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Consequences of SAC3/FIG4 deficiency to phosphoinositides in fibroblasts of patients with CMT4J

Jun Li, Assia Shisheva, Diego Sbrissa, Bo Hu

Wayne State University School of Medicine, Detroit, MI, USA

Introduction: Charcot-Marie-Tooth disease type-4J (CMT4J) is autosomal recessively inherited peripheral neuropathy caused by compound heterozygous mutations in FIG4 (also known as SAC3) gene, to result in severe loss/absence of the SAC3/FIG4 protein, which triggers neuronal degeneration, segmental demyelination, sensory disorder and limb muscle weakness. In mouse fibroblasts, the absence of the phosphatidylinositol (PtdIns) 3,5P2 5-phosphatase SAC3/FIG4 leads to reduced PtdIns(3,5)P2 due to disassembly of PtdIns(3,5)P2-metabolizing machinery, composed of the PIKfyve kinase, the ArPIKfyve scaffold and the SAC3/FIG4 phosphatase. Decreases of PtdIns(3,5)P2 over 70% is incompatible with life as shown in genetically modified mouse models deficient in either of the three genes. However, phosphoinositides (PIs) in humans with loss-of-function CMT4J mutations have never been evaluated. How changes in PIs relate to lysosomal phenotypes is also unclear. Methods: De-identified fibroblasts were obtained as previously described (Hu et al, 2016). Fibroblasts were labeled with myo-[2-3H] inositol to equilibrium. Extracted PIs were quantified by HPLC. Results: Compared to fibroblasts from normal human controls (n=9), both PtdIns(3,5)P2 and PtdIns5P levels were significantly decreased in CMT4J fibroblasts (n=13) by 36.4±3.6% and 43.1±4.4%, respectively (mean±SEM; p<0.0001). Whereas mean values for PtdIns3P levels remained unchanged vs. controls, there were high variations in PtdIns3P among individual patients. Morphological alterations in the form of multiple endolysosomal vacuoles, typically seen under PtdIns(3,5)P2 reduction, were apparent but not in fibroblasts from all CMT4J patients. Patients who failed to display aberrant cytoplasmic vacuolation exhibited significantly low levels of PtdIns3P vs. controls. Conclusions: 1). Our study assesses for the first time the PI profiles in humans with CMT4J. 2). The phenotypes in CMT4J patients may not be solely due to reduction of PtdIns(3,5)P2, but also to that of PtdIns5P, known to be involved in non-canonical autophagy. 3). Lack of vacuoles in fibroblasts from some CMT4J patients may be related to low PtdIns3P levels.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: U.S. Department of Veterans Affairs (IBX003385A)
Charcot-Marie-Tooth disease (CMT) is most commonly caused by duplication of a chromosomal segment surrounding Peripheral Myelin Protein 22, or PMP22 gene, which is classified as CMT1A. Several candidate therapies reduce Pmp22 levels in CMT1A rodent models, but development of biomarkers for clinical trials in CMT1A is a challenge given its slow progression and the difficulty in obtaining nerve samples. Quantitative PCR measurements of PMP22 in dermal nerves have been performed using skin biopsies in human clinical trials for CMT1A, but this approach does not show increased PMP22 mRNA in CMT1A patients compared to controls. One complicating factor is the variable amounts of Schwann cells (SC) in skin. The objective of the study was to develop a novel method for precise evaluation of PMP22 levels in skin biopsies that can discriminate CMT1A patients from controls. To accomplish this, we have developed methods to normalize PMP22 transcript levels to SC-specific genes that are not altered by CMT1A status. Several CMT1A-associated genes were assembled into a custom Nanostring panel to enable precise transcript measurements that can be normalized to variable Schwann cell content. Nanostring technology enables direct detection of transcripts without cDNA synthesis and amplification. The digital expression data from Nanostring analysis showed reproducible elevation of PMP22 levels in CMT1A vs. control skin biopsies, particularly after normalization to SC-specific genes. This platform should be useful in clinical trials for CMT1A as a measure of target engagement that can be used to optimize dosing, and the same normalization framework is applicable to other types of CMT.

References: None.

