisiran was effective and safe for ATTR-PN patients. More large-scale clinical trials and long-term studies are necessary to further validate its efficacy and safety

References:
No

Grant Support:

Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX01),and ZJLab

Keywords: Meta-analysis, Patisiran, Systematic review, Transthyretin amyloid polyneuropathy

Electrophysiological and pathological correlates of hereditary transthyretin amyloidosis

Poster No:
P 336

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Introduction:
Although hereditary transthyretin (ATTRv) amyloidosis is considered an axonal neuropathy, some patients exhibit decreased nerve conduction velocities and prolonged distal motor latencies, mimicking chronic inflammatory demyelinating polyneuropathy. To clarify this discrepancy, we investigated the correlation between electrophysiological and pathological findings in patients diagnosed with ATTRv amyloidosis.

Methods:
We analyzed the electrophysiological and pathological findings of sural nerve biopsy specimens from 45 patients with ATTRv amyloidosis. Motor and sensory conduction were measured in the median, ulnar, tibial, and sural nerves. The density of myelinated fibers was assessed in toluidine blue-stained semithin sections using a computer-assisted image analyzer. A fraction of the glutaraldehyde-fixed sample was processed for the teased-fiber study, and pathological conditions were microscopically assessed. The results were then compared with data obtained from 96 patients diagnosed with nutritional/alcoholic neuropathy.

Results:
Slowing of conduction velocities and prolongation of distal motor latencies correlated significantly with myelinated fiber loss in ATTRv amyloidosis and nutritional/alcoholic neuropathy. However, the slope of the regression line was considerably more pronounced in ATTRv amyloidosis compared to nutritional/alcoholic neuropathy. Teased-fiber preparations revealed openings in consecutive nodes of Ranvier, suggesting secondary demyelination due to axonal damage. In addition, patients with ATTRv amyloidosis occasionally exhibited demyelination at sites adjacent to the amyloid deposits.

Conclusions:
In patients with ATTRv amyloidosis, mechanisms other than axonal damage may be involved in the slowing of nerve conduction velocities and prolongation of distal motor latencies.

References:
No

Keywords: amyloid, amyloidosis, ATTRv amyloidosis, transthyretin

Nerve Wrap For Local Delivery Of Tacrolimus Accelerates Nerve Regeneration By Modulating Schwann Cell Activity

Poster No:
P 337

Authors:
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Introduction:
Peripheral nerve injuries (PNI) frequently result in functional disabilities. We previously demonstrated improved functional recovery using a novel Tacrolimus/FK506-impregnated Polyester urethane urea (PEUU) nerve wrap to treat PNI in a validated rat infraorbital nerve (ION) transection and repair model. With PEUU-FK506 treatment, FK506 blood levels measured at the lower limit of quantification. This study investigates the neurotrophic properties of PEUU-FK506 upon myelin and axonal neurofilament dynamics in our sensory nerve model.

Methods:
Twenty-four 8–10-week-old Lewis rats underwent surgical PNI and repair, before assessing ION afferent function. Treatment-groups included: cut & repair only, intraperitoneally (IP) injected 2.2mg/kg/day FK506, or 0.02%(w/v) PEUU-FK506 wrap (n=2-4/group). Animals were euthanized and IONs were dissected at four and six weeks postoperatively. ION samples of naïve rats served as controls. Each ION sample was immunolabelled with anti-neurofilament medium chain (NFM-FITC), anti-myelin (myelin-TRITC), and nuclei were stained with DAPI. Samples were imaged with confocal microscopy and fluorescence intensity was measured using ImageJ software. Comparative statistics on pooled intensity/treatment was performed using GraphPad Prism.

Results:
In the ION of naïve animals, myelin expression was greater compared to NFM ($P<0.01$). Both cut & repair and IP-FK506 groups exhibited greater NFM expression compared to myelin ($P<0.01$) and reduced myelin signal as compared to naïve controls ($P<0.01$). Conversely, PEUU-FK506 treatment increased the ratio of myelin:NFM, albeit not significantly. With PEUU-FK506 treatment, Schwann cell myelin expression was higher compared against both cut & repair and IP-FK506 treatments ($P<0.01$), but this increase was not significant when compared to naïve ($P=0.55$).

Conclusions:
Myelination in the proximal stump was greater in PEUU-FK506 treated IONs compared to IP-FK506 treatment up to 6-weeks following transection and neurorrhaphy. Site-specific delivery of Tacrolimus to PNI sites with a PEUU-FK506 wrap increases differentiated Schwann cell myelination, accelerating functional outcome. This modality holds promise for nerve regeneration and local immunosuppression in composite tissue allotransplantation.

References:
Yes

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Keywords: Vascularized Composite Allotransplantation, Tacrolimus, Neuroregeneration, Schwann Cell, Immunosuppression

Non Systemic Peripheral Nervous System Vasculitis: A Brazilian Case Series

Poster No:
P 338

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Introduction:
Nonsystemic vasculitis of the peripheral nervous system (NSVPNS) is a rare form of single-organ vasculitis that is considered difficult to diagnose, posing a challenge for physicians since incorrect diagnosis can lead to irreversible nerve damage and high morbidity complications for patients. Due to its rarity, most studies on the disease are limited to individual case reports or small case series. The present study aims to analyze this condition's most extensive case series in the Brazilian population, describing its clinical, diagnostic, and prognostic characteristics.

Methods:
In the sample, patients diagnosed with NSPNSV confirmed through nerve biopsy (with histopathological findings of definite, probable, or possible vasculitis) according to the guidelines of the Peripheral Nerve Society will be included. Patients showing evidence of systemic vasculitis or secondary vasculitis will be excluded from the study. The evaluation criteria will be a clinical examination (pattern of peripheral nerve damage, degree of impairment, presence of neuropathic pain), Electroneuromyography (EMG), nerve biopsy findings, and type and response of treatment.

Results:
Fourteen patients were included. The mean age was 61 years, and it was mainly composed of women (9:5). Most patients presented with subacute complaints and a pattern of mononeuritis multiplex on examination with asymmetrical axonal degeneration on EMG. One patient showed prominent involvement of cranial nerves, a finding never described in NSVPNS. Two patients had definite vasculitis criteria on histological examination. All but one patient complained of neuropathic pain, and all patients showed partial response to immunosuppressive treatment. All patients had residual deficits, primarily chronic pain.

Conclusions:
NSPNV is a rare condition that has a frequently late diagnosis due to its difficulty, even for centers that perform nerve biopsy, and is responsive to immunosuppressive treatments in most cases. Efforts must be made to shorten the delay from initial symptoms to the start of treatment.

References:
No

Keywords: Non-systemic Peripheral Nervous System Vasculitis, Vasculitis, Neuropathic pain

FOSMN syndrome(Facial Onset Sensorimotor Neuronopathy): A Case Series review and Comparative Analysis with Bulbar Onset ALS

Poster No:
P 339

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Introduction:
Facial onset sensory and motor neuronopathy (FOSMN) syndrome is a rare neurological condition, with only about 100 cases since its initial description in 2006. However, its exact prevalence, clinical courses, etiology and pathognomonic findings remains unknown to date.

Methods:
In this retrospective study, we analyzed four cases of FOSMN identified from a motor neuron disease (MND) cohort between April 2017 and October 2023. We conducted an in-depth review of each patient's medical history. For eligible patients, MRI, laboratory tests, genetic testing, and CSF analysis were performed. To understand FOSMN's distinctive features and patterns, we compared these cases with patients diagnosed with bulbar onset ALS during the same period.

Results:
The onset age for FOSMN patients ranged from 57 to 74 years, with 50% of females. The most frequently initial symptoms were facial paresthesia and numbness. Additionally, patients experienced progressive symptoms, including facial fasciculation, dysarthria, difficulties in mastication, facial palsy, dysphagia, and limb weakness. Despite immunotherapy, all patients showed relentless disease progression. Three patients required gastrostomy. Two patients expired 41 and 58 months after symptom onset, respectively. The onset and diagnosis age for FOSMN and bulbar onset ALS patients were similar. However, the time from symptom onset to diagnosis was much longer for FOSMN patients, indicating more insidious progression in FOSMN. At diagnosis, FOSMN patients had lower ALSFRS-R scores, suggesting more advanced disease severity in FOSMN compared to bulbar onset ALS. Notably, FOSMN patients had longer periods both from diagnosis to gastrostomy and tracheostomy or death, suggesting slower disease progression and potentially extended survival in FOSMN.

Conclusions:
This case series was the first reported FOSMN in Korea, detailing its frequency in the MND cohort and comparing clincial data with bulbar onset ALS. These findings enhance our understanding of FOSMN's pathogenesis and broden the spectrum of motor neuron disorders.

References:
No

Keywords: Facial Onset Sensorimotor Neuronopathy, Amotrophic lateral sclerosis, Motor neuron disease, Bulbar onset ALS, FOSMN

Regrowing Axons Through Local Growth Cone Manipulation: Roles Of Rac1, ERM Proteins And PTEN

Poster No:
P 341

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Introduction:
Manipulation of local of growth cone (GC) biology during adult axon regeneration is a largely unexplored strategy, despite substantial translational importance. Sensory neuropathies may benefit from an approach that encourages GC advancement within the skin.

Methods:
Using in vitro then in vivo models, we investigated roles and collaboration among Rac1 GTPase, its partnering ERM (Ezrin, Radixin and Moesin paralogous proteins) and PTEN (phosphatase and tensin deleted on chromosome ten protein) in adult sensory neuron regeneration.

Results:
Using immunohistochemistry and qRT-PCR we confirmed expression of both Rac1 and ERM in adult rat sensory neurons with rises in Rac1 mRNA ipsilateral to an axotomy injury. Rac1 was also expressed within intraganglionic axon branches ipsilateral to axotomy and within complex growth cones at sites of nerve transection. Rac activation using EGF (epidermal growth factor) was confirmed and generated rises in neurite outgrowth and branching in vitro in both naïve and previously axotomized adult sensory neurons. In axotomized neurons, a Rac inhibitor abrogated heightened outgrowth. Direct Rac1 activation of adult GCs also facilitated both attractive turning and advancement. Phosphorylated ezrin was identified in growth cone tips and ezrin knockdown by siRNA inhibited Rac1 growth indicating a previously undocumented role for ERM proteins in Rac1 support. PTEN inhibition, an approach that disinhibits the PI3K/pAkt growth pathway, added to Rac1 induced neurite outgrowth in vitro especially in naïve uninjured neurons. In vivo regeneration indices in mice including electrophysiological recovery, return of sensation, walking, repopulation of myelinated axons and reinnervation of the target epidermis indicated benefits of locally applied Rac1 activation.

Conclusions:
These indices suggested maximal local GC activation whereas local PTEN inhibition offered only limited added improvement. Our findings provide support for the concept of manipulating adult GCs, by emphasizing local Rac1 activation in directing therapy for axon regrowth.

References:
No

Grant Support:

Canadian Institutes of Health Research

Keywords: nerve regeneration, growth cones, axon regeneration, Rac1, ERM and PTEN, Rac1 activation

Nonglial cells of human peripheral nerves: unsung players of nerve regeneration?

Poster No:
P 345

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Introduction:
Our understanding of injury-driven Schwann cell (SC) reprogramming is based, almost entirely, on rodent models of nerve damage. To learn whether similar changes occur in human SCs, we analyzed intact and injured nerve tissues collected as part of a nerve transplantation clinical trial for Parkinson's disease.

Methods:
We performed bulk and single nuclei (sn) RNAseq, proteomics, and immunohistochemistry analysis of donor-matched nerve tissues (surgical remains) from subjects undergoing experimental axotomy. Most specimens were harvested within 1-2 weeks after nerve transection.

Results:
We found histochemical evidence of myelin phagocytosis, downregulation of myelinating SC-associated genes and increased expression of NGFR, a marker of repair, injury-activated SCs, in transected nerves. Yet, myelin degradation was incomplete and SC numbers did not increase in response to the injury. Surprisingly, the injury promoted dramatic changes, including proliferation, in assorted NGFR+/S100B-/SOX10- cells, herein referred to as nonglial cells, located in all connective tissue layers and surrounding the blood vessels. Similar to SCs, these nonglial cells reacted to the injury by strongly upregulating NGFR in their respective compartments. Data from snRNAseq analysis showed no evidence of transcriptional reprogramming or cell cycle re-entry in the SC groups. However, heterogeneous S100B-/SOX10- nonglial cells fully reprogrammed their transcriptome after injury concomitant with an increase in the expression of key mesenchymal stem cell genes (e.g., PDGFRA, EGFR, THY1, PRRX1, and TWIST1/2) and the activation of epithelial-to-mesenchymal transition and extracellular matrix remodeling pathways. These observations were confirmed by proteomics and RNAseq (bulk) analysis in sural nerve samples from various donors.

Conclusions:
Our studies indicated complex cellular and molecular changes in injured human nerves and an unexpected contribution of nonglial, mesenchyme-like cells to the injury response. Future studies will address the identification of the reprogrammable nonglial cells and their role in nerve regeneration.

References:
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Grant Support:

Ann Hanley Neuroscience Fund (University of Kentucky)
NEU STAR, Department of Neurosurgery (University of Kentucky)
BRAIN Alliance (University of Kentucky)

Keywords: Peripheral nerve, Schwann cells, Transcriptomics, human tissues

Vitamin D levels do not correlate with severity of idiopathic peripheral neuropathy

Poster No:
P 346

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Introduction:
Low levels of vitamin D have been associated with peripheral neuropathy (PN) in patients with diabetes and with some forms of chemotherapy-induced neuropathy. The role of vitamin D in idiopathic PN is unknown.

Methods:
We included 326 patients with idiopathic PN and 77 patients with diabetic PN enrolled in the Peripheral Neuropathy Research Registry (PNRR) who had a complete dataset including a plasma vitamin D level. We performed chi-squared, Kruskall-Wallis, and logistic regression of vitamin D insufficiency with the reduced total neuropathy score (TNSr) and demographic variables and mixed linear regression of vitamin D levels with TNSr controlling for demographic variables.

Results:
Twenty-six of 326 patients (8%) with idiopathic PN were vitamin D insufficient (<20 ng/mL). Patients with vitamin D insufficiency were younger (Age: normal 63 [54-71] v. insufficient 52.5 [42-63], median [IQR], $p < 0.01$). TNSr was not different in patients who had vitamin D insufficiency (normal 6 [4-9] v. insufficient 5 [3-10], median [IQR], $p = 0.6$). Patients with vitamin D insufficiency were more likely to have neuropathic pain (normal 70% v. insufficient 88% $p = 0.04$), though this did not remain significant after correction for covariates. Vitamin D levels were not correlated with TNSr in multiple linear regression (correlation coefficient 0 ± 0.01, $p = 0.8$). Patients with idiopathic PN were less likely than patients with diabetic PN to be vitamin D insufficient (idiopathic 8% v. diabetic 20%, $p < 0.01$).

Conclusions:
Among patients with idiopathic peripheral neuropathy, vitamin D levels do not correlate with the severity of the neuropathy or the presence of neuropathic pain.

References:
No

Grant Support:

Funding for the PNRR is provided by the Foundation for Peripheral Neuropathy.

Keywords: Neuropathy, Vitamin D

Profiling of Schwann Cell Subtypes in Sural Nerve Biopsy in Different Types of Neuropathies

Poster No:
P 347

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Introduction:
In the peripheral nervous system, Schwann cells (SCs) are the major glial cells that are required to promote peripheral nerve regeneration and restoration of function following trauma or disease. However, recovery is mostly suboptimal and disability is common. We aimed to understand the injury response profile of SCs in different types of neuropathies.

Methods:
Fifty-three neuropathy patients, 13 with vasculitis (age 61±10), 12 with chronic axonal neuropathy without inflammation (age 63±14), 14 with demyelinating neuropathy without inflammation (age 65±9) and 14 with demyelinating neuropathy with inflammation (age 56±14) to nerve biopsy findings, were included to the study. Twenty-µm sections of sural nerve were double-labelled with S100 and p16/Ki67/Sox2 antibodies and visualized in an inverted DMi8 thunder microscope (Leica). Gene expression levels of p16/Ki67/SOX2 markers were evaluated by quantitative PCR in 26 patients.

Results:
Manual counting in photomicrographs revealed that number of SCs in vasculitis was significantly decreased compared to the other groups. In this group, Ki67+ regenerating SCs tended to be the predominant SC subtype while the numbers of p16+ senescent SCs were significantly lower compared to demyelinating neuropathy. In chronic axonal neuropathy, numbers of Ki67+ SCs were lower than in the other neuropathy groups, while SOX2+ repairing SCs were higher compared to vasculitis and demyelinating neuropathy without inflammation. In demyelinating neuropathy without inflammation, p16+ SCs were in more numerous than Ki67+ SCs. PCR analysis showed that Ki67 mRNA levels were higher in vasculitis compared to other groups, which was attributed to Ki67 positive inflammatory cells in nerve sections shown by immunolabeling with CD68, CD3 and CD8 markers in addition to Ki67 and S100b.

Conclusions:
In vasculitis, loss of SCs may impair the regenerative processes causing severe axonal loss and disability. Addressing senescence in SCs may be a new target in treatment of neuropathies, particularly in neuropathies with long disease duration and demyelination.

References:
Yes

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Grant Support:

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Keywords: Schwann cells, Senescent Schwann cells, Repair Schwann cells, Proliferating Schwann cells, Nerve biopsy

Prevalence and Clinical Characteristics of Patients with Transthyretin Amyloidosis in the United States and Japan

Poster No:
P 348

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Introduction:
Transthyretin (ATTR) amyloidosis is a clinically heterogeneous and ultimately fatal disease. Recently, diagnostic and therapeutic advances have led to much greater awareness in clinical practice. The purpose of this analysis was to describe the epidemiological and clinical characteristics of patients diagnosed with ATTR amyloidosis in the USA and Japan.

Methods:
OverTTuRe is a multi-country study generating real-world evidence on patients with ATTR amyloidosis. Data for the USA cohort were extracted from the Optum's de-identified Clinformatics® Data Mart Database (2017-2022), and from the Medical Data Vision Database (2014-2022) for the Japanese cohort. The study population included patients aged ≥18 years with a reported ICD-10 diagnosis code for ATTR amyloidosis.

Results:
We identified 20,452 patients from the USA (median age 75 years; 48.8% males) and 12,072 from Japan (median age 73 years; 53.3% males). Between 2017 and 2022, there has been 100% and 97.3% increase in the recorded number of patients with ATTR amyloidosis in the USA and Japan. The most common cardiac comorbidities were hypertension (USA: 80.4%; Japan: 34.5%), arrythmia (39.7%; 23.4%) and heart failure (33.8%; 41.4%). Diabetes mellitus (36.6%; 22.5%), chronic kidney disease (stages III-V) (26.0%; 4.4%) and gastrointestinal dysfunction (18.5%; 17.6%) were the most frequent non-cardiac comorbidities.

Conclusions:
This study showed a remarkable and similar increase in patients diagnosed with ATTR amyloidosis in two countries. The results highlight substantial cardiac and non-cardiac comorbidities, stressing the importance of increased awareness to support early diagnosis and treatment to prevent disease progression and premature death.

References:
No

Keywords: Transthyretin amyloidosis, Heart failure, Arrythmia, Renal failure, Gastrointestinal dysfunction

Disease Progression In A Cohort Of Hirayama Disease

Poster No:
P 349

Authors:
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Institutions:
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Introduction:
BACKGROUND- Hirayama disease (HD) is a rare, monomelic amyotrophy involving from pure motor lower motor neuron type of weakness involving unilateral or asymmetric bilateral forearms and hands. The weakness stabilises usually within initial few years. AIM: We aim to assess the frequency of HD in patients presenting with focal upper limb amyotrophy and to assess factors contributing to disease progression.

Methods:
It is a single centre prospective observational study planned between November 2022 to November 2024. All patients presenting to our outpatient department fulfilling the inclusion criteria will be enrolled and assessed every 6 months. Motor system examination with modified MRC scale, dynamometry and functional scales (ONLS, MMN RODS, ALS FRS) are applied to assess patients periodically every 6 months. The first follow up is done for 12 patients till now.

Results:
70 patients presenting with focal upper limb amyotrophy were screened and 40 patients (83%) met the inclusion criteria. Males were 95% with mean age of 23.5 years (SD 7.925) and mean age of symptom onset 19.7years (SD 6.89). The symptoms started in left upper limb in 42.5% and right upper limb in 40% with eventual asymmetric bilateral involvement in 72.5%. Family history was positive in 2 patients.75% of the patients were found to be historical progressors at the time of enrolling. Mean baseline scores of ONLS, MMN RODS, ALS FRS were 1.875(SD 0.607), 37.72(SD 8.54), 46.35(SD 1.46). The mean power in worst limb by manual and digital dynamometry were 30.16 (SD 24.4) and 30.165 (SD 22.5) pounds respectively. The disability was mild in 77.5% and severe in 2.5%.

Conclusions:
HD should be considered in the differentials of focal upper limb amyotrophy especially in young Asian males. Factors affecting progression of disease is crucial to identify patients for any planned surgical intervention.

References:
No

Keywords: Focal amyotrophy, Hirayama

TREM2 Regulation Of Spinal Cord Microglia, Motoneuron Fate, And Functional Recovery Following Peripheral Nerve Injury

Poster No:
P 350

Authors:
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Introduction:
Motoneuron degeneration and loss of fine motor control are common hallmarks in patients recovering from Peripheral Nerve Injuries (PNI). Depending on PNI severity motoneurons die to varying degrees. Additionally, in severe cases of PNI, proprioceptive afferent information does not reach the spinal cord ventral horn motor circuits, resulting in abolition of stretch reflexes and loss of fine movement control. The loss of motoneurons and altered stretch reflex circuitry limit a patient's ability for full functional recovery following nerve regeneration and muscle reinnervation. Therefore, identification of mechanisms that govern selective motoneuron loss and spinal circuitry alterations following PNI is crucial for therapeutic advancement and may have implications for other motoneuron pathologies. We hypothesize they are related to spinal cord neuroinflammation triggered after PNI, more specifically to microglia activities.

Methods:
We utilize a mouse model of PNI with genetic alterations, immunohistochemistry/microscopy, electromyography, and behavioral experiments to investigate microglia's role in functional recovery after PNI.

Results:
Following PNI, spinal cord microglia proliferate, migrate, and surround motoneuron somas where they scan the motoneuron surface using dynamic filopodia. We observed different microglia morphologies and interactions with motoneurons depending on whether the motoneuron is regenerating or degenerating. Our evidence suggests that microglia receptor, Triggering Receptor Expressed on Myeloid Cells-2 (TREM2), is differentially upregulated in microglia that associate with regenerating motoneurons compared to microglia around dying motoneurons. TREM2 levels correlate with increases in the phagocytic marker, CD68, and therefore may be associated with synapse removal and/or degenerating motoneuron removal. Using a global TREM2 knockout, we investigate TREM2's role in microglia activation and response to PNI-induced motoneuron cell death, proprioceptive afferent synapse loss (labeled with the specific marker VGluT1), and functional recovery.

Conclusions:
Our results provide novel insights about the regulation of microglia function around injured motoneurons and suggest possible therapeutics to increase motoneuron survival, and circuitry preservation in pathological conditions.

References:
No

Grant Support:

F31 NIH NINDS awarded to Tana Pottorf (F31NS130993-01A1)
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R01 NIH NINDS awarded to Francisco Alvarez (R01NS111969-04)

Keywords: Motoneuron degeneration, Stretch Reflex, Peripheral Nerve Injury, Microglia, Neuroinflammation

Lengthy, Unrecognized Lipomatosis of Nerve Causing New, Severe Ulnar Neuropathy In An Older Adult

Poster No:
P 351

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Introduction:
Lipomatosis of nerve are tumor-like enlargements from fibrous and adipose infiltration of epineurium and perineurium. They typically affect the median nerve at the wrist/palm, are noticed in the first decade, and are associated with tissue overgrowth in two-thirds of cases. Ulnar affection, lengthy involvement, and unrecognized adult onset are rare.

Methods:
Review of clinical, electrophysiologic, imaging, and intra-operative photography findings.

Results:
A 63-year-old right-handed male presented with 18 months of progressive left hand weakness and paresthesias. Prior evaluations suggested ulnar neuropathy at the elbow. 12 months before presentation, exploratory surgery intra-operative photographs showed a 10 mm diameter thickened ulnar nerve along the exposed segment. Ulnar nerve transposition and Guyon's canal release was attempted 4 months later. Following surgery, paresthesias transitioned to fixed numbness of digits 4/5. Examination showed left-sided atrophy and weakness of ulnar-innervated hand and forearm muscles; sensory loss over digits 4/5; a palpable mass medial to the elbow extending several centimetres; and no tissue overgrowth. Electromyography showed a severe, chronic left ulnar neuropathy at or proximal to the branch to flexor carpi ulnaris. MRI neurography showed thickening of the left ulnar nerve along the visualized segment from the distal upper arm to wrist with hypertrophy of intervening fat compatible with lipomatosis. Mild thickening and increased T2-signal at the level of the transposition suggested superimposed neuroma in continuity. PMP22 duplication/deletion testing, rheumatologic studies, and ganglioside antibodies were unremarkable.

Conclusions:
Lengthy lipomatosis is an atypical presentation of a new, severe ulnar neuropathy in an older adult. Differential diagnosis includes benign and malignant nerve tumors, inflammatory neuropathies, and post-traumatic neuromas. The MRI appearance is pathognomic with T1-weighted imaging demonstrating low intensity, tubular structures representing individual nerve fascicles surrounded by high signal fat within the nerve. No surgical management is available and attempts at surgical correction may lead to further injury.

References:
No

Grant Support:

N/A

Keywords: Ulnar neuropathy, Lipomatosis of nerve, Lengthy lipomatosis, MRI neurography

Neurophysiological Assessment of Patients with Hereditary TTR Amyloidosis: Experience from an Irish Tertiary Centre

Poster No:
P 352

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Introduction:
Transthyretin amyloidosis due to mutations in TTR is the most prevalent subtype of hereditary amyloidosis, preferentially affecting peripheral nerve and heart, although other organ involvement can occur. We describe the neurophysiological phenotype of an Irish cohort of patients with hereditary TTR amyloidosis, primarily due to the T60A mutation.

Methods:
A retrospective review was performed of symptomatic TTR mutation carriers attending our tertiary referral center. Data was collected regarding clinical and neurophysiological characteristics, including autonomic and small fiber testing .

Results:
Sixteen symptomatic carriers of TTR) mutations were identified to date. The commonest mutation in our cohort is p.T80A, present in 88% of our cohort. Eighty-one per cent of patients had symptomatic neuropathy. The remainder had been identified as part of familial screening. Neurophysiology demonstrated a predominantly axonal, large fiber sensorimotor neuropathy in 31% of patients and an axonal sensory neuropathy in 13%. Fifty-six per cent of patients had normal routine nerve conduction studies . However, of those with normal NCS who had had all other studies completed, 40% had abnormal small fiber studies, and 20% had abnormal autonomic studies. Fifty per cent of patients had carpal tunnel syndrome. Small fiber studies were conducted in 11 of 16 of patients, of which 36% were normal, 18% had isolated a-delta fiber dysfunction, 18% had isolated c-fiber dysfunction and 36% had mixed small fiber dysfunction. Autonomic studies were conducted in all patients and were abnormal in 19 %.

Conclusions:
Neurophysiological studies in patients with hereditary TTR amyloidosis typically demonstrates a primarily axonal (and usually mixed sensorimotor) length-dependent neuropathy. Small fiber and autonomic dysfunction is also common in this cohort, and may occur independent of significant large fiber neuropathy on neurophysiology. Given that some disease-modifying treatments are only available for patients with neuropathy, these results highlight the importance of comprehensive neurophysiological assessment in such patients.

References:
Yes

Reference 1: Kapoor M, Rossor AM, Laura M, Reilly MM. Clinical presentation, diagnosis and treatment of TTR amyloidosis. Journal of neuromuscular diseases. 2019 Jan 1;6(2):189-99.

Keywords: amyloidosis, small fiber, autonomic

Schwann Cells Contribution To Neurovascular Interactions In Modelling Cutaneous Innervation

Poster No:
P 353

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Institutions:
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Introduction:
Schwann cells are indispensable components of cutaneous innervation and exert pivotal roles in skin physiology. They actively participate in the maintenance and regeneration of sensory nerve endings, which are vital for touch, temperature, and pain sensation. Through the secretion of growth factors and cytokines, Schwann cells support the health and survival of sensory neurons as well as influence the formation of blood vessels by stimulating endothelial cell proliferation and migration. The generation of a vascularized skin including a properly differentiated epidermis as well as functional innervation and vasculature still represents a major challenge in tissue engineering. The purpose of this work is to develop an innovative, fully human, skin-on-a-chip model enabling the investigation of cutaneous neurovascular interactions.

Methods:
Human induced pluripotent stem cells (Phenocell) were differentiated into sensory neurons (iSN) and Schwann cells (iSC) according to established protocols. Human dermal microvascular endothelial cells (HDMECs) and fibroblasts were isolated from human surgical waste with regulatory approval. In house microfluidic chips were electrostatically attached over glass coverslips previously coated with poly-D-lysine and laminin. HDMECs and fibroblasts were seeded in the lateral compartments while iSN and iSC were seeded in the central compartment.

Results:
Phenotypic and functional assays confirmed the obtention of sensory neurons and Schwann cells. Similarly, we defined that 14 days are necessary to obtain pseudo-vascular networks from HDMEC and fibroblast co-cultures in microfluidic chips. We then evaluated and quantified the effect of Schwann cell addition to the endothelial compartment on the formation and complexity of the vascular network. Proteome arrays allowed to identify pro-angiogenic cytokines secreted by the neural compartment.

Conclusions:
Initial data present sensory neuron and Schwann cell models and their effects on endothelial cell pseudo-vascular organization. We expect that our vascular and neural network model could promote a better understanding of cutaneous neurovascular interactions.

References:
No

Grant Support:

ANR NeuroSkin

Keywords: neurovascular interactions, skin-on-a-chip, cutaneous innervation, sensory neurons, Schwann cells

Leprosy neuropathy and demyelinating impairment: How should we interpret this neurophysiological pattern?

Poster No:
P 354

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Introduction:
Leprosy neuropathy (LN) is a chronic condition, which begins as an infection of the Schwann cell and may cause a demyelinating neuropathy which worsens during the leprosy reactions (LR). Type-1 LR (T1LR) occurs in patients with active cell-mediated immune response against M. leprae and Type-2 LR (T2LR) or erythema nodosum occurs in multibacillary cases. The patterns of nerve impairment are not clear since both demyelination and axonal degeneration are commonly found. This study aimed to describe how to interpret the demyelinating impairment in LN.

Methods:
It is a retrospective observational analysis of patients with leprosy in a National Reference Center in Brazil between 2014-2023. 117 patients underwent neurophysiological examinations that showed a demyelinating pattern defined by prolonged distal motor latency, reduction in motor conduction velocity and presence of conduction block (CB) and/or temporal dispersion (TD).

Results:
82.0% presented CB and 96.6% TD. 78.6% had both conditions. 46.1% had T1LR and 17.9% T2LR. When compared, 81.3% of the patients with LR and 83.3% without LR had CB (p= 0.78). 96,0% of LR group and 97,6% in the group without LR had TD (p= 0.64). Comparing T1LR and T2LR, 83.3% of T1LR and 76,2% of T2LR had CB (p= 0.47), and 94.4% of T1R and 100,0% of T2LR had TD (p=0.27). 92.3% of patients fulfill neurophysiological criteria for chronic inflammatory demyelinating polyneuropathy (CIDP).

Conclusions:
Leprosy is a spectral disease in which neural damage can manifest with different phenotypes. Therefore, demyelinating impairment is frequent and may vary according to the clinical form and the presence of LR. Even though CB and TD are relatively common on the studied population, they do not correspond to an active disease. It is important to emphasize that LN can also be misdiagnosed as other peripheral neuropathies, such as CIDP, especially in non-endemic areas.

References:
No

Keywords: leprosy, infectious neuropathy

Safety of Decade Plus Use of IgPro20 in the Real World: Post-Marketing Pharmacovigilance Report

Poster No:
P 355

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Introduction:
IgPro20 (Hizentra®, CSL Behring) is a subcutaneous human immunoglobulin approved since 2010 for the treatment of primary and secondary immunodeficiency, and since 2018 for maintenance therapy in chronic inflammatory demyelinating polyneuropathy (CIDP). We investigated spontaneous reports of thromboembolic events (TEEs) and infections in patients having received IgPro20.

Methods:
The CSL Behring safety database was used to retrieve all post-marketing cases (since product launch in 2010 until 31 May 2023), which registered adverse events from the 'Opportunistic infections' (broad) and 'Embolic and thrombotic events' Standardized MedDRA Queries. Reporting rates of adverse events are presented as cases per 100 patient years of exposure to IgPro20, calculated by dividing the total amount of IgPro20 sold by the estimated weekly CIDP (20g) or immunodeficiency (10g) dose. The indication for IgPro20 use was based on the reporter designation.

Results:
The reporting rate of TEEs was 0.36 (estimate based on CIDP dose) or 0.18 (estimate based on immunodeficiency dose) per 100 patient years. Infections were reported with a rate of 1.27 (CIDP dose estimate) or 0.63 (immunodeficiency dose estimate) per 100 patient years; the most frequent were COVID-19, Influenza and Herpes Zoster (respectively, 0.31, 0.27 and 0.09 per 100 patient years (CIDP dose estimate) or 0.15, 0.13 and 0.05 per 100 patient years (immunodeficiency dose estimate). For 36 TEE cases (6.9% of all reported TEE cases) and for 88 infection cases (4.8 % of all reported infection cases), the reported indication was CIDP. Patient exposure for IgPro20 was estimated to be between 144,000 patient years based on the CIDP and 287,000 patient years based on the immunodeficiency dose.

Conclusions:
Spontaneous reports of adverse events, collected over a period of more than ten years, show that adverse events of interest in patients having received IgPro20 (including TEEs and infections) were rare, including in patients with CIDP.

References:
No

Grant Support:

N/A

Keywords: chronic inflammatory demyelinating polyneuropathy, immunodeficiency, subcutaneous immunoglobulin, adverse event

Muscle Hypertrophy Following Neurogenic Injury: Case Report, Systematic Review And Analysis Of Existing Literature.

Poster No:
P 357

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Introduction:
Neurogenic muscle hypertrophy (NMH) is a rare condition characterized by muscle hypertrophy resulting from partial chronic denervation. The mechanisms behind NMH remain elusive, and the scattered literature on this topic hampers comprehensive understanding. Therefore, we conducted a systematic review to gain insights into the clinical, mechanistic, and therapeutic aspects of NMH.

Methods:
We systematically searched online databases for studies reporting muscle hypertrophy attributed to acquired neurogenic factors. We conducted an exploratory analysis of these cases to identify common features. Additionally, we present two clinical case reports encountered in our practice.

Results:
Our search identified 93 sufficiently characterized NMH cases. Additionally, we included our two patients. NMH predominantly associates with compressive radiculopathy (68.4%), mild/negligible muscular weakness (93.3%), and chronic, pauci-symptomatic muscle bulk increase. A striking finding in most neurophysiological studies (60.0%) is the presence of continuous spontaneous discharges within affected muscles, often hindering the analysis of voluntary activity traces. Some patients exhibited higher creatine phosphokinase levels, increased frequency of muscle pain, and signs of inflammatory infiltration at the muscle biopsy. These patients are often referred to in the literature as neurogenic "focal myositis". Secondary muscle inflammation, as an epiphenomenon of chronic denervation, could concur to muscle hypertrophy and functional impairment. Treatment trials encompassed corticosteroid administration, Botulinum Toxin A (BoNTA), decompressive surgery, antiepileptic medications, nerve blocks, each demonstrating varying degrees of efficacy, although BoNTA treatment yielded the most favorable response in terms of reducing spontaneous discharges at the EMG.

Conclusions:
This systematic review, accompanied by two typical NMH cases, aims to provide a structured description of this unusual presentation of a common neurological disorder. Continuous electrical stimulation associated with mechanical overload is likely sufficient to induce myonecrosis, focal inflammation and cell growth activation resulting in neurogenic muscle hypertrophy. However, questions persist regarding the pathophysiological mechanisms driving this specific phenotype and the potential for therapeutic interventions.

References:
No

Keywords: Muscle Hypertrophy, Radiculopathy, CRDs, Denervation, Focal Myositis

Real-World Safety and Treatment Pattern of IgPro20 in Japanese Patients with Chronic Inflammatory Demyelinating Polyneuropathy

Poster No:
P 358

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Introduction:
The subcutaneous administration of immunoglobulins (SCIG) represents a convenient alternative to intravenous immunoglobulin treatments. The SCIG IgPro20 (Hizentra®) is approved in Japan for the treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP). The real-world treatment patterns and safety profile of IgPro20 in Japanese CIDP patients are reported here.

Methods:
A Japanese, multicenter, observational post-marketing surveillance study of patients with at least six months follow-up on IgPro20 was performed between October 2019 and September 2022. Physicians completed a case report form for each patient.

Results:
A total of 108 patients from 38 sites were eligible for analysis. The most common clinical type of CIDP was typical (61%), followed by multifocal acquired demyelinating sensory and motor (MADSAM, 19%), and other atypical CIDP (15%). The mean (range) age was 51.4 (17–79) years, and 37% of patients were female. Comorbidity diagnoses at IgPro20 initiation included hypertension (15.7%), dyslipidemia (12.0%), diabetes (9.3%), malignancy (6.5%), and one case of hepatitis C (0.9%). For IgPro20 maintenance treatment, 52.8% of patients received an initial dosage of 200–400 mg/kg, followed by ≥400 mg/kg or <200 mg/kg (23.2% and 21.3% of patients, respectively). The mean dose administered was 306 mg/kg, and the median (range) treatment duration was 26 (1–40) weeks. During the observation period, 18.5% of patients discontinued treatment. Notably, 82.7% managed their regimen at home, with 74.9% of patients using self-administration and 14.1% receiving a caregiver facilitated administration. Steroids were the most frequently prescribed concomitant medication (38.0%). Adverse drug reactions (ADRs), specifically injection site reactions, were observed in 40 patients (37.0%). The predominant ADRs included injection site erythema (21.3%) and swelling (17.6%), with no documentation of serious ADRs.

Conclusions:
This study affirms that the safety profile of IgPro20 in real-world practice aligns with the findings from the IgPro20 phase 3 trials.

References:
No

Keywords: CIDP, Real-World Safety, Subcutaneous Immunoglobulin

Neurofilament Light Chain levels in large idiopathic peripheral neuropathy cohort

Poster No:
P 359

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Institutions:
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Introduction:
Neurofilament light chains (NfL) are associated with axonal degeneration, and elevated NfL levels have been observed in many neuromuscular diseases such as Amyotrophic Lateral Sclerosis, Multiple Sclerosis, or Parkinson's disease. More recently, elevated NfL levels were also confirmed in sensory or predominantly sensory neuropathies (PN) such as diabetic, chemotherapy-induced, and amyloid PN. This suggests NfL plasma levels as a potential biomarker to monitor disease activity in peripheral polyneuropathies.

Methods:
We evaluated NfL levels in a large cohort of patients with idiopathic peripheral neuropathy enrolled in the Peripheral Neuropathy Research Registry (PNRR). In order to qualify, patients needed to have plasma sample available, a complete data record that included confirmation of neuropathy through EMG and/or skin biopsy findings, and no abnormal laboratory testing on file. NfL levels were determined in plasma using singlicate SIMOA assay.

Results:
294 research participants met the inclusion criteria. The youngest person in the cohort was 21, the oldest 91, with a mean age of 65 years, with an onset of their PN symptoms between 0.3 and 39 years (mean 3.9 years) prior to sample collection. Height ranges from 152-208 cm (mean 178 cm), and the BMI ranged from 14.6 to 49.1 (mean 28.0). 72% percent of the participants reported neuropathic pain associated with their PN, and 61% had abnormal nerve conduction studies on record. The HbA1c's ranged from 4.1% to 5.9%, with four patients carrying a diagnosis of prediabetes. 20% of the cohort met the criteria for having metabolic syndrome.

Conclusions:
SIMOA assays are scheduled to be run by late February. We expect to be able to report results during the 2024 PNS meeting.

References:
No

Grant Support:

Merkin Peripheral Neuropathy and Nerve Regeneration Center grant

Keywords: idiopathic neuropathy, biomarker

Application of a table detected eight cases of two common anomalous innervations coexistence in arms

Poster No:
P 360

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Introduction:
Recognition of anomalous innervation in upper limb is important because the highest number of patients seen in any EMG clinics are entrapment neuropathies. To reach the accurate diagnosis, to explain the clinical atypicality, for proper grading, planning for appropriate therapy and to get the knowledge of this before surgically exploring the hand and forearm become crucial. We have utilized a table for recognition of common anomalous innervations and applied in our daily practices. We like to share the findings of our experiences.

Methods:
The table (please see in the poster) was based on awareness of median/APB CMAP irregularity (amplitude/distal latency) at the distal and proximal site, with a comparison to median SNAP data. This will trigger ulnar motor nerves stimulation at the wrist and at the elbow to figure this out. Patients attended the three neurophysiology clinics of different hospitals were screened for entrapment neuropathies. Reports of patients in fourteen months were reviewed. All studies were done following our protocols based on BSCN and AANEM.

Results:
We have tabulated the eight cases of Richie Cannieu Anastomosis (RCA) in hands and Martin-Gruber anastomosis type 2 coexisting in forearms of eight patients presented with carpal tunnel syndrome, cubital tunnel syndrome and lower cervical radiculopathy. Some cases are bilateral manifestations even in asymptomatic hands. Their demographics, presentations, findings were elaborated.

Conclusions:
The incidences of RCA and MGA are high, based on literature (cadaveric and on NCS studies). In our practice, we are seeing more of them today suggests that we missed many before. Increased awareness and the table have helped us. Awareness of anatomical variations resulted in understanding the atypicality of presentation, reaching an accurate diagnosis with a better grading of the severity. A simplified tool to explore the possibility will increase the yield of detecting them and help many in the future.

References:
No

Keywords: Common anomalous innervation and an anatomical variant

Absence of *NORAD* causes aberrant nerve regeneration with hypomyelination in mice

Poster No:
P 361

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Introduction:
NORAD (Non-Coding RNA Activated by DNA Damage) and its binding partner pumilio (PUM) 1/2 proteins are associated with several cellular mechanisms. It has previously been shown that absence of NORAD results in chromosomal instability and mitochondrial dysfunction, including reduction in cellular respiration. We hypothesized that the mitochondrial abnormalities and resulting energy deprivation due to absence of *NORAD* might impair regeneration process, being an energetically demanding cellular function. In this study, we explored the potential role of *NORAD* in nerve regeneration using the sciatic nerve crush paradigm in *Norad* deficient (*Norad*$^{-/-}$) mice.

Methods:
Right sciatic nerves of *Norad*$^{-/-}$ mice, aged 2-3 months (young cohort, n=10) and aged 11-12 months (old cohort; n=8 for histology cohort, n=16 for RNA-seq cohort), were crushed in a survival surgery. Sciatic nerve segments, immediate-to (D1) and 5 mm distal-to (D2) the crush site, were collected at 2- or 12-weeks post-surgery to assess the temporal evolution of regeneration process in young and old cohorts.

Results:
Histological analyses included quantification of myelinated and amyelinated fibers, total Schwann cell estimation, myelinated fiber size distribution and G ratio analysis for myelin thickness. *Norad*$^{-/-}$ mice showed aberrant myelination with impaired radial sorting in the axon-Schwann cell complexes, which became more prominent in the old cohort compared to wild type (WT). We observed a significant decrease in myelinated fibers and estimated number of Schwann cells at the D1 level in the old *Norad*$^{-/-}$ mice compared to age-matched WT controls. In addition, the regenerating *Norad*$^{-/-}$ nerves from D2 segments were hypomyelinated with significantly greater G ratio at 12 weeks post-crush compared to age-matched WT controls. Gene set enrichment analysis of RNA-seq data suggested that oxidative phosphorylation genes were upregulated in WT at two weeks post-crush, whereas this enrichment was not observed in *Norad*$^{-/-}$ mice.

Conclusions:
These results suggest involvement of *NORAD*-pumilio axis in peripheral nerve regeneration.

References:
No

Grant Support:

Internal grant

Keywords: regeneration, Schwann cells, Norad

The EULA project: exploring the upper limbs outcome measures

Poster No:
P 362

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Introduction:
Hereditary transthyretin amyloidosis polyneuropathy (hATTR) is a disabling neuropathy, affecting lower and upper limbs in the motor and sensor domains. The EULA-project is a multicenter study to collect data about the severity and progression of the hands symptoms in hATTR patients using a multiparametric approach based on clinical and sensorized testing. We analyzed the preliminary results and extrapolated data regarding the testing of specific muscles both in the dominant and non-dominant hand (DH e NDH).

Methods:
We analyzed the results of 49 hATTR-patients with different stages of the disease (F:21; M:28; age:62.16±12.65y) and 30 HC (F:17; M:13; age:49.50±16.80y). Evaluations in the DH and NDH hand by: HTS with 2 tasks and eyes closed (Finger-Tapping (FT) and Index-Middle-Ring-Little (IMRL) sequence); Thumb Opposition Test (TOT), dynamometry [handgrip (HG) and tripod pinch (TP)].

Results:
HG resulted significantly stronger in the DH of the HC compared to the patients (102.98±35.01N vs 77.98±40.99N, respectively,$p<0,05$). The HG in the NDH and the TP in both hands were not significantly different. FT and IMRL showed a better performance of the HC in the DH ($FTp<0.05$;$IMRLp<0.01$), but not in the NDH. TOT showed a significant difference between HC and patients for both hands ($DHp<0.0001$;$NDHp<0.0001$).

Conclusions:
In these preliminary data, the function of the hands is significantly affected in hATTR patients compared to HC. The evaluation of the DH flexors is more sensitive to discriminate between HC and patients based on the results of the HG. Moreover,TOT is a rapid and interesting test for evaluating hands function in hATTR patients. Finally, the high sensitivity of HTS in the IMRL task to changes allows to discriminate between the function of the dominant hand both HC and patients. More data are needed to clarify these results, also because patients showed a very high inter-patient variability, probably due to the different stages of the disease.

References:
No

Grant Support:

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Keywords: hATTR, Amiloydosis Neuropathy, Upper limbs, outcome measures, hereditary transthyretin amyloidosis

Drastically Accelerated Directed Differentiation Of Human Pluripotent Stem Cells Into Motor Neurons For Disease Modeling And Screening Applications

Poster No:
P 363

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Introduction:
Motor neurons are involved in the voluntary control of muscular contraction and are the primary cell type affected in amyotrophic lateral sclerosis (ALS), an incurable and deadly neurological disease resulting in paralysis. Given their unlimited potential for self-renewal and differentiation, it has been a longstanding goal to model ALS specifically using human pluripotent stem cell (hiPSC)-derived motor neurons for drug discovery in order to develop life-saving treatments for this disease. While numerous methods have been published to differentiate motor neurons from hiPSCs, all protocols to date demonstrate substantial donor-to-donor variability, which results in a failure to produce motor neurons at high yields and purity from each hiPSC line.

Methods:
Here, we report a drastically accelerated, developmentally guided, directed differentiation protocol based on small molecules and growth factors to generate motor neurons in only seven days from three different hiPSC lines (wild type - female, wild type - male, TDP43 ALS patient - male). Developmental stages of the differentiation and motor neurons were characterized via immunocytochemistry, qPCR, and RNA sequencing. Several functional assays were developed, including multi-electrode array (MEA) plates and microfluidic co-cultures with human skeletal muscle (hSKM).

Results:
Motor neurons generated from all lines expressed MNX1, ISLET1, ChAT, and TUJ1 at a purity greater than 80% as confirmed by immunocytochemistry. qPCR and bulk RNAseq results showed expression of key motor neuron genes and molecular similarity to primary human spinal motor tissues. On MEA plates, cultures exhibited rapid maturation with burst spiking within a week. Motor neurons co-cultured with hSKM in microfluidic devices formed neuromuscular junction morphologies, and controlled stimulation of the motor neurons resulted in muscle activation.

Conclusions:
In conclusion, we have demonstrated a rapid seven day protocol to generate motor neurons from multiple donor lines, along with their utility in various screening assays for disease modeling, ALS drug discovery, and basic research.

References:
No

Grant Support:

N/A

Keywords: motor neurons, human induced pluripotent stem cells, ALS, disease modeling, co-cultures

Useful And Cost-effective Workup In Chronic Polyneuropathy: The EXPRESS Study

Poster No:
P 364

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Introduction:
Polyneuropathy is a common disease that has many causes and risk factors. Knowledge gaps exist about the usefulness and extent of blood tests and nerve conduction studies in the workup of polyneuropathy. Our hypothesis is that in many patients with a clinical diagnosis of chronic polyneuropathy, a limited or no further workup improves cost-effectiveness without loss of diagnostic reliability.

Methods:
The EXPRESS study is a prospective observational multi-center study carried out in five large general hospitals and three neuromuscular expertise centers in the Netherlands. Adult patients with symptoms suspect for polyneuropathy, who are referred to a neurologist for an outpatient workup are eligible. Patients' electronic medical records (EMR) are used to gather all relevant data. Direct medical costs and other health care costs are determined from these data and questionnaires. The total sample size will be 750 patients. Real-time workup by patients' neurologists will be compared to a hypothetical limited or no further workup by a panel of neurologists with experience in neuromuscular diseases. The panel is blinded for the performed workup and established diagnosis by the patients' neurologists. Each patient is his own control and follow-up time is 6 months.

Results:
Primary outcome is effectiveness of a limited or no further workup expressed as concordance between panel diagnosis and patients' neurologists' diagnosis (i.e. percentage overlooked diagnoses). This will be related to differences in costs and impact on treatment or patient management. Other outcomes are burden/gain for the patients in terms of number of investigations, time to diagnosis, hospital visits, sick-leave, loss of productivity, expenses, and experienced quality of care.

Conclusions:
This study will provide clarity about cost-effective workup in chronic polyneuropathy and we will report prelimary results regarding the primary and secondary outcomes.

References:
No

Grant Support:

ZonMW ZE&GG grant

Keywords: Polyneuropathy, Cost-effective workup, Diagnostics

Clinical And Molecular Insights Into Homozygous And Heterozygous A97S Variants In Hereditary Transthyretin Amyloid Polyneuropathy

Poster No:
P 365

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Introduction:
Hereditary transthyretin (TTR) amyloid polyneuropathy (ATTRv-PN) is a rare yet treatable autosomal-dominant disorder resulting from TTR variants. This study aims to delineate clinical profiles and molecular characteristics of ATTRv-PN patients with the A97S variant from southern China.

Methods:
Fifteen ATTRv-PN patients with heterozygous A97S and one with homozygous A97S were included. Serum TTR tetramer concentration was quantified using ultra-performance liquid chromatography. A97S-TTR stability was assessed through urea-mediated tryptophan fluorescence experiments, and drug response was measured using nephelometry.

Results:
All patients exhibited late-onset sensory-motor neuropathy phenotype with autonomic and cardiac involvement. The homozygous A97S patient showed slower progression than heterozygotes. In vitro stability tests revealed higher kinetic stability of homozygous A97S-TTR. Tafamidis-treated patients displayed elevated TTR tetramer concentrations, nearing healthy controls' levels. Drug response assessment revealed tetramer stabilizers' inhibitory efficiency on both homozygous and heterozygous A97S-TTR.

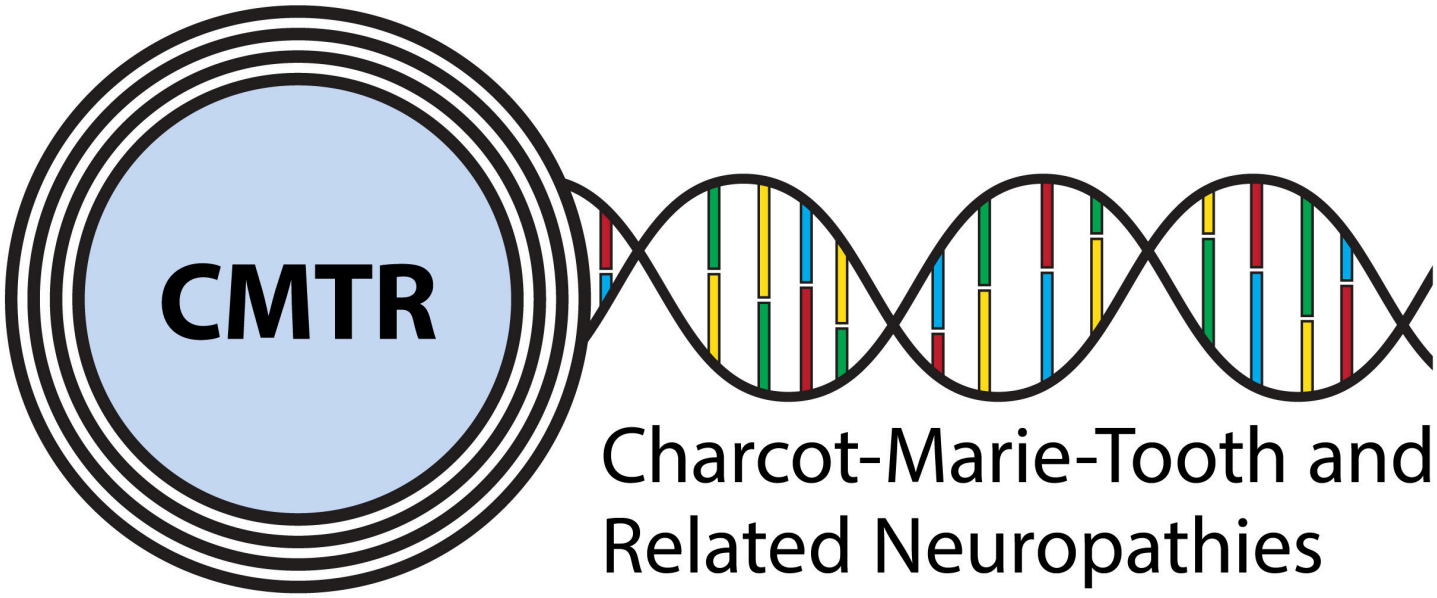
Conclusions:
This study provides valuable insights into the clinical heterogeneity among ATTRv-PN patients with A97S in South China, particularly in terms of disease progression and stability features between homozygous and heterozygous A97S variants.

References:
No

Grant Support:

No response

Keywords: A97S variant, hereditary transthyretin amyloid polyneuropathy, heterozygous, homozygous, in vitro stability



Charcot-Marie-Tooth and Related Neuropathies (CMTR) Abstracts

O 366 - 387

Inhibiting GCN2 and the Integrated Stress Response as a Treatment for tRNA Synthetase-Associated Forms of CMT

Poster No:
O 366

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Introduction:
Dominant mutations in tRNA synthetase genes activate the integrated stress response (ISR) through the kinase GCN2. Inhibiting GCN2 at disease-onset prevents ISR activation and mitigates neuropathy. Here, we provide additional preclinical data regarding the timing, efficacy, and scope of GCN2 inhibition in mouse models of CMT caused by mutations in tRNA synthetase genes.

Methods:
Using an experimental GCN2 inhibitor (GCN2iB), we treated mice in two studies: 1) beginning after the onset of symptoms (5 weeks-of-age) and treating for 5 weeks, and 2) beginning at the onset of symptoms (2 weeks-of-age), treating for four weeks, then following the mice for another 4 weeks post-treatment. We also bred Gars1/CMT2D and Yars1/diCMTC mice to a Gcn2 knockout strain to better understand the basis for the observed benefit and to test how generalizable GCN2 inhibition may be as a therapy.

Results:
When treatment with GCN2iB was started post-onset (P35) in Gars1/CMT2D mice, we saw improvements in body weight, motor performance and neurophysiological outcomes. When treatment was started at disease onset (P14) and continued for 4 weeks, the mice showed similar improvement, but regressed when treatment was stopped. In Gars1/CMT2D mice bred to the Gcn2 knockout strain, we saw improvement in the innervation of neuromuscular junctions between 7 and 26 weeks of age. We also saw a beneficial effect of Gcn2 heterozygosity, with mice improving in motor performance and neurophysiology outcomes at older time points. Yars1/diCMTC mice bred to the Gcn2 knockout strain also showed improvements in all outcome measures.

Conclusions:
Inhibiting GCN2 is beneficial in Gars1/CMT2D mice, even when treatment is started post-onset, but treatment needs to be ongoing. Improved innervation at NMJs explains some of the post-onset benefit, and even partial (heterozygous) reduction in Gcn2 produces benefit with time, reversing earlier deficits. These results also extend to mouse models of Yars1/diCMTC.

References:
No

Grant Support:

R37NS054154

Keywords: small molecule, CMT2D, GARS1, YARS1, preclinical

Investigating the Causative Role of Axonal Transport Defects in Charcot-Marie-Tooth Disease Type 2J

Poster No:
O 367

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Introduction:
Axonal degeneration is a common endpoint in peripheral neuropathies, either due to a primary axonopathy or secondary to myelin defects. In Charcot-Marie-Tooth (CMT) disease, a subgroup of patients presents with primary axonopathies (CMT2), but secondary axonal degeneration occurs in all demyelinating forms of CMT (CMT1) as well. Mutations in the MPZ gene encoding myelin protein zero (P0) typically lead to a severe, early-onset demyelinating neuropathy (CMT1B). Notably, the T124M mutation in P0 causes a late-onset axonopathy, referred to as CMT2J, with only minimal myelin defects. The mechanism by which a mutation in a myelin protein causes an axonal neuropathy is unclear but our preliminary data suggest impaired axonal transport, a process vital for cell maintenance and survival, and associated with a range of neurodegenerative diseases.