Keywords: CMTR, Schwann Cell, Other

Grant Support: This work was supported by U54NS065712 provided by NINDS/NCATS-ORD, a core grant to the Waisman Center from NICHD (U54 HD090256), and by a grant from the Charcot-Marie-Tooth Association.
Unravelling hallmarks of axonal degeneration in Charcot-Marie-Tooth type 2 using induced pluripotent stem cells

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Introduction: Our knowledge in the disease mechanisms of Charcot-Marie-Tooth (CMT) has significantly increased due to the successful generation of transgenic mouse models recapitulating the neuropathy phenotype. The human induced pluripotent stem cell (hiPSC) technology seems promising to substitute animal models of disease and may facilitate the identification and validation of reliable molecular therapies. We aimed to obtain an in vitro cellular model to study the hallmarks of axonal degeneration among different CMT2 subtypes. Methods: We reprogrammed fibroblasts derived from five CMT2 patients with different causal mutations in the MFN2, NEFL, HSPB8 and HSPB1 genes using Sendai-virus transductions. We differentiated these hiPSC lines, along with healthy controls, into spinal motor neurons using an established protocol [1]. We investigated: 1. signs of neurodegeneration using high content phenotypic screening, 2. cytoskeletal abnormalities disturbing axonal transport, 3. axonal transport deficits in mitochondria and 4. abnormalities in neuronal excitability using calcium imaging. Results: We successfully generated spinal motor neurons from hiPSCs with an efficiency of almost 95% from both patients and controls. A decrease in neurite area, length and branching for the MFN2, NEFL and HSPB1 patient lines indicated an altered neurite network. Deficits in mitochondrial trafficking and morphology were found in neurons from MFN2 and NEFL patient iPSC lines. Preliminary data revealed electrophysiological abnormalities based on calcium imaging, such as a shorter recovery time after stimulation in motor neurons derived from patients. Conclusions: Our findings provide insights into the molecular and cellular phenotypes of hiPSC-derived models for axonal CMT neuropathies.


Keywords: Axonal Biology

Grant Support: None.
Adult Polyglucosan Body Disease Presenting With A Peripheral Neuropathy: Broadening The Clinical Spectrum

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The purpose is twofold. First, to present a rare cause of a polyneuropathy with leukodystrophy as an initial presentation of a multisystemic polyglucosan body disease. Second, to expand the current knowledge concerning adult-onset GBE-deficiency phenotypes. A 49-year old man presented at our neuromuscular department with a two-year history of gait difficulties and distal sensory abnormalities. Distal weakness was noted as well as pedes cavi. Clinical examination was in keeping with a motor predominant peripheral neuropathy and mild pyramidal features. Nerve conduction studies showed a predominantly motor mixed axonal-demyelinating neuropathy. MR-imaging revealed confluent white matter lesions in both hemispheres. Family history revealed a younger brother with a similar albeit milder clinical phenotype. After five years of follow-up the patient had developed a progressively severe spasmodic gait with wheelchair use, neurogenic bladder dysfunction, discrete cerebellar ataxia and cognitive and behavioral changes. Progressive leukodystrophy and myelopathy were evident from serial MRIs. Distal weakness preceded proximal weakness in the lower limbs, analogous to a more pronounced motoric predominant neuropathy. Although mildly elevated serum CK levels (500-600U/L) were observed, muscle biopsy did not show primary myopathic abnormalities. Due to liver enzyme abnormalities, a liver biopsy was performed and showed a micro-macrovesicular steatosis. Whole exome sequencing showed compound heterozygous mutations (p.Thr254Ala and Ile694Asn) in Glycogen Branching Enzyme 1 (GBE1) and segregation in the family was confirmed. In conclusion, we report a case of an adult polyglucosan body disease (APBD) with a peripheral nerve system impairment dominating the initial presentation. We broaden the current knowledge of GBE1-related disorders by representing a combination of the two allelic forms of GBE1 deficiency, namely GSD-IV (glycogen storage disease type 4) and APBD. The first is associated with involvement of the liver and skeletal muscles in childhood, the second with peripheral neuropathy and central nervous system involvement in adults.

References: None.