Methods:
Our group generated and characterized mice carrying the Mpz-T124M mutation to replicate the axonopathy observed in CMT2J patients. Proteomic analysis, in vivo imaging and genetic manipulations are currently being performed to study the disease mechanism and identify targetable pathways for therapy.

Results:
Proteomic analyses on sciatic nerves lysates from T124M mice revealed downregulation of axonal transport machinery proteins. Additionally, the ratio of acetylated to total α-tubulin expression was lower, which reduces the microtubules' affinity for the transport proteins. Subsequently, in vivo imaging of retrogradely transported signaling endosomes showed that endosomes in T124M nerves pause more frequently and move slower overall. Ongoing experiments aim to investigate if the genetic ablation of histone deacetylase 6 (HDAC6), the major deacetylating-tubulin enzyme, can restore reduced acetylated α-tubulin levels in T124M mice.

Conclusions:
Taken together, this data suggests a general disturbance of axonal transport in T124M mice. Similar experiments are ongoing on T124M mice in which HDAC6 was genetically deleted, aiming to understand if HDAC6 inhibition can rescue transport defects and subsequent axonal degeneration in CMT2J.

References:
No

Keywords: Charcot-Marie-Tooth, MPZ, Axonal degeneration, HDAC6, Axonal transport

Investigating loss of Replication Factor Complex subunit 1 (RFC1) function in CANVAS patients and heterozygous AAGGG expansion carriers

Poster No:
O 368

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Introduction:
CANVAS is a recessively inherited condition caused in most cases by biallelic AAGGG expansions in RFC1. Despite the recessive mode of inheritance, RFC1 transcript or protein expression appear unchanged. Yet, the identification of compound heterozygous null variants causing CANVAS suggests a role of RFC1 function in the disease pathogenesis.

Methods:
Here we show that pathogenic AAGGG expansions form stable nucleic acid structures compatible with G-quadruplexes in vitro and lead to transcription inhibition in vitro and in reporter assays in a repeat-length-dependent manner.

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

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

References:
Yes

Reference 1: Cortese A, Simone R, Sullivan R, et al. Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia. Nat Genet. 2019;51(4):649-658.

Reference 2: Ronco R, Perini C, Currò R, et al. Truncating Variants in RFC1 in Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia Syndrome. Neurology. 2023;100(5):e543-554.

Grant Support:

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Keywords: CANVAS, RFC1, DNA damage repair, In vitro models, RNA sequencing

Can CRISPR/Cas9-mediated knock-out of small heat shock proteins ameliorate the axonal CMT phenotype?

Poster No:
O 369

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Introduction:
Small heat shock proteins (sHSPs) are a family of molecular chaperones whose main function is to maintain cellular proteostasis by recognizing, binding and eventually clearing misfolded and/or aggregated proteins. Mutations in sHSPs, namely HSPB1 and HSPB8, have been associated with axonal Charcot-Marie-Tooth (CMT2F and CMT2L respectively) and/or distal hereditary motor neuropathy (dHMN). Protein aggregation, axonal transport deficiency, mitochondrial dysfunction and autophagy impairment are common hallmarks associated with mutant HSPB1 and HSPB8. Furthermore, from studying our in-house developed Hspb8 knock-out (KO) mouse model (Hspb8-/-), we have learned that the absence of this gene does not reveal any neurodegenerative phenotype, thus supporting the idea that reducing the HSPB8 expression can be a therapeutic strategy to treat patients with mutant HSPB8. As it is presumed that sHSPs can compensate for each other's function, we aim to investigate if CRISPR/Cas9-mediated KO of HSPB1 and HSPB8 can ameliorate the phenotype of CMT2 in motor neurons differentiated from CMT2 patient pluripotent stem cells.

Methods:
In this study we will compare the shared pathological phenotypes of the mutant lines with the CRISPR/Cas9-KO and healthy control lines. Downstream analyses include, mitochondrial and lysosomal transport, mitochondrial morphology and respiration, immunofluorescence of autophagy specific markers and specific protein interaction of each sHSP among others.

Results:
Preliminary results on HeLa cells, mouse embryonal fibroblasts and motor neurons showed that some of the common hallmarks were rescued after sHSPs depletion, such as mitochondrial morphology, while autophagy activity and protein degradation remained impacted.

Conclusions:
The sHSPs depletion seems to hold potential as a therapeutic approach for improving the phenotype of CMT2, mostly for HSPB8, but might still present problems in long term, as the autophagy activity decreases with age.

References:
Yes

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Grant Support:

University Research Fund (BOF)

Keywords: CRISRP/Cas knockout, Charcot-Marie-Tooth neuropathy, HSPB1, HSPB8, iPSC-derived motor neurons

Nuclear envelope gene FAM169A causes combined lower and upper motor neuropathy through heterozygous loss-of-function mutations

Poster No:
O 370

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Introduction:
FAM169A encodes the nuclear envelope protein SLAP75, the function of which is largely unknown. In four independent families, we found heterozygous loss-of-function mutations in FAM169A co-segregating with a combined lower and upper motor neuron disease phenotype.

Methods:
Patients were examined by experienced neurologists. We analyzed exome and genome sequencing data using the GENESIS platform. For functional analyses, we performed western blots and mass spectrometry. The KO zebrafish model was created using CRISPR-Cas9 with guides targeting both homologues of FAM169A with a pigment-control.

Results:
Leading symptoms were progressive, distally pronounced muscle wasting and walking difficulties with a reported age-of-onset between 17 to 32 years. Most patients additionally developed brisk tendon reflexes or pyramidal signs. By cloning, we demonstrated the de-novo occurrence of one of the variants in a family, where the proband's mother was already deceased. By western blot, we demonstrated that SLAP75 is expressed in motor neurons derived from induced pluripotent stem cells from healthy controls. Mass spectrometry-based interactome analysis from HEK cells revealed a close interaction between FLAG-tagged SLAP75 and lamin A/C, a nuclear envelope protein previously linked to neuropathy. Other significant protein-protein interactions included components of the nuclear pore complex. By sequencing RNA and DNA from patient-derived fibroblasts available in one family, we showed that the respective variant causes nonsense-mediated RNA decay. Loss-of-function variants in FAM169A are extremely rare in healthy controls (pLI=1, GnomAD), suggesting that haploinsufficiency is the underlying disease mechanism. Using CRISPR-Cas9-based knock-out of the two FAM169A homologues in zebrafish, we found a severe motor phenotype. By day 2, KO fish showed truncated bodies with dorsal curvature and reduced eyes.

Conclusions:
Interestingly, the nuclear envelope has recently gained major attention in the context of other motor neuron diseases. In summary, FAM169A represents a novel Mendelian disease gene in the Charcot-Marie-Tooth and related motor neuron disease spectrum with genetic, biochemical, and animal model support.

References:
No

Grant Support:

NIH, German Research Foundation (DFG)

Keywords: CMT, Motor neuron disease, Nuclear envelope, Mass spectrometry, Zebrafish model

Measuring Longitudinal Function In Adults With CMT1A; Data From The Accelerate Clinical Trials in CMT (ACT-CMT) Study

Poster No:
O 371

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Introduction:
Reliable, valid and sensitive clinical outcome assessments (COAs) are essential for clinical trial readiness in CMT. The CMT-Functional Outcome Measure (CMT-FOM) is a reliable and valid COA for adults with CMT1A. The purpose of this study was to examine longitudinal changes in functional abilities in individuals with CMT1A.

Methods:
Adults with CMT1A were recruited to participate in Aim 1 of the Accelerate Clinical Trials in CMT (ACT-CMT) study. COAs, including the CMT-FOM, Overall Neuropathy Limitations Scale, and the Charcot Marie Tooth Exam Score (CMTES-R), were completed at baseline, 6-, 12-, and 24-month visits across 5 international sites. Preliminary analyses using paired t-tests were performed to examine changes from baseline.

Results:
215 individuals (59% female) with a mean age of 44.5 (range 18.1-75.1) enrolled and completed baseline study visits. Individuals with CMT1A had impaired function with a mean CMT-FOM score of 48.1 (range 21-84). Following the 24-month visit, none of the COAs demonstrated statistically significant change from baseline. However, individuals with mild functional impairment on the CMT-FOM at baseline (CMT-FOM scores ≤41) showed significant worsening of CMT-FOM scores over 24 months.

Conclusions:
Adults with CMT1A, demonstrate overall relatively stable function over 24 months. Without extended follow-up, it will be challenging to detect slowing of disease progression in adults with CMT1A utilizing disease specific COAs in future clinical trials, unless subgroups of patients with more rapidly changing function are identified. However, given the stability of the CMT-FOM, it may prove to be responsive to interventions aimed at improving function in adults with CMT1A. Continued collection of longitudinal data is necessary to understand how function is impacted by CMT1A disease progression as well as to understand how potential biomarkers can predict changes in function in adults with CMT1A. Lastly, these results help to refine inclusion criteria for future clinical trials.

References:
No

Keywords: clinical outcome assessment, CMT Functional Outcome Measure, CMT

Mechanisms of neurodegeneration and minigene therapeutic approach for Charcot-Marie-Tooth Disease Type 4B3

Poster No:
O 372

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Introduction:
Charcot-Marie-Tooth Disease Type 4B3 (CMT4B3) is an autosomal recessive, often severe, and clinically heterogeneous form of neuropathy that presents during infancy or early childhood. Symptoms of CMT4B3 vary dramatically from an isolated demyelinating sensorimotor neuropathy to a complex neurodevelopmental syndrome with neuropathy, cranial nerve involvement, and cognitive impairment. Sbf1 gene mutations cause CMT4B3, and results in dysfunction of the pseudo-phosphatase Myotubularin-Related Protein 5 (MTMR5). MTMR5 is an important regulator of autophagic and lysosomal traffic and is involved in the development of neurons and myelin. As an early-onset, recessive disorder, gene replacement therapy would be appropriate for CMT4B3, however, the cDNA of Sbf1 is larger (5,679bp) than the size limit of adeno-associated viral vectors (~4,700 bp), and the role of MTMR5 in neuronal homeostasis is poorly understood.

Methods:
To circumvent this challenge, we've sought to miniaturize MTMR5 into "mini-genes" based on several design principles, including comparative protein family, cross-species, and cross-domain investigations. Additionally, we have established four patient iPSC lines and derived motor neurons to elucidate the pathogenic mechanism of MTMR5 loss or dysfunction on axonal degeneration and to establish a cellular phenotype to assess the mini-gene replacement strategy.

Results:
In human iPSCs-derived motor neurons, CMT4B3 lines had decreased MTMR2 protein levels, and minimal MTMR5 expression remained. Motor neurons from several patients also exhibited increased NF-L leakage into supernatant cell culture media, indicating axonal damage. Preliminarily, autophagic flux also appears to be increased. Mini-gene candidates recapitulate the subcellular distribution of MTMR5 and co-precipitate with MTMR2, the active binding partner of MTMR5.

Conclusions:
Current functional studies include the identification of novel MTMR5 binding partners, further elucidation of aberration autophagic and mitophagic flux, and transcriptomic profiling. Such findings will inform further validation and refinement of candidate minigenes and will continue to inform the search for an image-based cellular phenotype suitable for high throughput screening.

References:
No

Grant Support:

NIH/NICHD F30HD11323; CMT4B3 Research Foundation

Keywords: CMT, iPSCs, Gene Therapy, Autophagy, Axonal Degeneration

Ultrasound-induced enhanced access of therapeutics to peripheral nerves of a demyelinating Charcot-Marie-Tooth mouse model

Poster No:
O 373

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Introduction:
In order to facilitate the potential of systemically delivered viral vectors to transduce Schwann cells in peripheral nerves for gene therapy, we studied the use of a Focused Ultrasound System (FUS) to enhance AAV9 vector penetrance through the blood nerve barrier (BNB) to achieve better biodistribution and expression in peripheral nerves.

Methods:
We first determined the optimal ultrasound electric power needed to induce transient BNB leakiness using different electric powers ranging from 20-120 Watt in wild type mice and the effects of FUS on sciatic nerve morphological and functional properties. We further tested the efficacy of AAV9 at different doses (2x, 1x and 0.5x1012 vg) to transduce Schwann cells following FUS application in Gjb1-null mice, a model of X-linked Charcot-Marie-Tooth disease (CMT1X). We assessed biodistribution by vector genome copy numbers (VGCNs) and expression rates of connexin 32 (Cx32).

Results:
Our data show that an electric power of 120 W is needed to achieve BNB disruption. We did not observe any morphological and functional abnormalities or inflammatory responses up to 4 hours post-sonication. VGCNs showed a trend for increase in sonicated nerves compared to non-sonicated controls in all groups. Cx32 expression rates were significantly increased in the high (61.1±4.98 % in control vs 80.2±5.67 % in sonicated nerves, p=0.0027) and mid-dose group (50.4±3.29 % in control vs. 64.6±4.80 % in sonicated nerves; p=0.0281) and showed a trend for increase in the low dose group as well (49.5±3.69 % vs. 60.1±2.86 %, p=>0.05).

Conclusions:
FUS application in sciatic nerves results in transient BNB disruption without any functional or morphological abnormalities or any inflammatory responses. Furthermore, FUS facilitates viral vector penetration into sciatic nerves and higher expression rates in Schwann cells. Application of the FUS may facilitate the delivery of therapeutics to peripheral nerves using lower systemic doses.

References:
No

Grant Support:

This work was funded by Muscular Dystrophy Association (MDA 963041 to AK)

Keywords: Charcot-Marie-Tooth disease, Gene therapy, Focused Ultrasound System, Schwann cells

Safety and Exploratory Efficacy of Mesenchymal Stem Cells in CMT1A Patients: Phase 1 Clinical Trial

Poster No:
O 374

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Introduction:
Charcot-Marie-Tooth disease type 1A (CMT1A) is an inherited peripheral neuropathy caused by a duplication mutation in the PMP22 gene and is one of the most common orphan diseases. CMT1A is characterized by symptoms such as sensory loss, muscle atrophy, and gait disturbances, and is estimated to affect 1.5 million people worldwide, but there is no cure. In this study, we conducted a Phase I clinical trial to determine the safety, tolerability, and exploratory efficacy of Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) in CMT1A patients.

Methods:
Nine CMT1A patients were recruited for this study. WJ-MSCs were administered intravenously, with three subjects assigned to the low-dose group (5×10^5 cells/kg) and six to the high-dose group (2.5×10^6 cells/kg). After administration, all subjects were monitored for dose-limiting toxicities (DLTs) for 4 weeks and evaluated for safety, tolerability, and exploratory efficacy for 16 weeks. Exploratory efficacy endpoints included CMTNSv2, CMTNSv2-R, CMTES, CMTES-R, ONLS, 10 MWT, NCS (Nerve conductivity study), and MRI.

Results:
There were four adverse events with Grade 1 (Mild). Two subjects reported headache and the other two subjects did injection site edema. The causality with the WJ-MSCs was determined to unrelated or unlikely. No DLT occurred. Statistically significant improvements in CMTNSv2, CMTNSv2-R, CMTES, and CMTES-R were observed in the high dose group. Significant improvements in CMTNSv2 and CMTES were also observed in all subjects. Improvements in disease severity classification were observed in the high-dose group. The average 10 meter-walking speed were increased after 16 weeks of stem cell treatment.

Conclusions:
Intravenous administration of WJ-MSCs to CMT1A patients reported 4 AEs with less causality to the WJ-MSCs and did not show any DLTs. Therefore, safety and tolerability were established. In addition, significant motor function improvements were observed, especially in the high-dose group. In conclusion, it is suggested that WJ-MSCs may be a possible treatment for CMT1A

References:
No

Grant Support:

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Keywords: Mesenchymal stem cell, Charcot-Marie-Tooth disease type 1A, Stem cell Therapy, Clinical trial phase 1

Correlations between serum neurofilaments light chain level and small nerve fibre damage parameters in hereditary transthyretin amyloidosis (ATTRv).

Poster No:
O 375

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Introduction:
Small nerve fiber dysfunction, evaluated with skin biopsy and quantitative sensory testing (QST), has been shown to be very early in ATTRv with polyneuropathy, even preceding the symptoms onset in pre-symptomatic carriers. At the same time, serum neurofilament light chain (sNfL) may also represent a sensitive, non-invasive, and easily repeatable marker of disease onset, helping to discriminate pre-symptomatic TTR mutation carriers from symptomatic patients. The aim of this study is to explore the relationships between these promising biomarkers in a cohort of ATTRv patients and pre-symptomatic carriers.

Methods:
We conducted a retrospective analysis of data from ATTRv patients and pre-symptomatic carriers participating to our two multicentric studies about small fiber dysfunction characterization through skin biopsy and QST, and sNfl dosage at different disease stages. sNfL concentration was measured using the Simple Plex™ cartridge-based assay on the Ella™ platform. Distal IENFD was considered as main outcome skin biopsy variable using both raw values and percentage of reduction considering age/sex adjusted normal values. The following QST parameters were evaluated: cold and warm detection thresholds (CDT and WDT); cold and heat pain thresholds (CPT and HPT); mechanical detection and pain thresholds (MDT and MPT).

Results:
We selected 34 ATTRv subjects, classified as pre-symptomatic (21) and symptomatic (13, 8 classified as PND1). sNfl correlates significantly with distal IENFD ($r=-0.47$, $p=0.005$) and QST parameters (CDT $r=-0.68$, $p<0.0001$; WDT=r 0.57, $p=0.0005$; HPT $r=0.6$, $p=0.01$; CPT $r=0.44$, $p=0.0002$). Simple linear regression showed a relation between sNfl and CDT ($R2$ 0.4, $p=0.0001$), WDT ($R2$ 0.5, $p<0.0001$), distal IENFD ($R2$ 0.3, $p=0.0009$) and sural SNAP ($R2$ 0.4, $p<0.0001$). Using a cut-off of 37.10 pg/mL, no pre-symptomatic subjects showed elevated sNFL, while only 2/13 (15%) symptomatic patients presented normal sNfl values.

Conclusions:
sNFL and small fibre nerve parameters (distal IENFD and QST) are correlated in ATTRv-PN. sNFL and IENFD/QST alterations are early in disease course (PND1)

References:
No

Keywords: serum neurofilament light chains, intraepidermal nerve fibre density, quantitative sensory testing, ATTRv

Motor neuropathy and cerebral folate deficiency: a new syndrome

Poster No:
O 376

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Introduction:
Distal hereditary motor neuropathies (dHMN) represent a homogeneous clinical entity characterized by a pure, length-dependent, peripheral motor involvement, with the etiology remaining unknown in approximately half of the cases. We describe a cohort of patients presenting dHMN associated with cerebral leukoencephalopathy, high cerebrospinal fluid (CSF) proteins, and intracerebral folate deficiency (CFD)

Methods:
In any unexplained chronic complex neurological condition, in addition to routine assessments, we conducted a measurement of 5-methyltetrahydrofolate (5-MTHF) levels in CSF.

Results:
We report five patients presenting with dHMN associated with severe intracerebral folate deficiency (and thus normal serum folate levels), high CSF proteins (> 1g/L), and a leukoencephalopathy affecting the corticospinal tracts and cerebellar white matter. Through genomic studies, we identified pathogenic variants in genes related to mitochondrial translation (MRPS34 in two patients, MRPS23), whose dysfunction was demonstrated through functional studies on fibroblasts. A variant of uncertain significance on SPTAN1 was identified in another patient, while for one patient genome was not conclusive. All patients were treated with high-dose folinic acid, resulting in clinical and electrical stabilization of dHMN and significant improvement of the leukoencephalopathy.

Conclusions:
Since the choroid plexus is responsible for transporting 5-MTHF into the CSF, we consider the hypothesis that dysfunction, particularly mitochondrial dysfunction, of the choroid plexus could be the cause of CFD in these patients. In conclusion, we described a new syndrome including dHMN potentially treatable by correcting the intracerebral folate deficiency.

References:
No

Keywords: Genetics, Choroid plexus, Biomarkers, dHMN

Elucidating the role of iron regulatory protein 2 in the peripheral nervous system

Poster No:
O 377

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Introduction:
Iron is an essential cofactor for multiple metabolic process, whose levels are tightly regulated to guarantee adequate iron availability for proper cellular function. Intracellularly, iron levels are controlled by two major proteins, known as iron regulatory protein (IRP) 1 and 2, that post-translational modulate the expression and activity of additional iron-sensing proteins involved in iron import, export, and storage. Our group has extensively described their role in the brain and spinal cord, during homeostasis, injury, and aging. However, there is no evidence about IRPs function in the peripheral nervous system (PNS).

Methods:
By using a genetic-engineered mouse lacking IRP2, along with molecular, cellular, and biochemical techniques, we aimed to elucidate the role of IRPs for PNS iron homeostasis and under injury-response.

Results:
We first observed that IRP2 transcripts were more abundant than IRP1 levels in mouse dorsal root sensory neurons. We used the Irp2-/- mice and documented aberrant iron accumulation in control and injured sciatic nerve, that was accompanied by increased ferritin and IRP1 protein expressions. Biochemical characterization revealed that mitochondria from Irp2-/- nerves have decreased activities of Complex I-II and reduced NDUFS1 and MTCO1 protein levels. We also demonstrated that Irp2-/- neurons have impaired growth capacity in vitro. After sciatic nerve crush, we documented increased IRP1/2 expression in wild-type mice, that was accompanied by significantly increase in iron levels and higher mitochondrial activity, suggesting a link between IRPs activation and iron availability during the injury-response. Interestingly, iron levels and mitochondrial complex activities did not increase in Irp2-/- mice, whereas ferritin levels increased. Finally, nerve conduction studies showed lower compound muscle action potentials in Irp2-/- sciatic nerve after crush, indicating poor nerve recovery.

Conclusions:
These data suggests that IRP2 plays a major role for PNS homeostasis and also during the injury-response, when tissue-energy demands increase.

References:
Yes

Reference 1: https://pubmed.ncbi.nlm.nih.gov/11175792/

Reference 2: https://pubmed.ncbi.nlm.nih.gov/22003390/

Grant Support:

This work was supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development

Keywords: Axonopathy, iron metabolism, iron regulatory protein 2, neurodegeneration, peripheral nerve system

AAV9-KDAR Gene Therapy is a Promising Treatment Approach for CMT1B

Poster No:
O 378

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Introduction:
Charcot-Marie-Tooth type 1B (CMT1B) is demyelinating neuropathy caused by >200 different autosomal dominant mutations in Myelin Protein Zero (MPZ) gene. Accumulation of mutant MPZ proteins in Schwann cells (SCs), induces the ER stress leading to defective myelination, reduced nerve conduction, and failure of peripheral nerve. In this study, we developed a novel, universal AAV gene therapy approach based on knockdown of mutated MPZ using RNAi, and replacement with a functional RNAi-resistant MPZ (rMPZ) gene. We called this approach AAV9-KDAR.

Methods:
We designed and screened several micro-RNAs (miMPZ) to target endogenous mutant and wild-type MPZ mRNA, and a replacement of rMPZ gene. After performing intensive screening of various AAV vectors to find the best serotype that transduces SCs in vitro, we treated an ex-vivo model of severe early-onset CMT1B-R98C's DRG/Schwann co-cultures with AAV-miMPZ-rMPZ. Myelination of SC, ER stress, and off-target effects were assessed using IF staining, western blot, qRT-PCR, and RNA-seq. Next, we delivered 2.5E+11 or 5E+11 vg of AAV9-miMPZ-rMPZ via intracerebroventricular or intrathecal injections on neonatal and adult CMT1B-R98C mice, respectively, followed by various molecular, behavioral, and electrophysiological assays 6 months post-injection.

Results:
In vitro and ex vivo studies demonstrated significant reduction in various mutant and wild-type MPZ levels, coupled with an increase in rMPZ expression. CMT1B-DRG/SCs co-cultures treated with AAV-KDAR exhibited enhanced myelination, increased numbers of MBP + internodes, and reduced ER stress biomarkers. Improvement in molecular outcomes, treadmill and rotarod motor performance, and CMAP and NCV electrophysiological outcomes have been detected in treated neonatal and adult CMT1B-R98C mice compared to untreated controls. Furthermore, we did not observe any significant off-targets by RNAseq analysis on lead miRNA-treated human SCs.

Conclusions:
This study provides proof of concept for treating CMT1B through AAV9-KDAR approach. Nonetheless, additional research is imperative to optimize AAV doses, enhance efficacy, and assess in vivo safety thoroughly.

References:
No

Grant Support:

CMT Research Foundation

Keywords: Charcot-Marie-Tooth type 1B, Gene therapy, knockdown-and-replace, Myelination, DRG/SCs co-culture

Efficacy of NT-3 Gene Therapy in *Sh3tc2*$^{-/-}$ mouse, a Model for CMT4C

Poster No:
O 379

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Introduction:
CMT4C is a demyelinating, autosomal recessive form of CMT caused by bi-allelic variants in the *SH3 domain and tetratricopeptide repeats 2 (SH3TC2)* gene. In this study, we assessed the efficacy of AAV1.tMCK.NT-3 gene therapy on the *Sh3tc2*$^{-/-}$ mouse, as a model for CMT4C.

Methods:
Four week old *Sh3tc2*$^{-/-}$ mice were injected intramuscularly with $1x10^{11}$ vg dose of rAAV1.tMCK.NT-3 vector (n=15, even sex distribution). Age- and sex-matched *Sh3tc2*$^{-/-}$ mice were used as untreated controls (n=16). Mice were sacrificed six months post-treatment. Functional studies included rotarod and grip strength, and quantitative histological studies were performed.

Results:
Rotarod and grip strength tests showed that NT-3 treated mice had preserved function and performance, surpassing the untreated cohort at endpoint by 16.7% and 16.8%, respectively (rotarod, p=0.0381; grip strength, p=0.0297). The mean endpoint nerve conduction velocity was significantly higher in the treated cohort, corresponding to a 30.8% improvement (NT-3: 29.7 ± 2.47 vs. UT: 22.7± 2.01 m/s; n=15 in each cohort, p=0.0256). NT-3 gene therapy resulted in improvements to myelin thickness, quantified as a significant reduction in the treated group g-ratio (p=0.0492). In both sciatic and tibial nerves, the density of small myelinated fibers (MFs) and Schwann cell (SC) nuclei associated with Remak bundles increased, suggesting that NT-3 stimulated SC proliferation and differentiation. The increase in the total MF density with treatment in sciatic nerves was not significant, however, a 21% increase was observed in the tibial nerve. Moreover, the treatment increased neuromuscular junction connectivity in the lumbricals significantly.

Conclusions:
Results show that AAV1.NT-3 gene therapy provided significant improvements in functional, electrophysiological and histopathological parameters in the *Sh3tc2*$^{-/-}$ mouse model for CMT4C. This is the fourth CMT subtype model for which we successfully showed efficacy of NT-3 with potential to provide disease modifying effects for the largest group of CMT patients.

References:
No

Grant Support:

Internal grant

Keywords: CMT, Sh3tc2, NT-3, Gene therapy, myelin

Recessive Variants In PIGG Cause A Motor Neuropathy With Variable Conduction Block, Childhood Tremor And Febrile Seizures

Poster No:
O 380

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Introduction:
Many fundamental cell surface proteins rely upon glycosylphosphatidylinositol (GPI) anchors. The GPI pathway involves the phosphatidylinositol glycan (PIG) group of genes. Biallelic variants in PIGG are reported to cause hypotonia, epilepsy, intellectual disability plus cerebellar features. The red blood cell antigen Emm is thought to be a GPI anchored protein and PIGG variants have independently been identified to cause Emm-negative blood group.

Methods:
Individuals with biallelic PIGG variants were phenotyped at five European centres. Genotyping was performed through next-generation sequencing. Blood samples from one family were tested for expression of the Emm blood group antigen on red blood cells by standard methods. Fluorescence-activated cell sorting analysis and Western Blotting were performed on PIGO/PIGG double knock-out (DKO) HEK293 cells transfected with promoter driven wild-type or mutant PIGG.

Results:
Eight patients (two male) from six non-consanguineous families were identified. All had a pure motor neuropathy with onset in first or second decade. Additional features included postural tremor (8/8), febrile seizures (6/8), and cerebellar signs (4/8). Neurophysiology revealed a predominantly axonal, pure motor neuropathy (8/8), and four individuals with conduction block (CB). Six pathogenic variants in PIGG were detected: p.(Trp505*), p.(Gly278Arg), p.(Gly41*), p.(Trp678*), c.2735+2T>C, p.(Asp876ArgfsTer111) and two variants in cis p.(Gly19Glu) and p.(Val339Gly) (variants of uncertain significance). Red blood cells from siblings with p.(Trp505*) and p.[(Gly19Glu)(Val339Gly)] showed no Emm expression. Wild-type PIGG restored the expression of GPI anchored proteins in DKO HEK293 cells whereas both missense mutants (p.(Gly19Glu), p.(Val339Gly)) could not restore GPI protein expression. Nonsense mutant p.(Trp505*) had partial activity. PIGG protein expression of the missenses was similar to the wild-type PIGG, and p.(Trp505*) had expression with the normal size demonstrating readthrough product.

Conclusions:
We demonstrate biallelic variants in PIGG cause a motor neuropathy with CB, tremor, febrile seizures and cerebellar features, broadening the established phenotype. We recommend addition of PIGG to neuropathy gene panels.

References:
Yes

Reference 1: Tremblay-Laganière C, Maroofian R, Nguyen TTM, et al. PIGG variant pathogenicity assessment reveals characteristic features within 19 families. Genet Med. Published online 2021. doi:10.1038/s41436-021-01215-9

Reference 2: Lane, W.J., Aeschlimann, J., Vege, S. et al. PIGG defines the Emm blood group system. Sci Rep 11, 18545 (2021). https://doi.org/10.1038/s41598-021-98090-w

Keywords: CMT, Charcot-Marie-Tooth, Genetics, PIGG, conduction-block

The INSPIRE trial in SORD Deficiency: Results from the Month 12 analysis

Poster No:
O 381

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Introduction:
Sorbitol Dehydrogenase (SORD) Deficiency is a recently discovered autosomal recessive hereditary neuropathy affecting approximately 3000 patients in the US, and 4000 patients in Europe. It is characterized by the inability to convert sorbitol into fructose, resulting in blood sorbitol levels > 100-fold greater than in healthy individuals. SORD Deficiency has been found to be one of the most frequent genetic causes of axonal Charcot-Marie-Tooth (CMT2) and distal hereditary motor neuropathy (dHMN).

Methods:
The ongoing INSPIRE study is an international, multicenter, randomized, double-blind, placebo-controlled investigational trial. The study is designed to assess the pharmacodynamic (PD) efficacy of AT-007 (govorestat) treatment as measured by sorbitol reduction in the blood, as well as the clinical benefit of long term administration in patients with SORD Deficiency.

Results:
Between May 2022 and March 2023, 56 patients with SORD Deficiency from 4 countries were randomized in a 2:1 ratio to active govorestat (AT-007) 20 mg/kg once daily or placebo. The mean age at randomization was 34.3 years (± 11 years); 18 patients (32.14%) were female. Twenty six patients (46.6%) had the previously described biallelic homozygous mutation c.757 delG (p.A253Qfs*27) variant. SORD Deficiency patients were stratified at the time of entry as mild, moderate, or severely affected based on the results of the 10-meter-walk-run test (10-MWRT): 34 (60.7%) were mild, 14 (25%) were moderate, and 8 (14.3%) were severe. The baseline mean for whole blood sorbitol levels was 30,200 ng/mL (± 5920). Govorestat treatment reduced sorbitol levels by approximately 52% (~16,000ng/ml) over 90 days of treatment ($p<0.001$). The clinical results through 12 months of treatment will be shown at the time of the presentation.

Conclusions:
In summary, SORD Deficiency is a severe and progressive neuropathy caused by abnormally elevated levels of sorbitol. The INSPIRE trial was designed to evaluate efficacy and safety of AT-007 in patients with SORD Deficiency.

References:
No

Grant Support:

Applied Therapeutics, Inc

Keywords: SORD Deficiency, SORD, CMT2, dHMN, Govorestat

Non-Human Primate Biodistribution and Safety Study Supports Translation of AAV9-mediated Gene Silencing Therapy for CMT1A Neuropathy

Poster No:
O 382

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Introduction:
CMT1A, the most common inherited demyelinating peripheral neuropathy, is caused by PMP22 gene duplication. PMP22 over-expression destabilizes the myelin sheath in Schwann cells leading to demyelination, secondary axonal loss and disability. We developed and validated an AAV9 vector expressing an engineered miRNA (miR871) that reduces PMP22 expression and improves neuropathy in a CMT1A mouse model after intrathecal injection. AAV9-U6-miR871 has received orphan drug and rare pediatric disease designations from FDA for the treatment of CMT1A.

Methods:
To demonstrate the safety and translational potential of this approach to treat CMT1A patients, we evaluated the biodistribution and possible toxic effects of AAV9-U6-miR871 in cynomolgus monkeys. We delivered 2 doses of AAV9-U6-miR871 (6e13 or 1.2e14 vg/animal) by lumbar intrathecal injection, and analyzed animals 6- or 12-weeks post-injection. PBS-injected animals served as controls. We performed clinical and neurological observations throughout the course of the study and collected longitudinal samples to assess hematology, serum, coagulation, chemistry, and urine parameters. Prior to study termination, animals underwent ophthalmic testing, electrocardiogram, nerve conduction studies, testing for AAV9 neutralizing Abs, followed by histopathological and molecular analysis.

Results:
Intrathecal injection with both doses of AAV9-U6-miR871 resulted in efficient transduction of PNS tissues and PMP22 target engagement. In-life observations and post-mortem analysis confirmed the safety of AAV9-U6-miR871, with animals showing no behavioral abnormalities, no clinical chemistry alterations, and no impairment of tibial nerve conduction studies. Minor, subclinical inflammation was found in DRGs of some treated animals.

Conclusions:
We provide for the first time detailed biodistribution analysis of an intrathecally-delivered AAV9 vector targeting Schwann cells in the PNS of cynomolgus monkeys, along with promising safety data. Collectively, these results support the scale-up potential and further clinical development of AAV9-U6-miR871 for CMT1A treatment and provide valuable information for AAV9-mediated gene therapies for other demyelinating neuropathies as well.

References:
No

Grant Support:

Armatus Bio

Keywords: Non human primates, AAV9, Lumbar intrathecal injection, Charcot Marie Tooth type 1A, Gene therapy

AAV-Mediated Delivery of Supplemental tRNA Rescues Neuropathy in Aminoacyl-tRNA Synthetase-Associated Mouse Models of Charcot-Marie-Tooth Disease

Poster No:
O 383

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Introduction:
Aminoacyl tRNA synthetases (aaRSs) represent the largest gene family associated with Charcot-Marie-Tooth disease (CMT). Dominant mutations in glycyl-tRNA synthetase (Gars) result in enhanced binding to tRNA-Gly, depleting free glycyl-tRNA and inhibiting protein synthesis. Evidence suggests this mechanism also underlies other aaRS-associated CMT. Transgenic overexpression of tRNA rescues translation deficits and neuropathy in CMT-aaRS animal models, and the present work demonstrates the effectiveness of delivering tRNAs postnatally via AAV, enhancing the clinical relevance of tRNA supplementation as a potential therapeutic strategy.

Methods:
Separate AAV9 vectors were created that express each of the 4 tRNA-Gly isoacceptors (ACC, CCC, GCC, and TCC), as well as an intronless version of tRNA-Tyr, all driven by a U6 promoter. Virus was delivered by intracerebroventricular injection to neonatal mice carrying mutations in Gars (C201R, ΔETAQ, and P278KY alleles) or Yars-E196K. Mice were analyzed for neuropathy phenotypes at timepoints after disease onset in untreated animals.

Results:
AAV9-mediated overexpression of tRNA-Gly rescued neuropathy in all Gars models, but the degree of rescue varied by isoacceptor, with GCC providing near complete rescue, TCC and CCC an intermediate level, and ACC having no effect. GarsΔETAQ mice treated with the GCC vector no longer differed from their WT littermates on wire hang time, nerve conduction velocity, and body weight. Consistent with the specificity of the tRNA/synthetase interactions, AAV9-tRNA-Tyr treatment had no effect in GarsΔETAQ mice. Studies to confirm the efficacy of AAV9-tRNA-Tyr in Yars-mutant mice are ongoing.

Conclusions:
Sequestration of tRNA by mutant synthetases is an attractive hypothesis to explain how dominant mutations in genes encoding aaRSs lead to disease via decreased translation and chronic activation of stress response pathways. Delivering supplemental tRNA via AAV9 targets a proximal stage in the disease mechanism of aaRS-associated CMT and is an effective therapeutic strategy, providing a near-complete rescue in mouse models.

References:
No

Grant Support:

R37NS054154 (RWB)

Keywords: gene therapy, Charcot-Marie-Tooth, mouse model

Dominant OGDH mutations cause peripheral neuropathy with ataxia and optical atrophy

Poster No:
O 384

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Introduction:
2-oxyglutarate dehydrogenase (OGDH) is an E1 component of α-ketoglutarate dehydrogenase complex (α-KGDH) that plays a pivotal role in the Krebs cycle metabolism. Biallelic variants in OGDH have been reported to cause OGDH deficiency (OGDHD; OMIM: # 203740), an early-onset neurodevelopmental and mitochondrial disorder. However, whether monoallelic OGDH variants could lead to dominant effects in humans had not been known.

Methods:
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Results:
In this study, we identified de novo OGDH c. 1909C>T (p.Arg637Trp), heterozygous c.162T>G (p.Ser54Arg) and heterozygous c.512A>G (p. Lys171Arg) variants by whole-exome sequencing (WES) in individuals exhibiting late-onset neurological phenotypes, including peripheral neuropathy, cerebellar ataxia and bilateral optic atrophy. Blood analysis for the individual with the p.Arg637Trp variant did not reveal ketogenosis, however lactate levels were increased in CSF. In patient lymphoblasts, OGDH protein levels did not appear altered, both in whole-cell lysate and in the mitochondrial fraction, compared to familial controls. Analysis of the enzyme activity showed reduced enzyme activity in patient cells. Analysis of the cellular mitochondrial functioning in patient-derived fibroblasts revealed defects in mitochondrial respiration. To determine whether the monoallelic OGDH variants act as dominant-negative mutations, we generated Drosophila models harboring UAS-dOgdh (p.Arg639Trp) and UAS-dOgdh (p.Thr58Arg) mutations, homologous to the human variants. We found that ubiquitous expression of dOgdh (p.Arg639Trp) or dOgdh (p.Thr58Arg) did not result in developmental lethality, but to locomotion defects in aged flies, confirming the human phenotype.

Conclusions:
These findings indicate that both variants act as document-negative mutations, consistent with the observed clinical manifestations in individuals carrying these monoallelic OGDH variants. Our data suggest that monoallelic OGDH variants disrupt α-KGDH function, thereby causing a late-onset neuropathy phenotype in patients.

References:
No

Keywords: Genetic causes for peripheral neuropathy, Mitochondrial Metabolism, Drosophila disease modelling, Patient-derived cells

PDE4D inhibition with Gebr32a stimulates Schwann cell differentiation and improves the functional outcome in models for Charcot Marie Tooth disease 1A

Poster No:
O 385

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Introduction:
Charcot-Marie-Tooth disease type 1A (CMT1A) is an inherited peripheral neuropathy caused by a duplication of the PMP22 gene and for which no therapy exists. CMT1A is characterized by Schwann cell dedifferentiation and demyelination, leading to decreased nerve conduction and subsequent functional deficits. Cyclic adenosine monophosphate (cAMP) is an important molecule involved in Schwann cell maturation and differentiation. Hence, increasing cAMP by inhibiting its natural regulators, phosphodiesterases (PDE), may be a promising therapeutic strategy in CMT1A.

Methods:
Recently we obtained a second Medical use patent for the use of Gebr32a, a specific PDE4D inhibitor, for demyelinating disorders. Here, the effect of Gebr32a was tested in the context of CMT1A using the C3-PMP22 mouse model and patient iPSC-derived Schwann cells.

Results:
Adult C3-PMP22 mice were injected subcutaneously with Gebr32a or its vehicle control for 10 weeks. We found that Gebr32a significantly increased the nerve conduction speed in C3-PMP22 mice indicating remyelination. In addition, we observed significantly improved sensorimotor functions in C3-PMP22 mice after Gebr32a treatment, using the beam walk and the grid walk test. Gebr32a-treated animals were also able to run longer on an accelerating rotarod compared to controls, and presented with an improved grip strength. Moreover, histological analysis revealed an increase in myelination in the sciatic nerve of Gebr32a-treated C3-PMP22 mice. In primary murine CMT1A Schwann cells, we observed a dose-dependent increase of Gebr32a in the expression of pro-myelinating factors Oct6, KROX20, MBP and PLP, and a decreased expression of the dedifferentiation marker c-Jun and hPMP22. Notably, this was confirmed in CMT1A patient iPSC-derived Schwann cells stimulated with Gebr32a, highlighting the clinical relevance of our findings.

Conclusions:
To conclude, inhibition of PDE4D with Gebr32a can be used to improve the functional and molecular outcome in model systems for CMT1A, and this study highlights its potential as a new therapeutic strategy for CMT1A disease management.

References:
No

Grant Support:

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Keywords: Charcot Marie Tooth disease 1A, Demyelination, Phosphodiesterases, Gebr32a, Therapy

SORD and SORD2P inversion: long read sequencing identifies a novel genetic mechanism underlying inherited neuropathy.

Poster No:
O 386

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

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

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

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

References:
No

Keywords: long read sequencing, optical genome mapping, SORD, SORD2P, inversion

Understanding The Transcriptional Regulation Of Human NMNAT2 And SARM1

Poster No:
O 387

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Introduction:
The programmed axon degeneration pathway (or Wallerian degeneration) has become an important drug target in a bid to tackle neurodegenerative diseases. Protein coding mutations in two of the key genes involved in this pathway, NMNAT2 and SARM1, are associated with human neurodegenerative diseases including ALS and peripheral neuropathy. SARM1, an NAD+ degrading enzyme, is considered the central executioner of programmed axon degeneration. In the uninjured axon, SARM1 activity is repressed by NMNAT2, an NAD+ synthesizing enzyme. Mouse studies have highlighted that the relative levels of NMNAT2 and SARM1 could impact disease progression and neurodegenerative outcome. Thus, understanding how human NMNAT2 and SARM1 are regulated on a transcriptional level has the potential to identify critical regions of these genes in which variation may modulate patient outcomes and disease progression.

Methods:
In the present study we use cell models, luciferase assays and in silico motif analyses.

Results:
We identify the promoter regions of human NMNAT2 and SARM1 and we investigate transcription factors which may contribute to the regulation of their expression. Moreover, preliminary data indicates a non-coding region 5' of the canonical transcriptional start site of human NMNAT2 that represses expression. Finally, we identify human variants in the promoter regions of NMNAT2 and SARM1, including a homozygous variant in peripheral neuropathy, and explore the impact of said variations on expression levels.

Conclusions:
In sum, this work describes the promoter gene regions important for human NMNAT2 and SARM1 expression, and begins to investigate how changes in expression levels of these genes may contribute to human disease, such as peripheral neuropathy. Advances in whole genome sequencing studies and genomic databases are likely to expand our understanding of the role of the programmed axon degeneration pathway and in which human diseases it is most relevant.

References:
No

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ALS Finding a Cure and ALS Association (23-SI-616)

Keywords: SARM1, NMNAT2, transcription, axon degeneration, NAD

International Diabetes Neuropathy Consortium

International Diabetes Neuropathy Consortium (IDNC) Abstracts

O 388 - 396

Impact of Tirzepatide, a GLP1/GIP Receptor Agonist, on the Relative Risk of Developing Diabetic Neuropathy in Patients with Type 2 Diabetes Mellitus:

Poster No:
O 388

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Introduction:
There is no known medication that decreases the relative risk (RR) of developing diabetic neuropathy (DN). This study assesses the impact in diabetes mellitus (DM2) of commonly used antidiabetic medications on reducing the RR of developing neuropathy.

Methods:
Utilizing the TrinetX global health research network, de-identified electronic medical records from 83 healthcare organizations were analyzed. Patients with DM2 were entered prospectively from 1/1/2022 to 12/31/2022 and new onset of neuropathy was determined using ICD10 coding. Groups were matched using propensity score matching based on age, sex, BMI, HbA1C, and blood glucose levels. Matched Cohort A had DM2 but was not using the assessed diabetes medication. Cohort B had DM2 and was taking the assessed medication.

Results:
The only DM2 medication that progressively reduced the RR of neuropathy over 2 years was Tirzepatide (n=41,893): 1 year (5.4% vs. 3.8%) and 2 years (A: 6.5% vs. B: 3.9%). Semaglutide (n=230,478) slightly decreased RR at 1 year (A: 5.4% vs. B: 5%) and 2 years (A: 6.5% vs. B: 5.8%). In contrast, continuous use of insulin progressively increased the neuropathy RR (n=1,063,464): 1 year (A: 4.9% vs. B: 5.8%) and 2 years (B: 5.9% vs. 6.8%). The neuropathy risk was minimally increased for Cohort A vs. Cohort B with Dulaglutide (n=228,961): 1 year (5.1% vs. 5.8%) and 2 years (6.1% vs. 6.8%); and Empagliflozin (n=295,307): 1 year (5.1% vs. 5.2%) and 2 years (6.1% vs. 6.2%). Metformin (n=1,242,660) did not affect neuropathy RR at 1 year (4.9% vs. 4.7%) and 2 years (5.8% vs. 5.6%).

Conclusions:
Tirzepatide is an analog of GLP-1 and GIP, mimics naturally occurring incretins, effectively promotes weight loss, and lowers glucose generation in the liver. Tirzepatide significantly and progressively decreases the RR of developing diabetic peripheral neuropathy. Further research is needed to identify subgroups that respond optimally.

References:
No

Keywords: Diabetic Neuropathy, Tirzepatide, GLP-1/GIP receptor agonists

Single-cell transcriptomics of primary sensory neurons identify oxidative phosphorylation deficiency as the primary defect in diabetic neuropathy

Poster No:
O 389

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Introduction:
Mitochondrial dysfunction has long been suspected as a primary cause of diabetic neuropathy (DN) due to energy metabolism dysregulation associated with diabetes. C57BL/6 mice, which are commonly used to create animal models of DN, happen to carry a spontaneous mitochondrial gene mutation. Although a number of mitochondria-associated pathways have been implicated in the pathogenesis of DN, the actual mechanism of mitochondrial dysfunction in primary sensory neurons remains to be elucidated.

Methods:
We generated DN mouse models by feeding the mice a high-fat diet followed by administration of low-dose streptozotocin. The mice were subsequently assessed by behavioral and morphologic analyses. Single-cell RNA-sequencing (scRNA-seq) was performed on dorsal root ganglia (DRG) from DN and control mice. Mitochondria-Nuclear Exchange (MNX) mouse models were used to evaluate the contribution of different mitochondrial DNA backgrounds to the development of neuropathy and neuropathic pain.

Results:
scRNA-seq identified 11 primary sensory neuronal cell types. The proportions of PEP1, NP3, Abeta RA-LTMR and proprioceptor neurons were decreased in DN mice, whereas the proportion of NP1 neurons was increased. Mitochondrial oxidative phosphorylation (OXPHOS) was the most affected pathway in DN: multiple genes of the OXPHOS pathway, both nuclear- and mitochondrial-encoded, were downregulated. The effect was seen in essentially all sensory neuron subtypes, with the mitochondrial-encoded OXPHOS genes most downregulated in C-LTMRs. In MNX mice which had C57BL/6 nuclei but C3H mitochondrial background, the diabetic mechanical allodynia phenotype was rescued. The finding highlights the importance of mitochondrial background or function in the development of DN.

Conclusions:
Our data suggest that differential expression of OXPHOS and related genes may have a significant impact on the pathogenesis of DN because of the importance of these genes in energy metabolism, which is compromised in diabetes. Restoration of the expression of OXPHOS genes may therefore represent a promising strategy for preventing or halting the progression of DN.

References:
No

Keywords: Mitochondria, Diabetic neuropathy, scRNA-seq, Dorsal root ganglia

Single-cell RNA-sequencing deconvolutes cellular and molecular responses to diet and exercise interventions in prediabetic neuropathy

Poster No:
O 390

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Introduction:
The growing prevalence of obesity, prediabetes, and type 2 diabetes has led to a parallel increase in their complications, including peripheral neuropathy (PN), a progressive, distal-to-proximal peripheral nerve degeneration. While tight glucose control is the primary therapeutic approach, it alone does not slow or reverse disease progression in these patient cohorts. Although new clinical guidelines advocate for diet and exercise as effective interventions for PN, the optimal regimen is not well-defined, with a lack of comparative studies on their efficacy and underlying mechanisms.

Methods:
To address this knowledge gap, we used single-cell RNA-sequencing (scRNAseq) to determine the effects of diet and/or exercise on peripheral nerve cellular composition and molecular mechanisms in the high-fat diet (HFD)-fed mouse model of obesity, prediabetes, and PN. The study consisted of five groups: 1) standard diet (SD), 2) HFD, 3) dietary reversal (DR) from HFD to SD, 4) HFD with running wheel exercise (EX), and 5) HFD with dietary reversal and exercise (DR-EX). Interventions began at 18 weeks and lasted for 8 weeks.

Results:
DR and DR-EX restored the metabolic and neuropathy phenotypes, while EX alone only improved PN. scRNAseq in sciatic nerves identified seven major cell types, including Schwann cells (SCs), smooth muscle cells, fibroblasts, pericytes, perineurial cells, macrophages, and endothelial cells. Most cell types remained quantitatively stable after interventions. However, EX significantly increased SC number versus controls. While interventions induced distinct transcriptional responses, fatty acid metabolism and insulin signaling were similarly regulated in SCs by diet and exercise. We also identified increased cell-cell communication patterns in DR and EX alone versus HFD, which mostly impacted SC subpopulations and might promote nerve recovery.

Conclusions:
Overall, our findings lay the groundwork for understanding the cellular and molecular changes that underlie the systemic and neuroprotective effects of diet and/or exercise, offering new therapeutic targets for PN.

References:
No

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Keywords: diabetic peripheral neuropathy, single-cell RNA-sequencing, exercise, dietary reversal, Schwann cells

Pain or no pain? Sensory excitability changes in painful and non-painful type 2 diabetes mellitus

Poster No:
O 391

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Introduction:
Diabetic neuropathy (DN) affects over 90% of type 2 diabetes mellitus (T2DM), despite pain is one of the main symptoms, it remains challenging to diagnose this complication, as no biomarker or clear consensus on the clinical definition of either painful or non-painful DN exists. The prevalence of painful DN in T2DM varies from 10-70% and approximately 40% of patients do not receive treatment. The pathogenesis of painful DN is complex and unclear while symptoms do not correlate to the clinical severity. The aim of this study is to elucidate sensory axonal changes of painful and non-painful T2DM to investigate patients treated with pregabalin to explore the underlying mechanisms for diabetic neuropathic pain.

Methods:
Clinical assessments, nerve conduction studies, sensory nerve excitability testing and visual analog score (VAS) pain score were assessed in 200 T2DM. 43 had symptoms of spontaneous painful sensation over feet or hands (painful) and 88 had no sensory symptoms (non-painful). We further categorise painful T2DM into cohort treated with pregabalin and without to investigate the effects of pregabalin.

Results:
Sensory nerve excitability of painful T2DM showed significant ($p < 0.05$) differences to non-painful cohort with increased refractoriness, superexcitability, TEd(peak), TEd(10-20ms), TEd(40-60ms) parameters with reduced subexcitability and stimulus for 50% of peak amplitude. Within the painful T2DM, patients with higher VAS score (>7) had significantly less TEd40(Accom) and TEh(overshoot) than patients with lower VAS score (<7). In addition, painful DN treated with pregabalin showed significant increase in S2 accommodation, stimulus-response slope and TEd40(Accom) in contrast to the non-treated cohort.

Conclusions:
These neurophysiological changes demonstrate the development of painful sensory DN maybe due to reduction in accommodative properties and dysfunction of ATP-dependent potassium (K+) channels. These findings provide insights into painful DN and effects of pregabalin which may provide a basis for early detection and neuroprotective strategies which are crucial to prevent further neuronal damage.

References:
No

Keywords: Painful Diabetic Neuropathy, Sensory axon, Nerve excitability, Pregabalin, ATP-dependent K+ channel

Uncovering Sensory Nerve Functions in White Adipose Tissue

Poster No:
O 392

Authors:
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Introduction:
White adipose tissue (WAT) stores energy and is innervated by sensory and sympathetic nerves enabling cross-talk with the central nervous system in energy-balance regulation. Norepinephrine, the sympathetic neurotransmitter, stimulates lipolysis, browning (brown adipocyte development in WAT), and thermogenesis. Conversely, WAT sensory nerves secrete the neuropeptide calcitonin gene related peptide (CGRP). Despite data confirming sensory nerve contribution to adipose tissue metabolism, and increased CGRP in circulation of obese humans, CGRP functions in regulating metabolic health remains understudied

Methods:
Whole-mount imaging of inguinal WAT depot from sensory nerve reporter mice (Nav1.8Cre x tdTomato) and intravital calcium imaging in WAT while co-injecting calcium dye and 13-HODE, a strong pro-inflammatory interoceptive oxylipin that agonizes transient receptor potential (TRP)V1 on sensory nerves. We administered 13-HODE into inguinal WAT and performed ELISA, qPCR, western blot analyses on the injected depots, dorsal root ganglia (DRG), and hypothalamus to identify neural activation. Lastly, we performed CGRP ELISA on adipose depots of mice subjected to altered energy balance states.

Results:
CGRP+ sensory nerves innervate WAT. 13-HODE promoted sensory activation in WAT, as seen by intravital calcium imaging. 13-HODE (and TRPV1-agonist resiniferatoxin) increased WAT CGRP levels with corresponding immediate early-gene and neuropeptide upregulation in DRG and hypothalamus after 30-minutes. In vitro, recombinant CGRP-treatment upregulated lipolytic pathways in pre-adipocytes (pHSL/HSL). In vivo, CGRP delivery to WAT increased free-glycerol levels by 120 minutes. CGRP levels changed with altered energy-balance states; isocaloric high-fat diet or chronic obesity (positive energy-balance), and beta-adrenergic agonists and 3-week exercise (negative energy-balance) increased CGRP. 10-day cold stimulation and 30-day caloric restriction reduced CGRP.

Conclusions:
CGRP promoted lipolysis in WAT, and CGRP levels changed with altered energy-balance states in WAT. Overall, these data indicate a sensory feedback-system in adipose, including oxylipin-induced sensory nerve activation and CGRP-induced lipolysis, suggesting adipose sensory nerves may be nociceptors communicating local inflammatory lipid levels to the brain.

References:
No

Keywords: Adipose tissue, Sensory nerves, Oxylipin, Sensory neuropeptide, Calcitonin Gene-Related Peptide (CGRP)

Epidermal Langerhans Cells as disease-driving immune cells in Painful Diabetic Neuropathy

Poster No:
O 393

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Institutions:
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Introduction:
Painful diabetic neuropathy (PDN) is one of the most common and intractable complications of diabetes, resulting in remodeling of the cutaneous innervation and neuropathic pain. Increasing evidence suggests the crucial role of epidermal non-neuronal cells in the development of PDN.

Methods:
To understand how epidermal cells communicate with cutaneous afferents and how this communication affects PDN, we performed single-cell RNA sequencing of the epidermis of mice fed a high-fat diet (HFD) for 10 weeks.

Results:
Among several epidermal cell clusters, we recognize Langerhans Cells (LCs) as critical players in neuro-immune communication and potentially involved in axonal degeneration/regeneration in PDN through semaphorin-plexin pathways. In addition, we have identified a panel of inflammatory molecules released by LCs and putatively linked to the onset and maintenance of PDN. To collect a more comprehensive understanding of the skin microenvironment in PDN, by applying 10X Genomics Visium method, we have characterized the spatial transcriptomic landscape of the skin of patients with painful and non-painful diabetic neuropathy and validated key targets through in-situ hybridization and immunohistochemistry. We have observed that LC epidermal density is increased in skin biopsy from PDN patients with painful but not in patients with non-painful diabetic neuropathy.

Conclusions:
Altogether, our results indicate that the altered neuron-immune communication between LCs and cutaneous afferents might contribute to neuropathic pain in PDN and remodeling of the cutaneous innervation in the skin of PDN in mice and patients. Indeed, identifying the pivotal role of LCs as disease-driving immune cells might open the way for therapeutic treatment strategies for PDN, such as antigen-specific immunotherapy.

References:
No

Grant Support:

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Keywords: painful diabetic neuropathy, spatial transcriptomics, neuro-immune communication, single-cell RNA sequencing, neuropathic pain

Saturated and Monounsaturated Fatty Acids Modulate Microtubule Acetylation and Mitochondrial Transport in Sensory Neurons

Poster No:
O 394

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Introduction:
Peripheral neuropathy (PN) is a common complication of diabetes and prediabetes resulting from distal-to-proximal dorsal root ganglion (DRG) sensory neuron damage. PN associates with dyslipidemia in type 2 diabetes and prediabetes indicating that elevated levels of dietary saturated fatty acid (SFAs) and reduced levels of monounsaturated fatty acids (MUFAs) contribute to DRG neuron damage. DRG neurons extend meters in length and require mitochondrial-derived ATP throughout the axon. To meet this high energy demand, mitochondria are transported along the axonal microtubule, which is frequently modified by post-translational modifications including acetylation. Microtubule acetylation state is regulated by acetylases and deacetylases, such as Sirtuin2, but the impact of SFAs and MUFAs on microtubule acetylation is unknown. We tested whether SFAs and MUFAs differentially modulate axonal mitochondrial transport by altering acetylation of α-tubulin.

Methods:
Cultured DRG neurons were treated with physiological concentrations of SFA palmitate, MUFA oleate, equimolar mixtures of oleate/ palmitate, or palmitate + 1 μM Sirtuin2 inhibitor SirReal. First, acetylated α-tubulin levels were assessed in treated DRG neuron lysates by fluorescent western blotting. Second, live-cell time-lapse confocal microscopy was used to evaluate mitochondrial motility in treated DRG neurons.

Results:
Palmitate reduced acetylated α-tubulin levels in DRG neuron lysates, whereas oleate alone and oleate/ palmitate mixtures preserved α-tubulin acetylation. Similarly, mitochondrial transport was significantly reduced in DRG neurons treated with palmitate, but unaffected in DRG neurons treated with oleate alone or oleate/ palmitate mixtures. Supplementing palmitate treatments with the Sirtuin2 inhibitor, SirReal, blocked the loss of acetylated α-tubulin induced by palmitate treatments, indicating that palmitate stimulates deacetylation of α-tubulin. SirReal also partially retained mitochondrial transport in palmitate-treated DRG neurons suggesting that deacetylation of α-tubulin impairs mitochondrial transport in palmitate-treated DRG neurons.

Conclusions:
These results indicate that microtubule acetylation is differentially modulated by SFAs and MUFAs, which impacts mitochondrial transport in DRG sensory neurons.

References:
No

Grant Support:

Support for this study was provided by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (R00DK119366), the Columbia University Diabetes Research Center Pilot and Feasibility grant (P30DK063608), and the Thompson Family Foundation Initiative (TFFI) at Columbia University.

Keywords: Diabetic Peripheral Neuropathy, Fatty Acids, Mitochondrial transport, Microtubule, Post-translational modifications

Exploring the Impact of Obesity and Metabolic Markers on Peripheral Neuropathy Severity in T2DM, IGT, and Healthy Individuals

Poster No:
O 395

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Introduction:
Obesity emerges as the second most significant factor predisposing individuals to peripheral neuropathy, following diabetes. The aim of this study is to evaluate obesity's impact on peripheral neuropathy markers among participants with diabetes,pre-diabetes,and those without these conditions.

Methods:
A cohort of 353 participants was assessed:208 with Type 2 Diabetes Mellitus(T2DM)(Mean Age: 50.5±0.58; Disease Duration: 8.7±0.50 yrs),55 with Impaired Glucose Tolerance (IGT) (Mean Age: 52.0±2.2 years),and 90 Healthy Controls (HC)(Mean Age:50.2±0.96 years). Comprehensive medical, neurological, and ophthalmological evaluations were conducted, encompassing lipid profiles, HbA1c levels, blood pressure, and BMI measurements.

Results:
Healthy Controls,both with(n=19) and without(n=71) obesity, clinical findings in lipid profiles, kidney function, and nerve fibers which measured with CCM(NFD,NBD,NFL) were within normal range.In the IGT group,although the HDL,LDL and eGFR had significant differences between the obese(n=25) and non-obese(n=30),there was no significant difference in neuropathy markers that were assessed with NDS,NCS,QST and autonomic function tests.The Corneal nerve parameters(NFD,NBD,NFL) showed significant reduction compared to the HC, but no difference between the obese and non-obese IGT.T2DM subjects were presented with significant neuropathy compared to HC and IGT.T2DM with Obesity (n=123) vs those without Obesity(n= 85) showed significant abnormality for Lipid profile, kidney function and neurological markers. NDS was significantly higher in obese subjects (4.28 vs 3.41).However, there was no significant difference in NCS,VPT,CPT,WST and CVR-R.Corneal nerve parameters were significantly reduced compared to HC and IGT, but there was no difference between obese and non-obese subjects.

Conclusions:
This groundbreaking study highlights that while T2DM individuals with Obesity showed the highest peripheral neuropathy levels, significant nerve damage was also evident in non-obese participants, aligning with IGT findings. Thus, elevated glucose levels appear to be the primary contributor to nerve damage, alongside lipid and metabolic factors. Longitudinal follow-ups are recommended to track disease progression and outcomes, particularly in severe obesity cases, offering deeper insights into these complex relationships.

References:
Yes

Reference 1: Lead author and Presenter: Mitra Tavakoli

On behalf of:
Fukashi Ishibashi, Miki Taniguchi, Aiko Kosaka, Harumi Uetake, Hassan Fadavi, Mitra Tavakoli

Grant Support:

This study was conducted without any associated funding.

Keywords: Peripheral Neuropathy, Diabetes, Obesity, Small nerve fibres, Microvascular

The Reactive Dicarbonyl, Methylglyoxal, Drives Intraepidermal Nerve Fiber Loss

Poster No:
O 396

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Introduction:
Intraepidermal nerve fiber loss (IENF) occurs in many human diseases, including, prominently in small fiber neuropathy in patients with diabetes. Understanding the mechanisms underlying IENF loss can provide insight into better therapeutic options and improved peripheral nerve health. The reactive dicarbonyl methylglyoxal (MGO) is elevated in diabetic patients and conditions associated with metabolic dysfunction. Here, we tested how MGO impacts epidermal axon health in preclinical mouse models and primary dorsal root ganglion (DRG) neurons.

Methods:
MGO (720ng) was injected intraperitoneal into multiple murine models and IENF density was assessed through immunochemistry. We repeated these experiments in primary (C57Bl/6) DRG cell cultures by treating DRG neurons with 720ng MGO at 2 hours and 48 hours post-plating.

Results:
Surprisingly, MGO injection significantly decreased IENF density in the hind paw (Control: 45.5 + 2.3, MGO-treated: 27.6 + 1.9 SEM) seven days after MGO injection. We know that consuming a ketogenic diet for one week prior to MGO injection prevents MGO-induced pain. Here, we show that seven days of a ketogenic diet also prevents IENF loss and can, importantly, stimulate the regeneration of MGO-damaged axons to control levels after MGO-induced IENF loss occurs. Next, we utilized a mouse substrain (BALB/cByJ mice) that overexpresses glyoxylase 1 (GLO1), an enzyme that breaks down MGO. BALB/cByJ mice injected with MGO had no changes in IENF density, suggesting GLO1 activity can prevent MGO-induced IENF loss. SARM1 is an enzyme involved in axon degeneration, and MGO injection in SARM1 null mutant mice did not decrease IENF density. MGO treatment significantly prevented neurite outgrowth in vitro.

Conclusions:
In conclusion, we add new evidence that elevations in MGO contribute to epidermal axon degeneration and prevent neurite outgrowth in vitro. We also show that a ketogenic diet, overexpression of Glo1, or knockdown of SARM1 in mice can combat these effects.

References:
Yes

Reference 1: Enders JD, Thomas S, Lynch P, Jack J, Ryals JM, Puchalska P, Crawford P, Wright DE. ATP-Gated Potassium Channels Contribute to Ketogenic Diet-Mediated Analgesia in Mice. bioRxiv [Preprint]. 2023 May 24:2023.05.22.541799. doi: 10.1101/2023.05.22.541799. Update in: This article has been published with doi: 10.1016/j.ynpai.2023.100138. PMID: 37292762; PMCID: PMC10245818.

Grant Support:

R01NS043314-17
5P20GM103418

Keywords: Methylglyoxal, Intraepidermal Nerve Fiber Density, Sarm1, Glyoxalase 1, Small Fiber Neuropathy

Neuropathic Pain Consortium (NPC) Abstracts

O 397 - 407

Unique Transcriptomic Profile Identified in Dorsal Root Ganglia of Patients with Chronic Neck Pain

Poster No:
O 397

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Introduction:
In this study, we used multiple transcriptomic approaches to characterize the changes to the cellular and molecular layout of the peripheral nervous system innervating the neck in patients suffering from chronic neck pain. Our primary goal was to gain insight into molecular changes in the C2-dorsal root ganglia (DRG) that might play a key role in promoting chronic neck pain.

Methods:
Patients with acute (<3 months) or chronic (≥3 months) neck pain undergoing C1-C2 fusion surgery were enrolled and completed quantitative sensory testing prior to surgery. DRGs innervating the C1-C2-joint, removed during surgery, were recovered and used for bulk RNA sequencing and spatial transcriptomics.

Results:
Ten DRGs recovered from 8 patients with acute pain and 7 DRGs from 5 patients with chronic pain were used for bulk RNA sequencing. This analysis showed distinct transcriptomic changes associated with chronic neck pain, including changes indicating increased artemin signaling that may sensitize nociceptors. Six DRGs recovered from 3 patients with acute pain and 7 DRGs from 5 patients with chronic pain were used for spatial transcriptomics, allowing transcriptomic analysis at near single-cell resolution and revealing 5 distinct neuronal subtypes in the C2 DRG. Integrated analysis of spatial transcriptomic data and bulk RNA sequencing is ongoing. This analysis can reveal complex interplays between cell-types within the DRG that may be targetable with existing or new therapeutic strategies. We are also comparing C2 DRG-associated transcriptomic phenotypes to other DRG-associated chronic pain phenotypes (thoracic vertebrectomy and diabetic neuropathic pain) to better understand unique features of chronic neck pain mechanisms.

Conclusions:
We conclude that the molecular changes in the C2 DRG associated with chronic pain are unique compared to previous findings in neuropathic DRGs from thoracic vertebrectomy patients and organ donors with a history of diabetic neuropathic pain, potentially because the C2 DRG has a different transcriptomic signature at baseline.

References:
No

Grant Support:

This work was supported by NIH grants U19NS130608 to TJP and MC, and R01AR078192 to MC, CPH and TJP

Keywords: Human dorsal root ganglia, C1/C2 DRG, RNA sequencing, Spatial transcriptomics, Chronic neck pain

Activation of Gq-GPCRs in keratinocytes reveals the skin as potential target for controlling DRG nociceptor excitability: Role of semaphorins

Poster No:
O 398

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Institutions:
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Introduction:
Degeneration of dorsal root ganglion (DRG) sensory neuron axons that innervate the skin, DRG neuron hyper-excitability and neuropathic pain, are hallmarks of painful diabetic neuropathy (PDN). We genetically expressed stimulatory DREADD (hM3Dq) receptors into KRT14-expressing KCs in mice to mimic the activation of KC Gq-GPCRs and activated the DREADDs by IP injection of the Clozapine-N-Oxide (CNO). As in diabetic neuropathy, mice overexpressing hM3Dq in KCs, had reduced in intraepidermal nerve fiber density and changes in DRG nociceptor excitability, transcriptomic profile, and electrical properties. Thus, indicating important role for the communication between keratinocytes (KCs) and cutaneous sensory neuron afferents (CSNs). However, the biochemical basis of this communication and how it impacts nociceptor activity remain to be discovered

Methods:
Using mice overexpressing hM3Dq in KCs, we proposed to elucidate the mechanisms of the above-described dialogue through, scRNA-seq to capture the changes in the epidermis, and CellChat to generate interactome maps and highlight ligand-receptor interactions.

Results:
We found that activation of KCs by CNO induced enhanced epidermal thickening as evidenced by an increased in KC proliferation and accumulation of keratohyalin granules, known to be associated with the granule cell layer (GRN). Analysis of scRNA-seq of the epidermis identified several clusters of immune cells, and KCs, including several differentially expressed genes such as filaggrin of GRN. We further found that class 3 semaphorins were downregulated in GRN KCs and their receptors NRPs were exclusively expressed by CSNs, indicating that GRN KCs are likely to modulate DRG neuron activity through KC release of semaphorins.

Conclusions:
Ongoing studies towards manipulating semaphorin signaling in microfluidics cocultures of DRGs (mice and IPSCs) using functional calcium imaging and MEA are likely to reveal semaphorins's functional role in the dialogue between KCs and CSNs and may offer new avenues for exploring epidermal communication for specific therapeutics to peripherally modulate DRG neuronal activity

References:
No

Grant Support:

We acknowledge NIH NIAMS R01AR077691 and P30AR079206 from their support in funding this study

Keywords: neuropathic pain, dorsal root ganglion neurons, excitability, skin, scRNA-seq

Alterations in blood–spinal cord barrier disruption in painful diabetic neuropathy

Poster No:
O 399

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Introduction:
Painful diabetic neuropathy is one of the most distressing complications of diabetes. Tight junctions, which form physical barriers to protect the endoneurial microenvironment in the central as well as peripheral nervous systems, can be disrupted under hyperglycemic milieu. In this study, we evaluated the tight junction proteins ZO-1, occludin and claudin-1, which were differentially expressed in the diabetic spinal cord and peripheral nerve compared to non-diabetic animals. The gap-junction protein connexin 43 (Cx-43) exhibited increased expression in the spinal cord of diabetic animals. Earlier, we established that histone deacetylase inhibitor (HDACi) could alleviate painful diabetic neuropathy with alterations in the expression of nerve regeneration markers and inflammatory mediators. However, the dynamic changes of the tight junction elements in the spinal cord and peripheral nerves are not fully established in diabetic conditions.

Methods:
In this study, type 2 diabetic animals were treated with HDACi Romidepsin at a dose of 1 mg/kg twice a week for 3 weeks. Non-diabetic and diabetic animals were evaluated for pain behaviors and compared with treatment group. All three groups were also assessed for distinctive expression of tight junction proteins, inflammatory mediators as well as epigenetic modifications in the peripheral nerve and spinal cord.

Results:
Our results showed that type 2 diabetic animals treated with Romidepsin exhibited significant alleviation in thermal hyperalgesia and mechanical allodynia along with changes in expression of tight junction and gap junction proteins including ZO-1, occluding, claudin-1 and Cx-43. The data also revealed alterations in inflammatory mediators such as IL1β, toll like receptor-4 (TLR-4), phospho p38 MAPK, C-X-C chemokine receptor type 4 (CXCR4) as well as changes in histone methylation.

Conclusions:
Overall, our study suggests that Romidepsin may protect the tight junction elements in the peripheral nerve and spinal cord and could offer alternative therapeutic approach towards the treatment for painful diabetic neuropathy.

References:
No

Keywords: diabetes, pain, neuropathy, tight junction, histone deacetylase

The Role Of Keratinocyte-Derived Exosomes In DRG Excitability And Nerve Outgrowth In Painful Diabetic Neuropathy

Poster No:
O 400

Authors:
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Introduction:
Painful diabetic neuropathy (PDN) is a debilitating and intractable complication of diabetes with patients suffering from a painful, burning sensation in their extremities. Current available treatments have limited effect in masking the pain without remediating the underlying mechanisms of the disease. The cellular hallmarks of PDN are cutaneous nerve-fiber degeneration and the hyperexcitability of the DRG neurons. Keratinocytes are closely juxtaposed to cutaneous nerve terminals, enabling bidirectional communication between keratinocytes and cutaneous nerves. One such ubiquitous mode of communication that is understudied in the skin is extracellular vesicles (EVs), namely exosomes, which are secreted nanoparticles that can produce substantial transcriptional and translational changes. However, the role of keratinocyte-derived exosomes in mediating DRG neuron hyperexcitability and axonal degeneration in PDN is unknown.

Methods:
Using primary adult mouse keratinocytes cultures, we've begun characterizing keratinocyte-derived exosomes (KDEs) in the high-fat diet (HFD) induced mouse model of PDN and their potential role on DRG excitability and neurite growth both in vitro and in vivo. Using size exclusion chromatography, we have isolated enriched KDEs and are performing an extensive, unbiased molecular characterization via proteomics and RNAsequencing in mice before translating this with the recently received patient samples.

Results:
Nanoparticle tracking analysis and negative stain electron microscopy suggest different rates of exosome secretion between RD and HFD mouse keratinocytes while preliminary proteomics revealed an upregulation in extracellular matrix proteins in the HFD keratinocyte-derived exosomes. In addition, using an in vivo EV reporter mouse, we have demonstrated that keratinocyte originating nanoparticles are trafficked into the DRG neuron cell body.

Conclusions:
Using the unbiased molecular characterization methods to study keratinocyte-derived exosomes is a novel investigation into the neuron-keratinocyte communication in diabetic skin. Our results could be translated into new topical interventions, which could fulfil the unmet need for new therapies for both small-fiber degeneration and neuropathic pain in diabetes.

References:
No

Keywords: Exosome, Diabetes, Neuropathy, Proteomics, Keratinocyte

Mitochondrial Homeostasis in Schwann cells is Linked to C-fiber Neuroenergetics and Neuropathic Pain

Poster No:
O 403

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Introduction:
Alterations to Schwann cell (SC) mitochondria and the consequences to peripheral axons are poorly understood. We previously showed that the low-density lipoprotein receptor 1 (LRP1) is upregulated in SCs after injury and contributes to the SC Repair Program. In addition, LRP1 binds and recruit phospholipid kinases to cellular membranes and regulates lipid metabolism.

Methods:
Using a SC-specific conditional LRP1 knock out mice (scLRP1-/-) we applied discovery-based approaches (proteomics and bulk RNA-Seq) to sciatic nerves and DRGs. Transmission electron microscopy (TEM) of sciatic nerves was used to quantify SC and axonal ultrastructure. Primary cultures of mouse SCs or DRG neurons isolated from scLRP1-/- and scLRP1+/+ mice and rat primary SCs transfected with siRNA for LRP1 or NTC, were used to measure mitochondrial dynamics and heterogeneities.

Results:
scLRP1-/- mice manifest evoked and spontaneous pain related behaviors without injury. LC-MS/MS revealed significant differences in metabolic pathways between scLRP1-/- and scLRP1+/+ nerves. Specifically, proteins in the mitochondria ATP synthase complex and in oxidative phosphorylation were upregulated in the scLRP1-/- mice. Ultrastructural analyses demonstrated that loss of LRP1 increased myelin splitting associated with enhanced mitochondria number in myelinated SCs, and significantly damaged mitochondria (reduced cristae surface area) in nonmyelinated SCs and C-fibers. Primary SC cultures isolated from scLRP1-/- mice showed decreased mitochondrial membrane potentials and mitochondrial heterogeneities, indicative of mitochondrial dysfunction. Moreover, absence of LRP1 in cultured SCs increased mitochondrial DNA copy number, consistent with reduced mitofusin-2 protein and increased dynamin regulated protein 1, supporting mitochondrial fission. LRP1-mediated regulation of SC mitochondria homeostasis also affected neuroenergetics of small diameter DRG neurons. Analysis of DRG neuron transcriptome from scLRP1-/- mice showed robust alterations in the ATP biosynthetic process and oxidative phosphorylation.

Conclusions:
Collectively, our study highlights the potential regulation by LRP1 in the complexity of SC bioenergetics and the importance of SC metabolic homeostasis in C-fiber function and pain.

References:
No

Grant Support:

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Keywords: Schwann cells, C-fibers, Mitochondria, nerve ultrastructure, proteomics

Pain-Associated Inflammatory Mediators in Patients with Diabetes and Painful Neuropathy: Are Fibroblasts The Persistent Producers?

Poster No:
O 404

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Introduction:
Peripheral neuropathy, a common neurological complication of diabetes, results in neuropathic pain in approximately half of the patients. Existing treatments for neuropathic pain, such as antidepressants and antiepileptic drugs, often lead to undesirable side effects and offer only partial relief for a subset of patients. In this context, we suggest that targeting the peripheral source of inflammatory pain mediators in the skin may establish a balanced metabolic environment, disrupting the inflammatory cascade and alleviating pain. Skin fibroblasts, a prominent cell population in the skin with intensive interactions with nerves and nociceptors, serve as an intriguing cell model for investigating peripheral pain sensitization in individuals with painful diabetic neuropathy when collected at the pain site.

Methods:
We have established a biobank of skin fibroblasts from 30 skin biopsies from deeply phenotyped patients, divided into four groups: patients with diabetes (1) without neuropathy, (2) with pain-free neuropathy, (3) with painful neuropathy, and (4) non-diabetic controls. We assessed IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, and TNF-α excretion from skin fibroblasts using Luminex Multiplex Technology and ELISA, under baseline and TNF-α or LPS stimulation.

Results:
Fibroblasts from patients with painful neuropathy showed a greater tendency to significantly produce and release IL-6 compared to the other groups. We did not detect the other cytokines in the growth media.

Conclusions:
The production of IL-6 by fibroblasts derived from patients with painful diabetic peripheral neuropathy could be due to a long-term metabolic stress and epigenetic remodeling caused by diabetes. Together, our preliminary data could suggest a potential connection between fibroblast behavior and painful neuropathy in patients with diabetes. This might provide a new perspective in understanding peripheral neuropathic pain.

References:
No

Keywords: Painful Diabetic Neuropathy, Fibroblasts, Inflammation

Neurovascular changes in skin biopsies of small fiber neuropathy with neurogenic pruritus

Poster No:
O 405

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Introduction:
Small Fiber Neuropathy (SFN) is a rare cause of neuropathic pruritus. Although a reduction of small fiber nerve density is the typical histological finding in skin biopsies, not much is known on neurovascular morphological alterations in SFN with neurogenic pruritus and their probable contribution to symptoms.

Methods:
Three standardized regions of interest (ROI) of 15 thigh skin biopsies of SFN patients having both neuropathic pain and pruritus and of 18 thigh skin biopsies of healthy individuals were double stained (CD31+PGP9.5) to highlight small fibers, capillaries, and neurovascular contacts. A specifically developed software was utilized for analysis of digital images acquired by a fluorescence microscope (Thunder, Leica). Non-parametric statistics were performed.

Results:
SFN patients reported a median pain intensity of 5 (range 3-8) on a numeric rating scale (NRS) and a median itch intensity of 4 (range 2-6) NRS. A significant reduction in small fiber density in the subepidermal area was observed between patients and controls. Neurovascular contacts were reduced in the subepidermal and dermal area (Mann-Whitney-U-Test $p=0.049$ and $p=0.015$ respectively) in patients, without differences in capillary density.

Conclusions:
The observed reduction of neurovascular contacts in dermal and subepidermal areas in skin punch biopsies in SFN with neurogenic pruritus adds to our understanding of the interaction between small fibers and the vascular system. Using this newly developed software, larger scale morphological quantitative neurovascular studies of skin biopsies can be achieved in a short time.

References:
No

Grant Support:

The study was funded by Deutsche Forschungsgemeinschaft (DFG/FOR 2690 Prusearch)

Keywords: small fiber neuropathy, skin biopsy, neurovaskular, pruritus

Plasma Derived Schwann Cell Extracellular Vesicles are Detected by Super-Resolution Imaging and are Regulated in Neuropathic Pain

Poster No:
O 406

Authors:
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Introduction:
Schwann cells (SCs) produce extracellular vesicles (EV) that participate in cell-cell communication. Previously, we showed that EVs isolated from primary cultured SCs express TNFR1 and regulate SC physiology, innate immunity and neuroinflammation.

Methods:
We developed a novel transgenic mouse line (TIGER-P0), derived from TIGER mice (Cre inducible tGFP-hCD9-His reporter) crossed with P0-Cre mice, that express tGFP-hCD9 only in SCs and SC EVs. TIGER-P0 and control mice were subjected to chronic constriction injury (CCI). Plasma and tissues were collected 0, 1 and 5 days post CCI. Plasma derived extracellular vesicles (pEVs) were collected by ultracentrifugation and size exclusion chromatography. Nanoparticle tracking analyses quantified concentration and determined EV size. Plasma derived SC EVs (pSCEVs) were identified by direct stochastic optical reconstruction microscopy (dSTORM), a technique enabling precise targeting of hCD9 exclusively in TIGER-PO mice through biotinylated hCD9 antibody capture of EVs.

Results:
Fluorometric analyses of TIGER-P0 tissues confirmed that tGFP was only present in sciatic nerves and not in the brain, liver, spinal cord, or lung. Time course studies of total pEVs revealed an increase in pEVs acutely after CCI, but pEVs were significantly decreased in number and size once neuropathic pain was established. Notably, 90-150 nm sized pEVs from neuropathic mice were significantly reduced, a size corresponding to exosome populations. The presence of pSCEVs was determined by nanoscopic colocalization or tGFP and hCD9-CF488 using dSTORM and two color localization at separate laser intensities. pSCEVs were identified in naïve TIGER-P0 mice. Immunoblotting TIGER-P0 pEVs with anti-tGFP confirmed pSCEV detection. After CCI, a three-fold increase in pSCEVs was observed compared to naïve. Studies with anti-hCD9-CF647 replicated initial findings.

Conclusions:
We identified pSCEVs in the plasma of naive and neuropathic mice. Our data suggest that pSCEVs may serve as a biomarker for the spatial and temporal regulation of painful peripheral neuropathies and systemically regulate neuropathic pain outcomes.

References:
No

Grant Support:

the Veterans Administration 101RX002484 to W.M.C

Keywords: super resolution microscopy, Schwann cell, exosome, nanoparticle tracking, neuropathic pain

The Neuronal Membrane Proteasome Mediates Inter-Neuronal Signaling to Modulate Pain and Itch Sensation In Peripheral Sensory Neurons

Poster No:
O 407

Authors:
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Introduction:
The proteasome is critical for peripheral nervous system (PNS) function through mechanisms that remain largely unknown. Here, we investigated proteasomes in the mammalian PNS and revealed the neuronal membrane proteasome (NMP), originally discovered in the central nervous system, on the somata and proximal and distal axons of peripheral sensory neurons and investigated its role in modulating PNS function.

Methods:
Using immuno-electron microscopy, surface protein biotinylation and purification, and antibody feeding approaches we revealed the presence of the NMP in PNS sensory neurons. Single cell RNA seq analysis was used to identify the specific subpopulations of somatosensory neurons that express the NMP. We used an NMP-specific membrane-impermeable inhibitor and classical behavioral approaches as well as calcium imaging in culture to investigate the function of the NMP in vivo and in vitro.

Results:
We determined that specific inhibition of the NMP on distal nerve fibers innervating the mouse hind paw led to an acute reduction in mechanical and pain sensitivity, but no change in heat sensitivity. Investigating the mechanisms of these findings, our experiments show that NMP is expressed primarily in Mrgpra3+ and Cysltr2+ somatosensory neurons and is not found on glial cells. We used the pruritogen histamine to selectively stimulate at least a subpopulation of these NMP expressing somatosensory neurons and found that both the histamine responsive and histamine non-responsive neurons exhibited an NMP dependent suppression in sensitivity to depolarization.

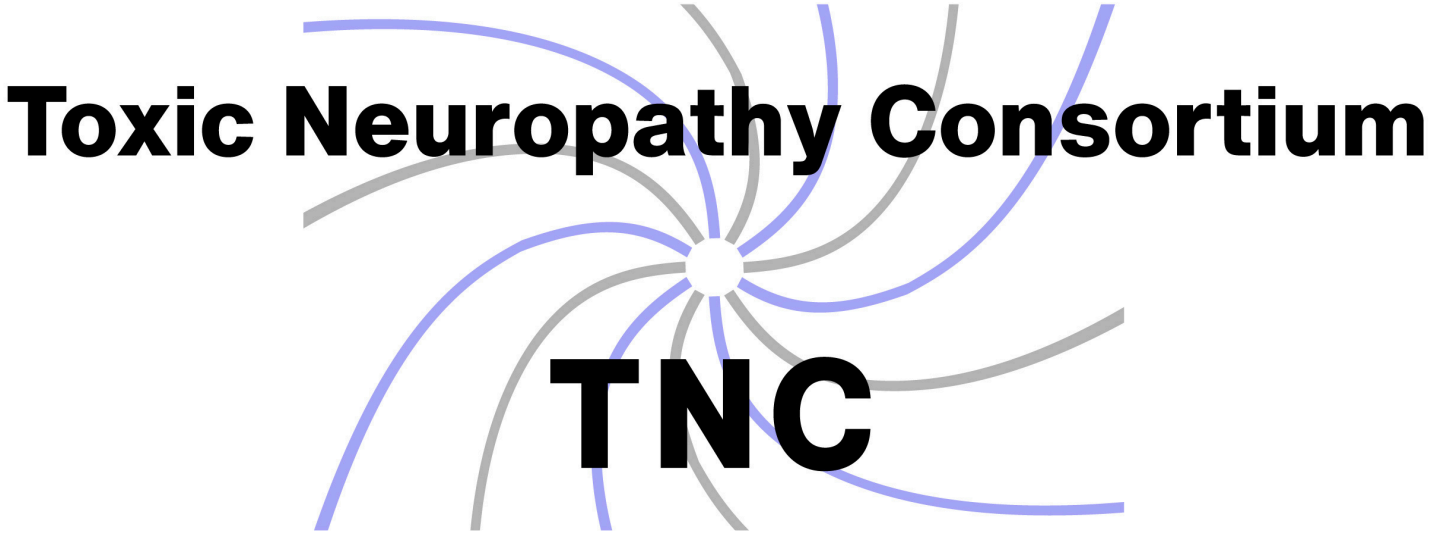
Conclusions:
Taken together, these data support a model whereby NMPs are expressed on a subset of somatosensory DRGs to modulate cell non-autonomous signaling between neurons of distinct sensory modalities. These observations provide critical insight into understanding NMP function in the PNS and potentially identify the NMP as a regulatory node between mechanical, pain, and itch as well as a potential critical target for controlling pain.

References:
No

Grant Support:

NIH-NIGMS NRSA F32NS119202 and Merkin Peripheral Neuropathy and Nerve Regeneration Center grant 22DF-C1/232

Keywords: Pain, Itch, neuronal membrane proteasome, Inter-neuronal communication, Sensory neurons



Toxic Neuropathy Consortium (TNC) Abstracts

O 408 - 419

Chemotherapy-induced peripheral neurotoxicity: socio-economical costs

Poster No:
O 408

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Introduction:
Chemotherapy-induced peripheral neurotoxicity (CIPN) hampers the quality of life of a growing population of cancer survivors. Up to now the magnitude of CIPN-related economic burden has not been addressed to a fully extent. We aimed to fill this gap by analyzing a large administrative data set of a large northern Italy area (10 million inhabitants): Regione Lombardia.

Methods:
We had access to administrative data from all adult citizens (2000-2021). There is no specific code for CIPN; therefore, we indirectly detected the population of interest by combining cancer patients (defined by 048 code) who were likely to have CIPN since they were both administered drugs causing CIPN and they accessed to out-patient services compatible with CIPN (e.g., electromyography). We were able to manage confounding factors not including patients affected by other conditions leading to peripheral neuropathies and/or already people assigned to a neuropathy type other than CIPN.

Results:
The estimated number of CIPN patients/year was 2.590 in 2004 up to 10.065 in 2019, with a 25% mean annual increase. Over the years we constantly observed a greater expense for CIPN patients. Mean expense/person in outpatient services was 18% higher in CIPN patients (statistically significant: t-test p-value 0,0313).

Conclusions:
We were able to indirectly estimate the expenses related to CIPN persistence over time over 20 years. We can therefore provide data to policymakers to undertake specific policies. Moreover, our data confirmed that CIPN is not an issue for the single person affected, but a general health condition having an impact on health care system budget allocation.

References:
No

Grant Support:

Paola Alberti is supported by Bicocca Starting Grant as PI (budget: 115,000 euros) for this project.

Keywords: chemotherapy-induced peripheral neurotoxicity, health economics, CIPN

ANGIOGENESIS-RELATED NEW MECHANISMS FOR CHEMOTHERAPY-INDUCED PAINFUL PERIPHERAL NEUROPATHY IN THE RAT

Poster No:
O 409

Authors:
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Institutions:
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Introduction:
Chemotherapy-induced painful peripheral neurotoxicity (painful-CIPN), with paresthesia, numbness, dysaesthesia, and neuropathic pain ranks among the most common dose-limiting toxicity of widely used anticancer drugs. Beside peripheral neurons, for several years considered the only reasonable target for painful-CIPN study, the recent evaluation of the microvascular angiogenesis in the somatosensory pathway, reveals other important actors in the neuropathic pain development and chronicization. To elucidate the relation between chemotherapy-induced neuropathic pain and vascular alterations, we evaluated the microvasculature in central and peripheral nervous compartments of rats exposed to neurotoxic chemotherapy.

Methods:
Rats were treated with paclitaxel 10 mg/kg once a week for 4 weeks, or with cisplatin 2mg/kg twice a week for 4 weeks or with their vehicles. Animals were tested for neurophysiological abnormalities and pain before and after the treatments. Post-mortem samples were analyzed at synchrotron radiation sources by X-ray Phase-Contrast Tomography (XPCT) Imaging and processed for quantitative and morphological analyses of microvascular structures. Complementarily, histochemical and molecular evaluations were performed to validate the results.

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

Conclusions:
These results can contribute to shed light on new pathogenetic mechanisms and potential novel therapeutic approaches for painful CIPN.

References:
No

Keywords: neuropathic pain, chemotherapy, peripheral neuropathy, XPCT analysis, imaging

UNCOVER BIPN: Gene And Protein Expression Analysis To Uncover Unknown Targets In Bortezomib-Induced Peripheral Neuropathy

Poster No:
O 410

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Institutions:
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Introduction:
Multiple Myeloma (MM) is a plasma cell disorder, treated in first line with bortezomib (BTZ). BTZ causes a side effect, the bortezomib-induced peripheral neuropathy (BIPN), characterized by sensory disturbances and pain. Most of the postulated pathomechanisms have been established in animal models or in very small cohorts of patients, which keeps the level of evidence for targets and mechanisms low. The aim of this study is to investigate the postulated pathomechanisms in a big cohort and uncover potential new targets via RNA Sequencing.

Methods:
In this interim analysis 109 MM patients were included. Patients were divided into 3 groups. FC: first cycle of BTZ treatment (N=23), OT: ongoing BTZ treatment (N=40), PT: BTZ treatment in the past (N=46). In addition, we analysed a subgroup of patients from FC and OT group in follow-up investigations after 3, 6, 12, or ≥ 18 months and assigned them to the appropriate subgroup: pain development (PD; N=6), pain resolving (PR; N=6), neuropathy development (ND; N=9). CCL2, IL-6, TNF-α and NfL were measured using the ELLA™ device (ProteinSimple, CA, USA). RNA sequencing is currently carried out and will be presented at the Congress.

Results:
Median NfL level was the highest in the OT group (93.4 pg/ml; $p < 0.0001$). In the PD subgroup, median CCL2 and TNF-α levels were higher at the follow-up examination (FU) compared to baseline (BL); (BL CCL2: 209 pg/ml, FU CCL2: 415 pg/ml, $p < 0.01$; BL TNF-α: 8.0 pg/ml, FU TNF-α: 15.7 pg/ml, $p < 0.05$). In the PR and ND subgroup, median CCL2 and TNF-α levels remained stable.

Conclusions:
NfL levels were highest under ongoing BTZ treatment, indicating axonal damage. Increasing CCL2 and TNF-α levels over time were associated with pain development. Since this is an ongoing project, updated results will be presented at the Congress.

References:
Yes

Reference 1: Cebulla N, Schirmer D, Runau E, Flamm L, Gommersbach S, Stengel H, Zhou X, Einsele H, Reinhold AK, Rogalla von Bieberstein B, Zeller D, Rittner H, Kortüm KM, Sommer C. Neurofilament light chain levels indicate acute axonal damage under bortezomib treatment. J Neurol. 2023 Jun;270(6):2997-3007. doi: 10.1007/s00415-023-11624-2. Epub 2023 Feb 18. PMID: 36802032; PMCID: PMC10188420.

Grant Support:

This study was part of KFO5001 ResolvePAIN, funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Project ID: 426503586.

Keywords: Bortezomib-induced peripheral neuropathy, CIPN, Neurofilament Light Chain, RNA Sequencing, Bortezomib

Inhibition of TNIK is a promising therapeutic approach for PIPN

Poster No:
O 411

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Introduction:
Chemotherapy is widely used as a primary treatment in cancers and Paclitaxel is administered for treating many types of cancer. However, it causes Paclitaxel induced peripheral neuropathy (PIPN), a debilitating, painful and dose-limiting side effect. The exact mechanism of PIPN is not fully understood and there are currently no effective therapies to prevent PIPN. MAP kinase kinase kinase kinases (MAP4Ks) belong to the mammalian serine/threonine kinases and studies have shown that MAP4K's induce JNK activation and correlate strongly with neurodegeneration.

Methods:
To better understand the mechanism of PTX neurotoxicity and determine if MAP4 kinase signaling promotes axonal degeneration, we treated embryonic rat dorsal root ganglion neurons with various kinase inhibitors together with PTX and performed ATP and NAD assays.

Results:
We found that several MAP4K4 inhibitors provided a robust protection against axonal degeneration in cellular models of PIPN. However, as the structures of TNIK (MAP4K7), MINK1 (MAP4K6) and MAP4K4 share a high degree of similarity, the MAP4K4 inhibitors also inhibit TNIK and MINK1 and the exact mechanism of this neuroprotection remains unclear. Therefore, we downregulated individual kinases in DRG neurons using siRNA approach, and found that inhibition of TNIK alone, is sufficient to prevent PTX induced neurotoxicity in DRG neurons. Furthermore, more specific inhibitors of TNIK, Mebendazole and KY-05009, were able to prevent neurotoxicity of PTX on DRG neurons.

Conclusions:
Axon degeneration cascade initiated by PTX can be prevented by genetic knockdown of TNIK or specific inhibitors of TNIK. This suggests that TNIK inhibitors can potentially be used as an adjunct treatment with Paclitaxel to prevent the onset of peripheral neuropathy.

References:
No

Grant Support:

The Merkin Peripheral Neuropathy and Nerve Regeneration Center

Keywords: Chemotherapy, Axonal Degeneration, Neuropathy, Kinase, Pharmological

Identification of Axonal Degeneration in Paclitaxel-Treated Patients Utilising Neurophysiological and Blood Based Biomarkers

Poster No:
O 412

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Introduction:
Chemotherapy induced peripheral neurotoxicity (CIPN) is a common side effect of chemotherapy that manifests as sensory neuropathy and produces degeneration of peripheral axons. Serum neurofilament light chain (NfL) is a protein biomarker of axonal degeneration which has been investigated as a method to identify individuals at risk of CIPN. This study aimed to identify the association of NfL with neurophysiological markers of axon degeneration, in patients receiving the neurotoxic chemotherapy paclitaxel.

Methods:
Patients were clinically assessed at beginning, mid, end of treatment. CIPN was assessed using a clinical grading scale (National Cancer Institute -Common Terminology for Adverse Effects (CTCAE) neuropathy scale), neurological grading scale (Total Neuropathy Score TNS clinical version), patient reported outcome measures (EORTC- CIPN20). Stimulus response parameters were recorded from the sensory median nerve, including amplitude and current required to generate 10%, 50% and 90% of maximal amplitude (i10, i50, i90). Serum samples were collected within the first 6 weeks of treatment and NfL was quantified using Quanterix SIMOA immunoassay.

Results:
93 paclitaxel-treated patients (mean age 57±12.8 years) were recruited. Neuropathy incidence and severity increased over the course of treatment ($p<0.001$). By the end of treatment, 82% (n=76) had developed CIPN, which was mild in 44% (n=41, grade 1) and moderate/severe in 38% (n=35, grade 2/3). There was a significant correlation between NfL and paclitaxel cumulative dose within the first 6 weeks of treatment ($p\leq0.0001$, $r=0.67$). Sensory peak amplitude significantly reduced over time ($p=0.001$). Current at i10, i50 and i90 was significantly correlated with NfL at mid- ($p=0.001$, $r=0.55$; $p\leq0.001$, $r=0.56$; $p\leq0.001$, $r=0.57$) and end of treatment ($p=0.01$, $r=0.43$; $p=0.006$, $r=0.46$; $p=0.03$, $r=0.38$).

Conclusions:
Serum NfL levels were associated with paclitaxel cumulative dose and neurophysiological parameters, including stimulus current at mid and end of treatment. Stimulus response parameters and NfL quantification may provide relevant markers of axon degeneration in patients who are vulnerable to CIPN.

References:
No

Keywords: Axonal, Neurofilament, Neuropathy

4-Aminopyridine (4AP) promotes durable reversal of chemotherapy induced peripheral neuropathy (CIPN)

Poster No:
O 413

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Institutions:
[1]University of Rochester Medical Center, Rochester, NY, [2]University of Rochester Medical Center, Rochester, United States

Introduction:
Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating condition with potentially devastating effects on cancer patients. 650,000 patients are treated with chemotherapy every year in the US, and between 30-70% of these patients will develop symptoms of CIPN. Currently, there are no established treatments for CIPN. 4-aminopyridine (4AP), principally a K+ channel inhibitor, is a promising candidate to treat CIPN. Separate to improving gait in Parkinson's patients, 4AP has recently been used to treat acute peripheral nerve injuries with enhanced durable functional recovery and repair of myelin damage. The aim of this study is to test the hypothesis that 4AP can durably reverse the effects of CIPN.

Methods:
Methods: 16-week-old C57BL/6 mice were used in all experiments. CIPN was induced using two agents, paclitaxel (PTX) and cisplatin (CSP). After 6 (PTX) or 8 weeks (CSP), animals were separated into the following groups: 1) Treatment (4AP, 1mg/kg ip., daily) and 2) Control (NaCl, equivalent volume ip., daily). Outcomes included functional (von Frey testing, gait analysis, thermosensitivity, and electrophysiology), and histological evaluation (qualitative myelin analysis, epidermal sensory innervation, mitochondrial damage, dorsal root ganglion changes).

Results:
Results: After 8-weeks of treatment with either PTX or CSP, all animals developed signs of CIPN. 4AP treatment significantly improved all functional outcome assessments and restored normal nerve conduction. Histology analysis revealed that 4AP treatment led to better myelination, more regularly shaped axons that had healthier appearing mitochondria. Following cessation of 4AP treatment, there was no deterioration in functional or histological outcomes.

Conclusions:
Conclusions: This preclinical study demonstrates that 4AP provides an effective treatment of established CIPN in a murine model. Additionally, the benefits of 4AP continued after treatment was stopped that may be associated with a pro-reparative process that has similarly been demonstrated following peripheral nerve injury. Transition to evaluating its efficacy clinical trials is currently underway.

References:
No

Grant Support:

R21CA277447 (National Cancer Institute)

Keywords: Peripheral Neuropathy, Chemotherapy

Identifying the Optimal Outcome Measure to Assess Chemotherapy-Induced Peripheral Neurotoxicity

Poster No:
O 414

Authors:
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Institutions:
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Introduction:
Chemotherapy-induced peripheral neurotoxicity (CIPN) is a significant and often persisting side-effect of anticancer treatments, with the assessment of CIPN being critically important in both research and clinic settings. Despite this, there is a lack of consensus on the optimal method of CIPN assessment. The present study sought to compare the validity and responsiveness of various approaches of evaluating CIPN: patient reported outcome measures (PROMs), neurophysiological and sensory functional measures.

Methods:
A dual study design evaluated patients treated with neurotoxic chemotherapy across two cohorts: patients commencing treatment were assessed prospectively, and patients who completed treatment were assessed cross-sectionally. CIPN was assessed via PROMs (EORTC-CIPN20, FACT/GOG-Ntx, PRO-CTCAE), neurological and neurophysiological assessment (Total Neuropathy Score, sural and tibial compound nerve amplitudes) and sensory functional measures (Grating orientation, Von Frey monofilament and 2-Point discrimination tasks). Convergent and known-groups validity was assessed cross-sectionally following treatment completion, and responsiveness was evaluated prospectively during treatment. Neurological, neurophysiological and sensory outcome measure scores were compared between high and low CIPN symptom reporters.

Results:
A total of 1,033 patients were recruited to this study, incorporating 1,623 assessments. PROMs demonstrated best ability to capture CIPN (convergent validity; α=0.75-0.85, all $P<0.001$), to discriminate between CIPN severity (known-groups validity; all $P<0.001$) and to detect changes in CIPN development (responsiveness; Cohen's d=0.65-0.83). Other measures did not achieve threshold for convergent validity ($\alpha<0.7$). Neurophysiological and sensory functional measures did not demonstrate acceptable responsiveness (Cohen's $d<0.5$). Neurological, neurophysiological and sensory outcome measures were significantly impaired in patients who were high compared to low CIPN symptom reporters (all $P<0.05$).

Conclusions:
PROMs represent a valid method of CIPN assessment, with preferential properties over other approaches to assessing neuropathy. Adoption of PROMs in clinical practice and research settings will allow for accurate representation of CIPN morbidity.

References:
No

Keywords: chemotherapy-induced peripheral neurotoxicity, clinimetrics, neurophysiology, patient reported outcome measures

Microvascular Distribution in Skin Biopsies: Diabetic Neuropathy vs. Chemotherapy-Induced Neuropathy

Poster No:
O 415

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Institutions:
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Introduction:
This study aimed to investigate the relationship between microvascular structures and small nerve fibers in the superficial dermis and sweat glands, comparing skin biopsies from individuals with diabetic neuropathy (DN) and chemotherapy-induced peripheral neuropathy (CIPN).

Methods:
Methods: Three groups were included: 10 healthy controls (HC), 8 patients with DN, and 9 individuals with CIPN. DN and CIPN groups had similar low intraepidermal nerve fiber density (IENFD) and sweat gland nerve fiber density (SGNFD). Skin biopsies were taken from the distal leg using a 3mm diameter skin rotary knife. Immunohistochemical and double fluorescence staining were performed using specific antibodies: rabbit anti-PGP9.5, mouse anti-CD31, rabbit anti-CGRP, rabbit anti-elastin, and rabbit anti-Iba1. Confocal microscopy and stereological analysis were used to assess microvessel density.

Results:
Results: CD31+ microvessels in the superficial dermis and sweat glands did not colocalize significantly with small nerve fibers. Additionally, CD31+ microvessels did not overlap with elastin-positive fibres. Iba1-positive macrophages were observed around microvessels. Quantification revealed a significant reduction in microvessel density in the superficial dermis (3.59± 0.33% vs. 5.23± 0.49%, $p = 0.03$) and sweat glands (10.8± 3.34% vs. 24.8± 3.48%, $p = 0.016$) of DN patients compared to HC subjects. This corresponds to a 31% decrease in dermal microvessels and a 56% decrease in sudomotor microvessels compared to HC samples. In contrast, microvessel density did not differ significantly between HC and CIPN subjects. Microvessel density in CIN skin was 4.67± 0.54% in the superficial dermis and 17.75± 2.73% in sweat glands. Activated Langerhans cells were present in HC and CIN groups but absent in DN samples.

Conclusions:
Conclusion: This study reveals prominent microvascular rarefaction in DN skin, particularly in sweat glands. In contrast, no significant microvascular changes were observed in CIPN. Microvascular injury and Langerhans cell involvement may contribute to small fiber loss in DN specifically.

References:
No

Keywords: skin biopsy, microvessel density, diabetic neuropathy, , chemotherapy-induced neuropathy, , Langerhans cells.

Insight Into Chemotherapeutic-Agents-Induced-Neuroinflammation In Rat Experimental Neuropathies

Poster No:
O 416

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Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect in patients receiving anticancer treatments including Paclitaxel (PTX) and Vincristine (VCR), and can lead to chronic pain and worsening quality of life. In severe neuropathy, chemotherapy dose reduction or withdrawal can occur, with possible impairment of oncological outcome. The lack of effective therapy is partly due to an incomplete knowledge of CIPN pathogenesis. Emerging studies suggest a possible role for neuroinflammation in CIPN.

Methods:
We evaluated the inflammatory response in two preclinical models. Female Wistar rats were treated intravenously with PTX at dosages of 10 mg/Kg 1qwx4, while VCR were injected with 0.2 mg/kg 1qwx4. Multimodal assessment of CIPN was performed (neurophysiology and behavioral tests) periodically during treatment and neuroinflammatory markers in dorsal root ganglia (DRG) and spinal cord were investigated.

Results:
PTX and VCR- treated rats showed allodynia and neurophysiological alterations, with reduction in intraepidermic nervous fiber (IENF) density, but showed different severity of axonopathy in peripheral nerves. With PTX, peripheral nerves initially showed increased M1-macrophages infiltration, with subsequent glial fibrillary acid protein (GFAP) upregulation in DRG satellite cells and spinal astrocytes. Conversely, VCR showed no significant macrophage infiltration in peripheral nerves, but induced a positive microglial reaction for ionized calcium-binding adapter molecule 1 (Iba1) in the spinal cord, suggesting involvement in the maintenance phase of persistent pain state.

Conclusions:
Our findings suggest the need for targeting different neuroinflammatory pathways to restore or relieve neuropathic phenotypes and indicate the need for better understanding of the roles of peripheral and central glial cells in relationship with CIPN.

References:
No

Grant Support:

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Keywords: neuroinflammation, peripheral neuropathy, macrophages, glial cells, chemotherapy

Cell Autonomous and Non Cell Autonomous Regulation of the Schwann Cell Injury Response

Poster No:
O 417

Authors:
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Institutions:
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Introduction:
After peripheral nervous system injury, axons degenerate in a process termed Wallerian degeneration, and Schwann cells adopt a repair phenotype. While we know some key regulators of Wallerian degeneration, such as axonal sterile-α and toll/interleukin 1 receptor motif containing protein 1 (SARM1), and Schwann cell JUN, much remains unknown about the interactions of these pathways and the induction of the Schwann cell injury response. As there is increasing evidence from pre-clinical disease models and human disease that some of the pathways implicated do not only contribute to acute degeneration after traumatic injury, but contribute to neurodegeneration in humans, for instance in ALS and peripheral neuropathies, understanding these axon Schwann cell interactions is vital.

Methods:
To further investigate axon Schwann cell interactions after peripheral nervous system injury, we have used RNA-Sequencing and a range of different transgenic mouse models.

Results:
We describe both axon degeneration and the Schwann cell injury response after peripheral nervous system injury with unprecedented temporal resolution. We show that specifically, after traumatic injury at the sciatic notch, unmyelinated axons distal to the site of injury degenerate prior to myelinated axons. This timing of degeneration coincides with early gene expression changes in the nerve, by 18-24 hours after injury. Further investigating these early gene expression changes, we characterize important regulators of the Schwann cell injury response, such as the transcription factor JUN or histone deacetylases (HDACs), and their role in regulating gene expression changes. Using a range of different mouse models, we show how this Schwann cell injury response can be regulated both cell autonomously and non cell autonomously.

Conclusions:
Overall, these results describe the early injury response after peripheral nervous system injury in extraordinary detail, show how the Schwann cell injury response can be regulated cell autonomously and non cell autonomously, and highlight key differences between myelinated and unmyelinated axons that warrant further investigation.

References:
No

Keywords: Schwann cell, Wallerian degeneration, Injury, Sarm1

A Human Peripheral Nerve Model For Neuroprotection Assays

Poster No:
O 418

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Institutions:
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Introduction:
NerveSim® is a 3D human peripheral nerve model comprised of iPSC sensory neurons and human primary Schwann cells for screening potential neuropathic treatments. In this study, we targeted SARM1, a mediator of neurodegeneration, to ameliorate vincristine-induced peripheral neuropathy. SARM1 is a positive regulator of neuronal cell death and plays a key role in Wallerian degeneration following axonal injury. Its intrinsic NADase activity is normally autoinhibited but is activated in response to neuronal injury leading to axonal NAD^+ depletion, metabolic disfunction, and cell death.

Methods:
We selected three compounds from literature to assess the efficacy of SARM1 inhibition in protecting NerveSim® from vincristine induced electrophysiological dysfunction and morphological degeneration. DSRM-3716 and NB-7 inhibit SARM1's NADase activity through adduct formation during NAD^+ hydrolysis while WX-02-37 prevents the formation of active SARM1 through covalent modification that locks it in the autoinhibited state. Daily electrophysiological recordings were performed for the first 3 days of dosing with images taken Monday/Wednesday/Friday.

Results:
All three inhibitors demonstrated protection by delaying electrophysiological dysfunction of our 3D human peripheral nerve model. Vincristine exposure without SARM1 inhibition exhibited a time-to-50% electrophysiological activity of 1.1 days. This time was increased to 1.4, 1.6, and 1.5 days for DSRM-3716 (6 µM), NB-7 (0.6 µM) and WX-02-37 (0.24 µM), respectively. Morphological protection was assessed through quantification of fiber length from brightfield images and showed more pronounced structural preservation than electrophysiological protection. Notably, after 7 days of dosing, NB-7 (3 µM) and WX-02-37 (0.24 µM) demonstrated significant morphological protection that resembled controls not exposed to vincristine.

Conclusions:
Limitations of this study include the use of a high, sustained dose of vincristine that deviates from *in vivo* plasma concentration curves. This disparity may explain the relatively modest observed functional protection. In conclusion, human NerveSim® is a novel pre-clinical peripheral nerve model well suited for evaluating neuroprotection.

References:
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Keywords: Chemotherapy induced peripheral neuropathy, Neuroprotection, SARM1, Embedded Electrode Array, Human peripheral nerve model

The Role Of Mesencephalic Astrocyte-Derived Neurotrophic Factor (MANF) In Schwann Cells

Poster No:
O 419

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Institutions:
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Introduction:
Peripheral nerve injuries affect millions worldwide, yet no pharmacological therapies are available for effective nerve repair. Identifying effective therapeutic candidates and developing strategies to deliver them in a sustained manner in the injured nerve is of great interest. Mesencephalic Astrocyte-derived Neurotrophic Factor (MANF) is a neurotrophic factor previously studied in CNS disease models and was shown to protect CNS neurons encountered with endoplasmic reticulum (ER) stress. We found that MANF promotes neurite outgrowth in adult rat primary sensory neurons. Here, we evaluated the role of MANF in primary Schwann Cells (SC) to explore if MANF-loaded SCs can be therapeutic for peripheral nerve repair.

Methods:
Primary SCs isolated from the sciatic nerve of adult SD rats and the SC line S16 were used. Proliferation and migration were evaluated using MTT, scratch assay, and transwell migration assays after treating them with MANF in a time and dose-dependent manner. Secretion of MANF by SCs was estimated using ELISA in the supernatants of normal and MANF overexpressed SC cultures with and without induction of mild ER stress. We also evaluated the effect of SC-derived MANF on neurite outgrowth by culturing neurons in the presence of SC supernatant.

Results:
We found basal expression of MANF in both primary SCs and S16 cells. Supplementation of MANF to these cultures increased proliferation and migration indicating that exogenous MANF could induce desired cellular responses in SCs for nerve repair. In addition, we found that mild ER stress promotes MANF secretion in SC cultures. Interestingly, SC-derived MANF modified the outgrowth response in primary sensory neurons.

Conclusions:
Overall, our results suggest that MANF may be therapeutic for nerve repair by promoting SC proliferation and migration. Given that SC-derived MANF modifies neurite outgrowth in vitro, primary SCs loaded with MANF and mild ER stress induction may be a potential therapeutic approach for repairing nerves.

References:
No

Grant Support:

CoMRAD - College of Medicine Research Award
CoMGRAD - College of Medicine Graduate Student Award
NSERC - Natural Sciences and Engineering Research Council of Canada.

Keywords: MANF, Schwann Cells, Nerve Regeneration, UPR, ER Stress

Inflammatory Neuropathy Consortium

Inflammatory Neuropathy Consortium (INC) Abstracts

O 420 - 433

Efficacy and Safety of Subcutaneous (SC) Efgartigimod PH20 in Chronic Inflammatory Demyelinating Polyneuropathy: ADHERE/ADHERE+ Trials

Poster No:
O 420

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Introduction:
Efgartigimod, a human immunoglobulin G (IgG)1 antibody Fc fragment, blocks the neonatal Fc receptor, decreasing IgG recycling and reducing pathogenic IgG autoantibody levels. Multi-stage, double-blinded, placebo-controlled ADHERE, and open-label extension ADHERE+, assessed the efficacy and safety of efgartigimod PH20 SC (co-formulated with recombinant human hyaluronidase PH20) in chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods:
Enrolled participants had CIDP (diagnosis confirmed by external committee) with active disease (treatment-naïve or on standard treatments [withdrawn during a run-in period]). Deteriorating participants received efgartigimod PH20 SC 1000 mg once weekly (Stage A). Responders were randomized (1:1) to efgartigimod PH20 SC 1000 mg or placebo once weekly (Stage B). Participants with clinical deterioration in Stage B or who completed ADHERE could enter ongoing ADHERE+ (efgartigimod PH20 SC 1000 mg once weekly). Primary outcomes were evidence of clinical improvement (assessed with aINCAT, I-RODS, or grip strength; Stage A), efficacy (time to first aINCAT score deterioration [relapse]; Stage B), and safety (treatment-emergent adverse events [TEAEs]; ADHERE+).

Results:
In Stage A, 214/322 (66.5%) participants demonstrated evidence of clinical improvement. In Stage B, efgartigimod significantly reduced the risk of relapse by 61% (HR: 0.394; 95% CI: 0.253–0.614) vs placebo (P=0.00004). 99% of eligible participants entered ADHERE+. No new safety signals emerged in ADHERE+; 57.5% of participants had ≥1 TEAEs (most mild/moderate) and 9.2% had ≥1 serious adverse events (one treatment-related death occurred). Participants who relapsed in Stage B (efgartigimod: 27.9%; placebo: 53.6%) demonstrated clinical improvement in aINCAT score in ADHERE+; those who had not relapsed maintained their aINCAT scores in ADHERE+. Clinical improvements were also demonstrated with I-RODS and mean grip strength.

Conclusions:

ADHERE+ demonstrated long-term effectiveness of efgartigimod PH20 SC for prevention of relapse. The safety profile of efgartigimod PH20 SC was similar between ADHERE and ADHERE+, and longer exposure did not lead to increased TEAE frequency or severity.

References:
No

Keywords: Efgartigimod, Chronic Inflammatory Demyelinating Polyneuropathy, immunoglobulin G, FcRn, Inflammatory neuropathies

Serum Periaxin Is Elevated In Patients With Guillain-Barré Syndrome And Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Poster No:
O 421

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Introduction:
Immune-mediated demyelination is the primary pathological process in the majority of patients with Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). However, no reliable blood biomarkers of demyelination exist for the diagnosis and management of peripheral neuropathies. Periaxin is a structural protein exclusively expressed by myelinating Schwann cells. Due to its high specificity for peripheral nerve myelin, we postulated that periaxin could serve as a biomarker of peripheral demyelination.

Methods:
Using an electrochemiluminescence-based immunoassay, we measured serum periaxin in samples from patients with the acute inflammatory demyelinating polyneuropathy (AIDP, n=11) and acute motor axonal neuropathy (AMAN, n=7) variants of GBS (n=18 in total), CIDP (n=22), non-neurological disease controls (NNC, n=17) and healthy controls (HC, n=5). We also evaluated whether periaxin is released in myelinated co-cultures following immune-mediated demyelination and axonal damage, and compared results with control, uninjured cultures.

Results:
We found higher concentrations in GBS (679.2 pg/ml) and CIDP (425.2 pg/ml) versus NNC (66.23 pg/ml) and HC (22.0 pg/ml): GBS vs NNC, $p = 0.0005$; GBS vs HC, $p = 0.0051$; CIDP vs NNC, $p = 0.0151$; CIDP vs HC, $p = 0.0184$. AIDP levels (874.4 pg/ml) were higher than controls (AIDP vs NNC, $p = 0.0083$; AIDP vs HC, $p = 0.0275$). In vitro, 48 hours after antibody- and complement-mediated demyelination, periaxin levels were higher (8119.9 pg/ml) compared with axonal damage (3171.2 pg/ml) and control conditions (217.6 pg/ml).

Conclusions:
Periaxin may serve as a biomarker of peripheral nerve demyelination. Larger cohorts of samples from patients with GBS, CIDP and other neuropathies are being tested. We will further validate the assay using cell-based models of immune-mediated neuropathy, and assess periaxin in parallel to markers of axonal degeneration (peripherin and neurofilament) to establish their individual and combined contributions to clinical assessment.

References:
Yes

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Grant Support:

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Keywords: Peripheral Neuropathy, Biomarker, Guillain-Barré syndrome, CIDP, Demyelination

$CD27^{+}IgD^{-}$ Memory B-Cells Produce Germline-Like NF155 & NF186 Autoantibodies in a Pan-Neurofascin Autoimmune Nodopathy Patient

Poster No:
O 422

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Introduction:
Immunoglobulin (Ig)G-subclass autoantibodies targeting both neurofascin-186 (NF186) and neurofascin-155 (NF155) (pan-neurofascin, panNF) characterise a severe, rapidly progressive autoimmune nodopathy (AN). While B-cell depletion (via rituximab) may promote disease remission in some cases, variable patient responses necessitate further investigation into B-cell dynamics to develop more targeted therapies.

Methods:
We isolated and sorted $CD27^{+}IgD^{-}$ switched memory (SM) B-cells from a single $panNF^{+}$ AN patient using fluorescence-activated cell sorting and cultured them in 96-well plates for 21 days. We then tested for NF155 and NF186 reactivity using enzyme-linked immunosorbent assay and live cell-based assay. RNA isolated from reactive wells underwent RT-PCR and two nested PCRs to amplify heavy chain (H) and kappa (κ) and lambda (λ) light chain Ig transcripts. The resulting Nanopore and Sanger sequences were analysed using IgBLAST.

Results:
Among 480 single SM B-cells, a small fraction displayed reactivity to NF186 (2/480; 0.4%) or NF155 (1/480; 0.2%). The strongly NF186-reactive sample also showed minor cross-reactivity to NF155. These cells expressed diverse immunoglobulin transcripts: two IgG-H, three IgG-κ, one IgG-λ, and one IgM-H, all harbouring κ light chains and one additionally having a λ light chain. Genetic analysis revealed few somatic mutations from germline sequences, with only four variable region nucleotide alterations, mainly in the IgG-κ locus, and only a single mutation expected to result in amino acid replacement. Moreover, two silent mutations were detected in the IgG-H locus's joining region. Overall, the autoreactive BCRs utilised a broad range of Ig genes.

Conclusions:
We observed a low frequency of panNF-reactive memory B-cells displaying minimal somatic hypermutation and a variety of Ig genes in autoreactive BCRs. These findings suggest potential early tolerance defects contributing to $panNF^{+}$ autoreactive B-cell generation and a polyclonal antibody response. Ongoing work will generate, assess, and compare the polyreactivity, autoreactivity, and peripheral nerve reactivity of monoclonal antibodies from these autoreactive BCRs.

References:
No

Grant Support:

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Oxford-Oriel Basil Reeve Scholarship

Keywords: autoimmune nodopathy, neurofascin anitbodies, memory B-cells, somatic hypermutation, B-cell receptor diversity

Clinical and immunological relapses are infrequent in patients with anti-CNTN1 autoimmune nodopathy

Poster No:
O 423

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Introduction:
Our study analyzes long-term clinical and biomarker features of anti-contactin-1 (CNTN1) autoimmune nodopathy (AN).

Methods:
We included patients with anti-CNTN1 AN detected in our laboratory from which clinical information was available. Clinical features, treatment response and functional scales were retrospectively collected. Autoantibody, serum neurofilament light (sNfL) and serum contactin-1 levels were analyzed at baseline and follow-up.

Results:
Twenty-three CNTN1 AN patients were included. Median age at onset was 57 years. Patients presented with progressive (78%) motor-sensory (74%), proximal and distal weakness (52%) with ataxia (71%) and severe disability (median mRS at diagnosis 4, INCAT 6). Seven patients (30%) had facial weakness, and nine (39%) kidney involvement (5/9 membranous glomerulonephritis). Median follow-up time was 39 months. IVIg were used in all patients, but none achieved remission only with IgIV requiring all a second therapy. Corticosteroids were used in 19 patients (82%) as second therapy, and four (4/23, 17%) did not need further treatments. Rituximab was effective in 15/17 patients (two patients pending post-treatment evaluation). Only 1 patient presented a clinical and immunological relapse after a median follow-up from effective treatment of 25 months (range 6-233). IgG4 anti-CNTN1 were predominant in all patients; anti-CNTN1 antibodies were negative in all patients tested after treatment (17/23). sNfL levels were significantly higher in anti-CNTN1 patients than in healthy controls (median 121.9 vs 7.45pg/mL,p< 0.0001) and Guillain-Barré Syndrome patients (48.04pg/mL,p=0.01). sNfL at onset correlated with anti-CNTN1 titers (r=0.75,p<0,0001) and maximum mRS achieved (r=0.58,p=0.01); and decreased to normal levels after treatment (13.65pg/mL,p< 0.0001). Results in serum contactin-1 levels will be presented at the meeting.

Conclusions:

Patients with anti-CNTN1 AN have a characteristic clinical profile. Clinical and immunological relapses are infrequent after successful treatment, suggesting that continuous treatment is unnecessary. sNfL and anti-CNTN1 antibodies are useful to monitor disease status in these patients.

References:
No

Grant Support:

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Keywords: Autoimmune nodopathy, Contactin-1

Clinical And Therapeutic Profile Of Patients With Anti-MAG Neuropathy According To MYD88 Mutation And Underlying Hemopathy

Poster No:
O 424

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Introduction:
Anti-MAG neuropathies are associated with an IgM monoclonal gammopathy of undetermined significance (MGUS) or with a malignant haemopathy. Our objective was to determine whether the presence of an haemopathy or somatic mutations of MYD88 and CXCR4 genes influences disease presentation and response to rituximab (RTX).

Methods:
We included 79 patients (mean age 74 years, disease duration 9.68 years) who had a bone marrow aspiration with morphologic and immunophenotypic analysis. MYD88L265P and CXCR4 mutations were analysed in peripheral B-cells. Information collected included: inflammatory neuropathy cause and treatment sensory sum score (ISS), MRC testing, overall neuropathy limitation scale (ONLS), Rash-built Overall Disability Score (RODS), ataxia score, anti-MAG titres, peak IgM dosage, neurofilament light chain levels, motor and sensory amplitudes, motor unit index (MUNIX) and motor unit size index (MUSIX) sum scores.

Results:
Malignant haematological disorders were discovered in 17 patients (22%): 13 Waldenstrom macroglobulinemia, 3 marginal zone lymphoma and one mantle cell lymphoma. MYD88L265P mutation was detected in 29/60 (48%) patients and CXCR4 in one single patient. Disease severity, biological and electrophysiological data and response to RTX were comparable in patients with MGUS/lymphoma and patients with/without MYD88L265P mutation. Twenty-six patients received RTX monotherapy and were evaluated before and 12 months after the first infusion. Fifteen patients (58%) were clinically improved based on both ONLS and RODS scores. These patients had significantly lower ISS scores and higher MUSIX sum scores before treatment compared with non-responder patients.

Conclusions:
MYD88L265P mutation and underlying haemopathies are not predictive of a more severe disease. However, in cases of resistant and progressive neuropathy, they provide an opportunity to prescribe newly available drugs such as Bruton tyrosine kinase inhibitors.

References:
No

Grant Support:

no

Keywords: MAG, MYD88, Rituximab, BTK inhibitor, Waldenstrom

Autoantibodies against dihydrolipoamide S-acetyltransferase in immune-mediated neuropathies

Poster No:
O 425

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Introduction:
This study aimed to identify disease-related autoantibodies in the serum of patients with immune-mediated neuropathies including CIDP, and to investigate the clinical characteristics of patients with these antibodies.

Methods:
Proteins extracted from mouse brain tissue were used to react with sera from patients with CIDP by Western blotting (WB) to determine the presence of common bands. Positive bands were then identified by mass spectrometry and confirmed for reactivity with patient sera using ELISA and WB. Reactivity was further confirmed by cell-based and tissue-based indirect immunofluorescence assays. The clinical characteristics of patients with candidate autoantibody-positive CIDP were analyzed, and their association with other neurological diseases was also investigated.

Results:
Screening of 78 CIDP patient sera by WB revealed a positive band around 60–70 kDa identified as dihydrolipoamide S-acetyltransferase (DLAT) by immunoprecipitation and mass spectrometry. Serum IgG and IgM antibodies' reactivity to recombinant DLAT was confirmed using ELISA and WB. A relatively high reactivity was observed in 29/160 (18%) CIDP patients, followed by sensory neuropathy (6/58, 10%) and multiple sclerosis (2/47, 4%), but not in Guillain–Barré syndrome (0/27), hereditary neuropathy patients (0/40), and healthy controls (0/26). Both the cell-based and tissue-based assays confirmed reactivity in 26 out of 33 CIDP patients. Comparing the clinical characteristics of CIDP patients with anti-DLAT antibodies (n = 29) with those of negative cases (n = 131), a higher percentage of patients had comorbid sensory ataxia (69% vs. 37%), cranial nerve disorders (24% vs. 9%), and malignancy (20% vs. 5%). A high DLAT expression was observed in human autopsy dorsal root ganglia, confirming the reactivity of patient serum with mouse dorsal root ganglion cells.

Conclusions:
Reactivity to DLAT was confirmed in patient sera, mainly in patients with CIDP. DLAT is highly expressed in the dorsal root ganglion cells, and anti-DLAT antibody may serve as a biomarker for sensory-dominant neuropathies.

References:
No

Grant Support:

This work was supported in part by the Health and Labour Sciences Research Grant on Intractable Diseases (Neuroimmunological Diseases) from the Ministry of Health, Labour and Welfare of Japan (20FC1030) and JSPS KAKENHI (20K07882, 23K14751).

Keywords: chronic inflammatory demyelinating polyneuropathy, sensory neuropathy, dihydrolipoamide S-acetyltransferase, dorsal root ganglion

Regulatory effects of gut microbiota in immune responses in Guillain-Barré syndrome

Poster No:
O 426

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Introduction:
Guillain–Barré syndrome (GBS), life-threatening post-infectious disease with an autoimmune response against the peripheral nervous system. GBS progression determinants and clinical outcomes are yet unclear. The host gut microbiota has a crucial role in cellular immune response regulation, influencing pathogenic T-helper cell subsets and regulatory T and B-cells (Tregs and Bregs).

Methods:
A case-controlled study with GBS patients (n=57) and healthy controls (HCs) (n=57) compared gut microbial taxa via 16S rRNA V4-region sequencing and assessed the immune response of Th-cells (Th1, Th2, Th17), Tregs and Bregs using flow cytometry. Sequence data was analyzed using QIIME2-DADA2 pipeline. Spearman's rank correlation coefficient was performed to find correlation between gut-microbiota and immune response.

Results:
The median age of patients was 33 years (IQR: 40-25) with 86% severely affected. Distinct microbial community profiles were found in GBS patients compared to HCs (p=0.001), with significant differences between severe and mild GBS cases (p=0.011). Notably, Enterococcaceae, Streptococcaceae, and Bacteroidaceae families and class Bacilli were differentially abundant in GBS, while phyla Bacteriodota and class Negativicutes were higher in HCs. Flow cytometry analysis demonstrated a reduction in CD4+CD25+FoxP3+ Tregs and CD4+IL4+ (Th2) cells during acute GBS compared to HCs. Conversely, CD4+IFNγ+ (Th1), CD4+IL17+ (Th17) cells and CD19+CD38hiCD24hiIL10+ Bregs increased significantly during the acute phase. High Verrucomicrobiota phyla abundance correlated with low CD4+FoxP3+ and CD4+CD25+FoxP3+ Tregs expression, while Actinobacteria abundance negatively correlated with CD4+CD25+ Tregs. Proteobacteria correlated with IgM+ B-cells upregulation, while Acidaminococcaceae and Eubacteriaceae families downregulated IgM+ B-cells and IL10-producing B-cells. Veillonellaceae family upregulated switched-IgA+IL10+ and CD19+IL10+ B-cells, while Leuconostocaceae, Erysipelatoclostridiaceae, and Erysipelotrichaceae families favored CD19+CD38hiCD24hiIL10+ Breg expressions.

Conclusions:
Our findings underline the regulatory role of host gut microbiota in shaping immune responses, particularly the modulation of regulatory T- and B-cells, leading to the breach of immune tolerance during GBS development. Further validation through shotgun sequencing will illuminate species-level contributions to immune dysregulation in GBS.

References:
Yes

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Reference 3: Honda K, Littman DR. The microbiome in infectious disease and inflammation. Annual review of immunology. 2012;30:759-95.

Grant Support:

This research activity was funded by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (USA), under award number R21TW012184.

Keywords: Guillain-Barré syndrome, Gut microbiota, Regulatory T and B cells, Differentially abundant

Understanding Blood-Nerve Barrier Physiology and its Relation to Axonal Degeneration and Regeneration

Poster No:
O 427

Authors:
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Introduction:
The blood-nerve barrier (BNB) is the set of vascular characteristics found in PNS endothelial cells that strictly regulates what enters the endoneurium. It serves to maintain proper endoneurial homeostasis and is analogous in function to the blood-brain barrier (BBB) in the CNS. However, little is known about the cellular and molecular mechanisms responsible for BNB formation and function in health and dysfunction in disease or trauma. We sought to describe the molecular and functional development of the BNB, uncover the relationship between BNB breakdown and axonal degeneration following traumatic injury, and unveil the transcriptomic differences between the BBB and the BNB.

Methods:
We used immunofluorescent imaging of barrier markers and a biotin permeability assay of mouse sciatic nerves across postnatal timepoints to describe the BNB's development. To assess the link between axonal degeneration and BNB breakdown, sciatic nerve crush injuries were performed on adult wild-type mice and *Sarm1-KO* mice (which have an impaired axonal degeneration phenotype) and BNB function was assessed via a biotin permeability assay. Furthermore, we are performing single-nuclei RNA-sequencing of mouse sciatic nerves (BNB), optic nerves (BBB), and cortex (BBB).

Results:
We found that the mouse BNB matures gradually after 14 days of age, with specific barrier markers increasing and levels of permeability decreasing after this time. After sciatic nerve crush injury, BNB breakdown was widespread in wild-type mice, but began gradually recovering at later timepoints when axonal regeneration commenced. *Sarm1-KO* mice had significantly reduced levels of BNB breakdown after crush injury.

Conclusions:
The mouse BNB develops gradually postnatally and its reversible breakdown following crush injury is dependent on axonal degeneration. Further studies elucidating the pathways involved in BNB formation, breakdown, and recovery, could identify factors to be used for improved drug delivery or novel therapeutics for PNS diseases, especially those with a strong vascular component such as diabetic neuropathy.

References:
Yes

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Reference 2: Richner, M. et al. Functional and Structural Changes of the Blood-Nerve-Barrier in Diabetic Neuropathy. Front. Neurosci. 12, 1038 (2019).

Grant Support:

HHMI Gilliam Fellowship (Grant Number: GT15717)

Keywords: Blood-Nerve Barrier, Development, Axonal Degeneration, Trauma, Vascular

A Randomized Controlled Trial with Rituximab to Prevent Clinical Worsening in CIDP after Immunoglobulin Suspension

Poster No:
O 428

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Introduction:
Introduction: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic immune mediated neuropathy often responding to steroids, immunoglobulins and plasma exchange. These therapies need however to be continued to avoid worsening after therapy suspension. We assessed whether rituximab is more effective than placebo in preventing clinical worsening after suspending immunoglobulin in patients with CIDP.

Methods:
Methods: We performed a randomized, placebo-controlled, double-blind study in patients with CIDP diagnosed according to EFNS/PNS criteria who were under chronic effective therapy with immunoglobulins. Patients were randomly assigned to receive intravenous rituximab (1g day 1, 15 and 180+7) or matching placebo and received the current dose of IVIg or SCIg for six months after starting rituximab/placebo. The primary end-point was the difference in the proportion of patients treated with rituximab or placebo who worsened within six months after suspending immunoglobulins by at least one point in the INCAT score, two points in MRC sum-score or four points in R-ODS score. Secondary end-points included the difference in the proportion of patients deteriorating within 12 months after immunoglobulin suspension, suspending therapy for adverse events or voluntary reasons and the mean time to deteriorate after immunoglobulin suspension.

Results:
Results. Thirty-seven patients were included in the study (19 rituximab, 18 placebo). A similar proportion of patients had deteriorated by 6 months after suspending immunoglobulin including 12/19 treated with rituximab (63.2%) and 12/18 (66.6%) with placebo. There was no significant difference after 12 months and for each scale at month 6, 12 and 18. Even if there was some differences in the mean time to worsen (5 months for rituximab, 4.3 months for placebo) the difference was not significant. Only one patients suspended treatment with rituximab for adverse event.

Conclusions:
Conclusion. Rituximab was not more effective than placebo in preventing clinical deterioration after suspending effective chronic therapy with immunoglobulin in patients with CIDP.

References:
No

Grant Support:

The Study was supported by a Grant from Agenzia Italiana Farmaco (AIFA-2016-02364540), Rome Italy

Keywords: Chronic inflammatory demyelinating polyradiculoneuropathy, CIDP, Rituximab, Randomized Controlled Trial, Immunoglobulins

Phase 2 Efficacy and Safety of Riliprubart, a C1s-Complement Inhibitor, in Chronic Inflammatory Demyelinating Polyneuropathy

Poster No:
O 429

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Introduction:
Riliprubart, a first-in-class humanized IgG4-monoclonal antibody, selectively inhibits activated-C1s within the classical complement pathway. Here, we report efficacy and safety results of riliprubart in chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods:
This global, multicenter, Phase-2, open-label trial (NCT04658472) evaluates riliprubart across three subgroups: Standard-of-care (SOC)-Treated (immunoglobulins/corticosteroids), SOC-Refractory, and SOC-Naïve. Participants undergo 24-week treatment (Part-A), followed by optional treatment-extension (Part-B: 52-weeks, Part-C: until end-of-study). In Part-A, the primary endpoint for SOC-Treated is percentage of participants with relapse (i.e., ≥1-point increase in adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] disability score) after switching from SOC to riliprubart. For SOC-Refractory and SOC-Naïve, the primary endpoint is percentage of participants with response (i.e., ≥1-point decrease in adjusted INCAT score) from baseline up to 24-weeks. Part-B evaluates efficacy durability based on percentage of relapse-free participants (SOC-Treated) or those with sustained-response (SOC-Refractory/Naïve), defined as no-increase in adjusted INCAT score ≥2-points relative to 24-weeks. Exploratory endpoints include additional efficacy measures (INCAT, I-RODS, MRC-SS, grip-strength), change in total complement (CH50), and plasma neurofilament-light chain (NfL). Safety is also evaluated.

Results:
As of May-2023, Part-A results from pre-specified interim-analysis show 88% (N=22/25) SOC-Treated participants improved/remained stable (44% [N=11/25] improved), and 12% relapsed (N=3/25). 50% (N=9/18) SOC-Refractory participants responded to riliprubart. Clinically meaningful improvements were observed across secondary efficacy measures. Sustained inhibition of complement activity and reduction in NfL levels were observed with riliprubart in SOC-Treated and SOC-Refractory subgroups. Treatment-emergent adverse events (TEAEs) occurred in 60% (N=15/25) and 72% (N=13/18) of SOC-Treated and SOC-Refractory participants, respectively. Two deaths were reported in participants with significant medical comorbidities aside from CIDP. Most frequent TEAEs were headache, fatigue, and nasopharyngitis. Available Part-A and Part-B data for all three subgroups will be presented at the meeting.

Conclusions:
These preliminary results support proof-of-concept for riliprubart in CIDP, with a favorable benefit-risk profile, and support further investigation in Phase-3.

References:
No

Grant Support:

Study funded by Sanofi

Keywords: Chronic inflammatory demyelinating polyneuropathy, Efficacy, Phase 2, Riliprubart, Safety

Monitoring of B lymphocytes to predict treatment response in chronic immune-mediated neuropathy

Poster No:
O 430

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Introduction:
B-cell depleting therapy is increasingly used to treat patients with chronic immune-mediated neuropathies, especially when standard immunotherapy fails. However, not all patients respond to B-cell depleting therapy, and biomarkers that are associated with clinical outcome remain undiscovered. Here, we aim to elucidate whether monitoring B lymphocytes is a feasible method to predict treatment response and clinical outcome.

Methods:
Patients with autoimmune nodopathy (n=3) and chronic inflammatory demyelinating polyneuropathy (n=6) were included in a prospective observational study. Blood samples were obtained at different time points after treatment (entry, 1, 3, 6, and 11 months) with Rituximab. Absolute counts of B lymphocytes were determined in whole blood using Trucount tubes. B lymphocyte subpopulations were quantified using isolated peripheral blood mononuclear cells and multi-color flow cytometry. The subpopulations cover naïve and transitional B lymphocytes, IgD+ CD27+ cells, CD27+ and CD27- memory cells, plasmablasts, and plasma cells.

Results:
Within one to three months after treatment, all patients showed an overall depletion of B lymphocytes of >99%. Absolute counts of all B-cell subsets, including circulating plasmablasts and plasma cells, were reduced. The strongest reductions were observed for naïve, transitional, and IgD+ CD27+ B lymphocytes, whereas residual memory B lymphocytes, plasmablasts, and plasma cells remained detectable in the peripheral blood. At the six-month time point, overall B lymphocyte depletion remained 34-99%, but counts of all subsets started to increase.

Conclusions:
Treatment with rituximab reduces all B lymphocyte subpopulations in the peripheral blood of patients with chronic immune-mediated neuropathy. Decreased numbers of CD20-negative plasmablasts and plasma cells are likely explained by reduced differentiation due to the depletion of memory B lymphocytes. Further analysis is needed to unravel the association between disease course and clinical outcome. Preliminary results will be presented at the conference.

References:
No

Keywords: Chronic immune-mediated neuropathy, B lymphocytes, Biomarker

Potential of peripheral nerve gene therapy using a novel adeno-associated virus serotype 2.5

Poster No:
O 431

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Introduction:
Gene therapy can be achieved in vivo by direct gene delivery or ex vivo through transduction of cells to be transplanted. Adeno-associated viruses (AAVs) are commonly used to deliver genes and are considered safe. Different cell types have selective affinity for certain AAV serotypes. Rat Schwann cells are transduced well by AAV1 while AAV2 and AAV6 are better for human Schwann cells. Rat nerve segments have been shown to be well transduced by AAV1, 5, 7 and 9, while human nerves prefer AAV2. We utilize a AAV serotype 2.5 vector that consists of an AAV2 vector modified with 5 amino acids from AAV1, providing it characteristics of both vector types. The ability of AAV2.5 to transduce cells of the PNS is not well characterized.

Methods:
In this study we determine the tropism of AAV2.5 for PNS tissues. We hypothesized that AAV2.5 would be effective. Neurons were isolated from rat DRGs of embryonic day 15 rats and primary Schwann cells from sciatic nerves of postnatal day 5 rat pups. Human Schwann cells were isolated from cervical nerve roots of patients undergoing dorsal rhizotomy for toricollis. Cells were transduced at a density of 125,000 cells per well using 104 – 106 vg/cell.

Results:
GFP expression in cultured neurons and Schwann cells was evident using AAV2.5 and was more effective than using AAV2. Cell survival and gene product production by AAV2.5 was also greater than with electroporation. Both rat and human Schwann cells were equally transduced.

Conclusions:
This evidence suggests that AAV2.5 can be used to transduce human and rat peripheral nerve cells for in vivo gene therapy or ex vivo cell therapy. AAV2.5 is also a clinically viable viral vector that is currently in use in phase 1 clinical trials for osteoarthritis (NCT02790723). This vector type presents an interesting clinical translation opportunity for peripheral nerve injuries/diseases.

References:
No

Grant Support:

Phase 1 clinical trials for osteoarthritis (NCT02790723)

Keywords: gene therapy, Schwann cells, AAV vectors

Molecular Mechanisms Involved in The Neurotoxic Phenotype of Schwann Cell Infected with *Mycobacterium Leprae*.

Poster No:
O 432

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Introduction:
Leprosy is caused by *Mycobacterium leprae* infection. Affecting skin and peripheral nerves, this pathogen promotes the lost axonal support by infected Schwann cells, with subsequent demyelination and axonal loss. The consequences involve permanent or transitory neuropathic pain, sensory and motor dysfunctions, and deformities. Although axonopathy is an important characteristic during infection, little is known regarding the mechanism that initiates this process, therefore, the main goal of our work is to identify cellular processes and signaling pathways involved in the disturbance of Schwann cell's axonal support induced by *M. leprae* infection, identifying drugs to avoid this process.

Methods:
Using high-content screening microscopy, we observed mitochondrial depolarization, glucose uptake, and ROS production induced by *M. lepra.* or *M. bovis* (BCG) expressing *M. leprae* surface antigen PGL-1 in human Schwann cell line ST8814. We evaluate the Schwann cell conditioned media neurotoxicity in SK-N-AS human neuroblastoma cell line. Finally, we used label-free-MS quantification to define the ubiquitinated proteome of M. leprae-infected Schwann cells.

Results:
M. leprae and BCG-PGL-1 infection in Schwann cells are followed by a strong mitophagy process, with a huge amount of ubiquitinated mitochondrion-associated proteins. Infected Schwann cells deviate lactate carbons to long-chain fatty acid synthesis. Most of this metabolic rewiring is done by PGL-1 activation of ERbB2/AKT pathway. Pharmacological inhibition of AKT or knockout of fatty acid elongase ELOVL1 has a neuroprotective effect in our in vitro model.

Conclusions:
M. leprae induces mitophagy through the PGL-1 antigen, by directly mitochondrial uncoupling and activation of ERbB2 pathway. This remodeling induces a fermentative state, followed by lipid accumulation and subsequent Schwann cells neurotoxic phenotype. We also found that the proteasome system is crucial for the success of the infection, and their subversion by the pathogen may be the genesis of leprosy neuropathy. Pharmacological inhibition of AKT and ELOVL1 may be a tool in controlling leprosy neuropathy.

References:
No

Keywords: Leprosy Neuropathy, Mitophagy, Proteomics, Mycobacterium leprae, Schwann cell

Empasiprubart (ARGX-117) in Multifocal Motor Neuropathy: Initial Safety and Efficacy data of the Phase 2 ARDA Study

Poster No:
O 433

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Introduction:
Multifocal motor neuropathy (MMN) is a chronic, immune-mediated neuropathy characterized by progressive asymmetric weakness. MMN is often associated with anti-GM1 IgM autoantibodies leading to activation of the classical complement pathway which drives subsequent axonal damage. Currently, IVIg is the only proven efficacious therapy. Empasiprubart (ARGX-117) is a monoclonal antibody that inhibits complement factor 2 and was shown in vitro to block IgM-mediated classical pathway complement activation targeting motor neurons in MMN. ARDA is a phase 2, multicenter, randomized, placebo controlled, double-blinded, parallel-group study (NCT05225675). It is the largest study in MMN and will assess safety, efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity of empasiprubart in adults with MMN.

Methods:
ARDA enrolled 52 participants with probable or definite MMN (per 2010 EFNS/PNS guidelines). All had proven IVIg dependency and were on a stable IVIg regimen leading into randomization. MMN diagnosis and IVIg dependency were confirmed by a MMN confirmation committee (MCC). Enrolled participants were assigned to one of two dosing cohorts; with each randomized 2:1 to empasiprubart or placebo. Key efficacy endpoints include IVIG retreatment, change in muscle strength, and disability scores.

Results:
Cohort 1 randomized 27 participants. The median age was 49 (range 37-78) years, and the majority were male (n=16, 59.3%). Pre-randomization IVIg intervals were every 2 or 3 weeks (n=15) or every 4 or 5 weeks (n=12) with a median dose of 1.5 g/kg (range 0.40-2.00). During double blind treatment period, empasiprubart demonstrated a 91% reduction (HR: 0.09 95% CI (0.02; 0.44)) in the risk for IVIg retreatment compared to placebo. Empasiprubart was well tolerated overall, with most adverse events being mild or moderate. Additional results will be presented at the congress.

Conclusions:
The early efficacy and safety signals in cohort 1 from the ongoing ARDA study support proof of concept of empasiprubart in MMN.

References:
No

Keywords: Immune Mediated, Empasiprubart, MMN, IVIg, Complement

PERIPHERAL NERVE SOCIETY

Non-SIG Related Abstracts

O 434 - 435

Antagonizing Endothelin B Receptor Improves Aging-Dependent Neuronal Regenerative Decline

Poster No:
O 434

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Introduction:
Sensory neurons can regenerate their axon after peripheral nerve injury to enable functional recovery. However, functional recovery from nerve injury in humans remains very limited because of the slow growth rate of axons and the long distances that growing axons face to reconnect with their targets. Furthermore, the axon regenerative capacity declines with age, but our understanding of how age impacts nerve repair remains poorly understood. Aging produces a wide range of modifications in cell signaling, metabolism, immunity, gene regulation, and protein translation, which affect tissue homeostasis. Excessive production of endothelin-1 (ET-1), a potent vasoconstrictor, is linked to many diseases whose severity increases with age. However, the role of ET-1 and its receptors on axon regeneration is unknown.

Methods:
We used a combination of in vivo axon regeneration assays, ex vivo nerve regeneration assays, electron microscopy, single cell RNA sequencing and immunohistochemistry on mouse and human dorsal root ganglia.

Results:
Using a single cell RNAseq approach in both mouse and human dorsal root ganglia, we reveal that satellite glial cells (SGCs), which completely envelop the sensory neuron soma, express the endothelin B receptor (ETBR), while ET-1 is expressed by endothelial cells. Blocking ETBR ex vivo in dorsal root ganglia explant cultures improves axon growth in both young and aged conditions. In vivo, treatment with the FDA-approved compound Bosentan improves axon regeneration and reversed the age-dependent axon regeneration decline. Mechanistically, antagonizing ETBR enhances the expression of connexin 43 in SGCs after injury in young mice and rescues the age-related decline in connexin 43 expression in SGCs.

Conclusions:
Our study demonstrates that endothelin signaling represents a mechanism that slows axon regeneration, in part by reducing Cx43 expression levels in SGCs. Our results highlight that this mechanism contributes to the age-related decline in regenerative capacity, providing potential new avenues for the treatment of nerve injuries.

References:
No

Keywords: Dorsal root ganglion, Endothelin B receptor, Satellite glial cells, Axon regeneration, Aging

Activity Of Follow-on Dosing For An Investigational In Vivo CRISPR-Based LNP Therapy In Transthyretin Amyloidosis

Poster No:
O 435

Authors:
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Introduction:
In vivo CRISPR-based gene editing delivered by a lipid nanoparticle (LNP) non-viral system is being studied as a one-time treatment in various diseases. In an ongoing phase 1 trial (NCT04601051), NTLA-2001, an investigational in vivo CRISPR-based therapy, has been administered as a single-dose treatment for transthyretin amyloidosis. Data from 72 patients support a one-time 55mg dose for future trials. We report early findings for follow-on dosing of cynomolgus monkeys, and human subjects who previously received sub-optimal doses, to achieve target pharmacodynamic effect.

Methods:
A study of cynomolgus monkeys included 4 groups: negative (vehicle) control, multiple dosing entailing human equivalent dose (HED) of NTLA-2001 surrogate (0.3mg/kg on 3 occasions followed by a 4th HED of 1mg/kg), duplicate dosing of HED 1mg/kg on 2 occasions, and positive control receiving a single HED of 1mg/kg. Dosing was intravenous; multiple and duplicate doses were separated by ~2 months. In the phase 1 trial, 3 patients received an initial dose of 0.1mg/kg NTLA-2001, were observed for 2 years, then received a 55mg dose (0.7mg/kg equivalent).

Results:
In the preclinical study serum TTR was unchanged in the negative control group and declined (mean) 88% from baseline in the positive controls. Multiple dosing yielded mean TTR reductions from baseline at 28-days post-dose of 28%, 37%, 57%, and 64%; for duplicate 1mg/kg dosing 85% and 94%. In the phase 1 study, median reduction [range] in serum TTR at Day 28 post-infusion of 0.1mg/kg was 52% [47% to 56%]. The first subject to receive follow-on dosing experienced a Grade 1 infusion-related reaction. Twenty-eight days post-infusion, serum TTR reduction from baseline was 92%. Serum TTR and safety data will be presented for all 3 patients.

Conclusions:
Preliminary data suggest follow-on dosing in subjects who received sub-optimal dosing of an in vivo CRISPR-based LNP therapy is feasible with evidence of a pharmacodynamic effect.

References:
No

Keywords: TTR, Amyloidosis, CRISPR, Cardiomyopathy, Gene Therapy

Inflammatory Neuropathy Consortium

Inflammatory Neuropathy Consortium (INC) Abstracts

O 436

OPTIC Trial: Intravenous Immunoglobulin And Intravenous Methylprednisolone As Induction Treatment In CIDP

Poster No:
O 436

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Introduction:
The OPTIC trial (ISRCTN15893334) is an investigator-led, randomized, double-blind, placebo-controlled trial assessing whether induction treatment with intravenous immunoglobulins (IVIg) and methylprednisolone (IVMP) leads to more remissions than IVIg alone.

Methods:
Adults diagnosed with definite or probable CIDP according to the EFNS/PNS 2010 criteria are being included, comprising three categories: 1) Treatment naïve patients; 2) Relapse patients following a year or more without treatment; 3) Patients having received a single loading dose of IVIg in the last three months with initial improvement and subsequent deterioration. Patients are randomized to receive IVIg + IVMP (1000mg) or IVIg + placebo (sodiumchloride 0.9%) every three weeks for 18 weeks. IVIg treatment consists of a 2 g/kg loading dose over 3-5 days and six maintenance courses of 1 g/kg over 1-2 days. Primary outcome is the number of patients in remission at 52 weeks. Remission is defined as sustained improvement between week 18-52 without needing additional treatment. Improvement is assessed at 18 week and defined as an increase of at least the minimal clinically important difference (MCID) on the Inflammatory Rasch-Built Overall Disability Scale (I-RODS) and/or improvement of ≥ 1 point on the Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale compared to baseline. Follow-up is 2 years and includes long-term safety, clinical assessments, and an economic evaluation.

Results:
From February 2018 to January 2024, 77 of 96 patients enrolled, of which 65 completed one-year follow-up. Seven deteriorated during treatment, of whom three had paranodal antibodies. Forty-eight of 58 patients completing the blinded protocol improved at 18 weeks; 21 sustained improvement at one year. Four patients suffered a thrombo-embolic event during treatment, prompting early enrollment termination due to safety concerns. Treatment allocation will be disclosed in February 2024, with results presented at the conference.

Conclusions:
The results will be available after deblinding and will presented at the conference.

References:
No

Grant Support:

Prinses Beatrix Spierfonds (Dutch Charity), ZonMw (the Netherlands Organization for Health Research and Development).

Keywords: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy, corticosteroids, intravenous immunoglobulins, randomised controlled trial

PERIPHERAL NERVE SOCIETY

Non-SIG Related Abstracts

O 437

New Enhancements for the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT)

Poster No:
O 437

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Introduction:
The Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) was established by the National Institute of Neurological Disorders and Stroke (NINDS) within the U.S. National Institutes of Health (NIH) in 2011. The charge of NeuroNEXT was to expedite development of new therapies across neurological diseases by improving the quality and efficiency of multicenter clinical trials. NeuroNEXT has consistently met recruitment targets on time in their multicenter clinical trials.

Methods:
The most recent grant cycle of NeuroNEXT has added enhancements that 1) streamlines the application and review process, and 2) provides a pathway to fund trials clinical trials of gene-based and gene-targeted therapies for ultra-rare neurological diseases.

Results:
For the first Enhancement, NINDS recently published a new process for NeuroNEXT submission and review of clinical trials. This two-stage process is iterative and not limited to standard NIH deadlines (See NIH documents OTA-24-013 and OTA-24-014). It is anticipated that this process will significantly reduce the time from clinical trial protocol submission to activation. For the second Enhancement, NINDS published a process to submit clinical trial protocols to study gene-based and gene-targeted therapies for ultra-rare neurological diseases (See NIH documents OTA-24-011 and OTA-24-012). This process is an extension of the NIH Ultra-Rare Gene-base Therapy (URGenT) Program.

Conclusions:
The new enhancements within NeuroNEXT offer increased opportunity to fund and complete clinical trials in peripheral neuropathy, which both will decrease trial activation timelines and provide a new funding opportunity for gene therapy trials. Notably, a recently published clinical trial within NeuroNEXT investigated topiramate as a disease altering therapy for cryptogenic sensory peripheral neuropathy (Smith et al., JAMA Neurology, 2023).

References:
No

Keywords: Clinical Trials, Grant Mechanisms, NeuroNEXT

Inflammatory Neuropathy Consortium

Inflammatory Neuropathy Consortium (INC) Abstracts

O 438

Antibodies In Small Fiber Neuropathy

Poster No:
O 438

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Introduction:
Small fiber neuropathy (SFN) is a peripheral neuropathy that manifests clinically with somatic symptoms characterized by pain and autonomic complaints. Despite several causes have been identified, including diabetes mellitus, metabolic abnormalities, immune-mediated and inflammatory conditions, over 50% of cases are idiopathic (iSFN). Some studies suggest a possible autoimmune etiology and have described several antibodies associated with SFN, although with contrasting results. Here, we aimed to investigate the frequency of autoantibodies against neuronal targets in SFN.

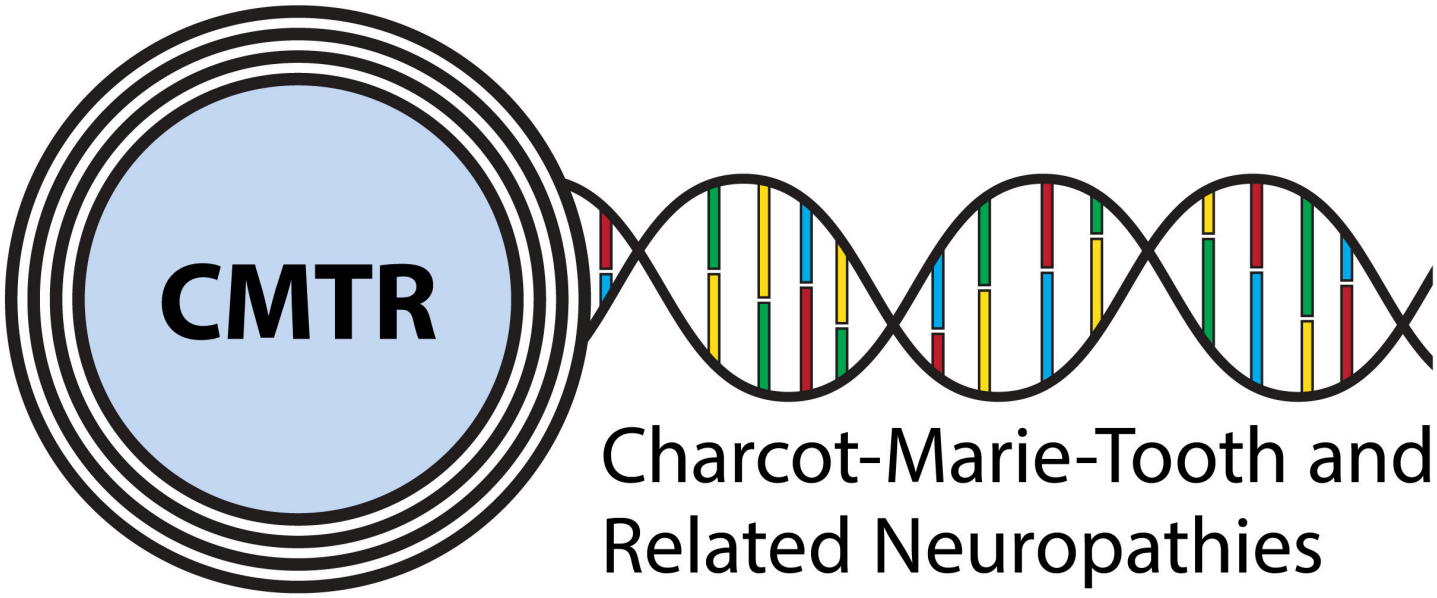
Methods:
We studied sera of patients undergoing skin biopsy for a suspected Small Fiber Neuropathy. The presence of antibodies against specific targets (including FGFR3, MX1, DBNL and KRT8) was assessed by in house cell-based assays (CBAs).

Results:
We included sera from 245 patients (M:61, F:184) with suspected SFN and 15 patients with other neurological disorders without sensory symptoms, used as disease-control group. Skin biopsy showed a reduced skin innervation in 77,6% (190/245) of patients (M:28,4%; F:71,6%). Antibodies against targets possibly associated with SFN were identified in 1,63% of cases (FGFR3: 1/245; MX1: 2/245; DBNL: 1/245; KRT8 0/245). Pre-absorbing and the co-localization studies demonstrated the specificity of the antibodies. All seropositive cases showed reduced epidermal nerve fiber density at the skin biopsy.

Conclusions:
In conclusion, antibodies against FGFR3, MX1, DBNL, and KRT8 are rare in patients with SFN.

References:
No

Keywords: antibodies, SFN, markers



Charcot-Marie-Tooth and Related Neuropathies (CMTR) Abstracts

O 439

Can Severely De-myelinated Axons be Recovered? Positive Evidence in 12-Month old C3 Mice.

Poster No:
O 439

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Introduction:
For CMT1A, the C3 mouse model is a useful model for comparison to human disease progression. C3 mice contain 3 copies of the human PMP22 gene (in addition to the mouse PMP22 gene) and have been well studied, both in terms of the molecular biology overproduction of PMP22 protein, as well as phenotypic behavior, including axon demyelination, walking and balance degradation, grip strength loss, and degraded electrophysiologic properties. A key question in the treatment of CMT has been "Can long-term demyelinated axons be returned to functionable or are they permanently disabled." This question is especially important when considering potential disease altering drugs for CMT1A, since it will affect what benefit can be expected for patients that have suffered from CMT1A for years.

Methods:
Here, we studied the phenotypic assessment and axon pathology of 12-Month-old C3, CMT1A mice that were severely damaged. Their physical capabilities have been hampered by long term demyelination due to the overproduction of PMP22 protein.

Results:
After treatment with an exon-skipping morpholino ASO that inhibits human PMP22 production and rebalances the total amount of protein, these animals gained significant physical improvement. Additionally, we describe a method where the axon pathology was assessed (at scale) in these animals. Overall, total myelination in the treated animals improved as did the number of axons that showed significant myelination.

Conclusions:
These preliminary studies indicate that demyelinated axons can indeed be restored to function over time (even in severely damaged axons) when treated with a therapeutic that rebalances the PMP22 protein production. This suggests that it may be possible to actually "improve" the performance of CMT1A patients treated with disease modifying therapeutics.

References:
No

Keywords: CMT1A, ASO, Morpholino, C3 Mouse, RNA

Inflammatory Neuropathy Consortium

Inflammatory Neuropathy Consortium (INC) Abstracts

O 440

Genome-Wide Association Study In Patients With Guillain-Barré Syndrome

Poster No:
O 440

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Introduction:
Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy. Although its pathophysiology has been well-described, factors involved in disease susceptibility remain largely unknown. Since only specific microbe strains lead to the development of GBS, pathogen factors likely play a role in disease susceptibility. However, these infections trigger GBS only in a minority, suggesting that host factors may be involved. So far only small-scale genetic studies have been performed in patients with GBS. In this study, we determined large-scale single nucleotide polymorphisms (SNP) in patients with GBS through genome-wide association studies.

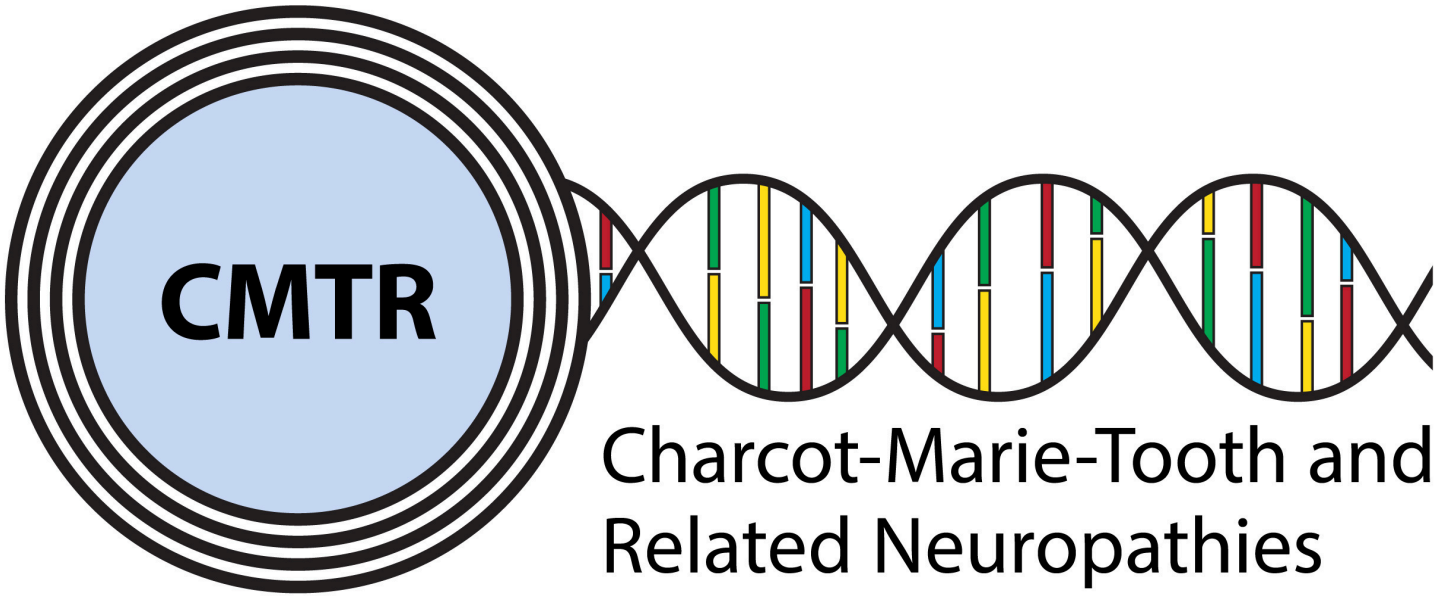
Methods:
In total, 1,079 patients with GBS (caucasians from the International GBS Outcome Study and Dutch trial cohorts) and 20,225 controls were included. Quality control (QC) was applied for call rates (<97.5%), Harvey-Weinberg equilibrium (p<=1*10-7), minor allele frequencies (<1%), palindromic variants, excess heterozygosity, and gender mismatches. Participants with non-European ancestry were excluded. Patients were matched to controls (1:4) through propensity scores based on age, sex, and ancestry. Imputations were performed using the Haplotype Reference Consortium version 1.1. Logistic regression analyses were applied with SNP, age, sex, and principal components as covariates. In post-analyses QC, SNP with low imputation quality (R2<0.3), missing information, or extremely large estimates (beta>50) were excluded.

Results:
Following QC and matching, 461,481 SNP from 1,021 patients and 4,084 controls remained available for analyses and 40,359,612 SNP were imputed. The quantile-quantile plot showed overrepresentation of loci with low p-values without inflation, indicating true signals. Among analyzed SNP, 19 were genome-wide significant and 23 were suggestive. Genome-wide significant SNP were located on chromosomes 1, 2, 3, 5, 11, 13, 15, and 22.

Conclusions:
The frequency of several SNP may be increased in patients with GBS, indicating that these could play a role in disease susceptibility. Further post-analyses QC will be applied and further interpretation of findings will be presented at the PNS Meeting.

References:
No

Keywords: Guillain-Barré syndrome, Genome-wide association study, Disease susceptibility



Charcot-Marie-Tooth and Related Neuropathies (CMTR) Abstracts

O 441

Minimal Clinically Important Difference (MCID) for the CMT Pediatric Scale (CMTPedS)

Poster No:
O 441

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Introduction:
The CMTPedS is a performance-based Clinical Outcome Assessment validated in accordance with the FDA to measure disability in children with CMT and related neuropathies. The minimal clinically important difference (MCID) represents the smallest change considered worthwhile by a patient. To ensure future disease-modifying trials make meaningful changes for children with CMT, it is essential to understand the MCID for the CMTPedS. Our aim was to identify the MCID of the CMTPedS in >1000 children with CMT enrolled in the international, prospective, natural history study of the NIH-funded Inherited Neuropathy Consortium.

Methods:
Demographic, anthropometric and genetic data were collected at annual clinic visits over 12 years in the US, UK, Italy and Australia. Disability was assessed using the CMTPedS by trained clinical evaluators and scored on ClinicalOutcomeMeasures.org. Child and Parent-reported change over the previous year was collected with the Patient's Global Impression of Change on the pCMT-QOL (Child-Report 8-18 years, Parent-Report 3-18 years). Those reporting a worsening ("A little worse/Much worse/Very much worse") were used to calculate the MCID for the CMTPedS.

Results:
A total of 1143 children (46.2% female) aged 10.9±4.6 years with CMT (50.2% CMT1A, 6.2% CMT2A, 3.5% CMTX1, 3.4% CMT1B, 2.1% CMT4C) were assessed with the CMTPedS (mean 18.8±9.5, range 0-44 points). Child-Reported MCID for the CMTPedS was 1.6 points and Parent-Reported MCID for the CMTPedS was 1.7 points on the 0-44 point scale. Correlation between Child and Parent-Reports was $r=0.4$, $p<0.001$. The MCID is being verified using the standardised distribution-based method and the Delphi approach to ensure a precise MCID is identified.

Conclusions:
This is the first report of the MCID for the CMTPedS. Understanding the magnitude of how children and their parents perceive change on the CMTPedS is essential for adequately powering clinical trials of disease-modifying interventions to ensure treatment effects are meaningful for patients.

References:
No

Keywords: Charcot-Marie-Tooth disease, Clinical Outcome Assessments, Minimal Clinically Important Difference, Clinical Trials, Pediatric

Inflammatory Neuropathy Consortium

Inflammatory Neuropathy Consortium (INC) Abstracts

O 442

Design of a Phase 3 Study Evaluating ANX005 in Patients with Guillain-Barré Syndrome

Poster No:
O 442

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Introduction:
In Guillain-Barré syndrome (GBS), infection triggers IgM and IgG antibodies cross-reacting with gangliosides in peripheral nerves, causing C1q binding to immune complexes and classical complement pathway activation. ANX005 is a fully humanized recombinant IgG4 monoclonal antibody targeting C1q that blocks the entire classical complement cascade and rapidly reduces complement-mediated nerve damage.

Methods:
This phase 3, multicenter, double-blind, placebo-controlled study (GBS-02, NCT04701164) evaluated multiple doses of ANX005 in patients with GBS, onset of weakness ≤10 days prior to infusion, and GBS-Disability Score (DS) of 3, 4, or 5 at screening. Sites in Bangladesh and the Philippines were chosen based on high GBS prevalence locally and limited IVIg availability, enabling a placebo-controlled trial. Patients were stratified by established prognostic factors of muscle strength (Medical Research Council [MRC] sum score) and time from onset of weakness. In total, 241 patients were randomized 1:1:1 to a single IV infusion of 30 mg/kg or 75 mg/kg ANX005 or placebo. All patients received best supportive care. Primary endpoint was at 8 weeks with follow-up through 6 months.

Results:
The primary endpoint of GBS-DS at week 8 was analyzed using a proportional-odds model assessing the likelihood of patients reaching a better health state following treatment with ANX005 vs placebo. Key secondary endpoints included MRC sum score at day 8 and week 8, GBS-DS at week 26, and duration of mechanical ventilatory support over 26 weeks. The proportion of patients with treatment-emergent adverse events (TEAEs) and discontinuations due to TEAEs were evaluated.

Conclusions:
ANX005 presents an important therapeutic approach to GBS, as it fully and rapidly inhibits C1q to stop ongoing nerve destruction during the progressive phase of disease. This novel study will provide insights into the efficacy and safety of ANX005 as well as contributing evidence for use of GBS-DS score at week 8 as a primary endpoint.

References:
Yes

Reference 1: Laman JD, Huizinga R, Boons GJ, Jacobs BC. Guillain-Barré syndrome: expanding the concept of molecular mimicry. Trends Immunol. 2022;43(4):296-308. doi:10.1016/j.it.2022.02.003

Reference 2: Lansita JA, Mease KM, Qiu H, Yednock T, Sankaranarayanan S, Kramer S. Nonclinical development of ANX005: a humanized anti-C1q antibody for treatment of autoimmune and neurodegenerative diseases. Int J Toxicol. 2017;36(6):449-462. doi:10.1177/1091581817740873

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Keywords: Guillain-Barré Syndrome, ANX005, complement, C1q, GBS-Disability Score

PERIPHERAL NERVE SOCIETY

Non-SIG Related Abstracts

O 443

Immune Cell Infiltrates In Dorsal Root Ganglia May Contribute to Sickle Cell Disease Pain

Poster No:
O 443

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Introduction:
Sickle cell disease (SCD) is a blood disorder characterized by sickled erythrocytes that cause vaso-occlusive events and both acute and chronic pain in patients. SCD mouse models also show allodynia and hypersensitivity behaviors relative to controls. Inflammatory processes have been documented in both SCD and neuropathic pain. Serum collected from patients with SCD indicates that cytokine and chemokine levels are elevated relative to patients with sickle cell trait or normally functioning hemoglobin. However, how these cytokines and chemokines contribute to neuropathic pain associated with SCD is poorly understood. We hypothesized that there is increased immune cell infiltration in the dorsal root ganglia (DRG) in SCD, at both steady state baseline and following a vaso-occlusive event.

Methods:
To investigate neuroinflammation in SCD, we isolated bilateral lumbar DRG from mice with mutated hemoglobin (Townes SS) and mice with unmutated hemoglobin (Townes AA) at steady state baseline and following experimentally induced hypoxia and reoxygenation to simulate a vaso-occlusive event. We then assessed immune cell infiltrates in the DRG by immunofluorescent microscopy. We quantified the number of macrophages, neutrophils, and T-cells during both steady state baseline and after hypoxia and reoxygenation.

Results:
We found increased numbers of macrophages and neutrophils in SS mice compared to AA mice at steady state baseline. Macrophage and neutrophil numbers were further increased after hypoxia and reoxygenation relative to steady state baseline in SCD samples.

Conclusions:
The increased immune cells in the DRG may sensitize the neuron via proinflammatory factors, thereby contributing to the allodynia and hypersensitivity previously observed in mice with SCD. The work herein is the first to describe neuroinflammatory changes in sickle cell disease DRG following a simulated vaso-occlusive event. Further, we identify immune cell infiltrates as novel therapeutic targets for development of analgesics that may alleviate the chronic and episodic pain behaviors in preclinical models of SCD.

References:
No

Grant Support:

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R37 NS108278 (CLS), Javits award

Keywords: sickle, immune, pain