Keywords: Human Genetics

Grant Support: None.
A recessive repeat expansion causes CANVAS and is a common cause of Late-Onset Sensory Ataxia

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Late-onset ataxia is a common reason for neurological consultation, but its cause often remains idiopathic. Cerebellar dysfunction, but also proprioceptive or vestibular impairment, can lead to ataxia. When in combination, this more severe type of ataxia is termed cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS). Both sporadic and familial cases of CANVAS have been reported, suggesting the possibility of a recessive transmission of the disease. The aim of this study was to identify the genetic cause of CANVAS. We performed non-parametric linkage analysis and genome sequencing. We identified an intronic recessive pentanucleotide repeat expansion in RF gene as the cause of CANVAS and a common cause of late-onset sensory ataxia. The presence of the repeat expansion was confirmed by repeat-primed PCR, long-range PCR and southern blot. Functional studies were performed to assess the effect of the repeat expansion on the expression of the repeat-hosting gene. The recessive repeat expansion, ranging in patients from 400 to several thousand repeats, showed full segregation in 23 cases from 11 families. Additionally, 33 (22%) out of 150 sporadic cases with late-onset ataxia from a single-centre carried the recessive repeat expansion. The percentage raised to 62% in patients with sensory neuronopathy and cerebellar involvement and 92% in full-blown CANVAS disease. Screening of additional cases with late-onset ataxia or CANVAS from Australia, New Zealand and France identified another 18 positive cases from seven unrelated families. Notably, the pentanucleotide repeat expansion does not affect expression of the repeat-hosting gene at mRNA and protein levels in patient fibroblasts. These data, together with the observation of an allelic carrier frequency of the expanded repeat of 0.7% in the European population, suggests that this biallelic pentanucleotide repeat expansion represents a frequent cause of late-onset ataxia and identifies an unconventional disease-causing mechanism in this late-onset recessive disorder.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: A.C. is funded by the inherited neuropathy consortium, which is a part of the NIH Rare Diseases Clinical Research Network (RDCRN) (U54NS065712) and Wellcome Trust (204841/Z/16/Z). A.M.R. is funded by a Wellcome Trust Postdoctoral Fellowship for Clinicians (110043/Z/15/Z). H.H. is also supported by Rosetrees Trust, Ataxia UK, The MSA Trust, Brain Research UK, MDUK, The Muscular Dystrophy Association (MDA), Higher Education Commission (HEC) of Pakistan and The Wellcome Trust (Synaptopathies Strategic Award). The INC (U54NS065712) is a part of the NCATS Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR), NCATS, funded through a collaboration between NCATS and the NINDS. S.Z. thanks the National Institute of Health (4R01NS075764) for its support.
Whole genome sequencing (WGS) as a single molecular genetic test is very appealing with the ability to simultaneously sequence both nuclear and mitochondrial genomes. It can reliably detect coding, splice-site and non-coding single nucleotide variants (SNV) as well as large balanced and unbalanced structural variants. As part of the 100,000 Genome Project which was launched in 2012, we have recruited 290 pedigrees for WGS, who had genetically undiagnosed CMT despite gene panel and other molecular genetic testing.

We present the phenotypic and initial WGS analysis of our first 40 CMT cases, with a provisional genetic diagnosis achieved in 10 pedigrees (25%) to date. Analysis of SNV and small insertions/deletions (indels) in all genes known to cause monogenic Mendelian disease (mini-exome) has been carried out and we identified variants in MORC2, HINT1, MT-ATP6, IGHMBP2, POLG, VRK1, MME and WARS. The avalanche of sequence data that accompanies WGS necessitates effective filtering of variants and this can be aided by setting a maximum credible population allele frequency for pathogenic variants in dominant and recessive CMT genes. As illustrated by some of our cases, the inclusion of trio-based WGS studies (affected proband and unaffected parents) allows the identification of de novo variants and the determination of variant phase in cases of compound heterozygosity. Furthermore, in more complex pedigrees, the recruitment of multiple affected and unaffected individuals from the same pedigree allows linkage through genome-wide genotyping of a large number of single nucleotide polymorphisms.

Incorporating WGS as a first-line test in CMT clinical practice will be normal practice in the future. Our caseload illustrates the multiple advantages of this approach as current gene panel-based and other molecular genetic testing does not achieve a diagnosis in 40% of our CMT cases.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: This research was made possible through access to the data and findings generated by the 100,000 Genomes Project.
Epidemiology Of Hereditary Transthyretin (hATTR) Amyloidosis: A Real-World Analysis Of A US Commercially Insured Population

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Introduction: This study’s objective was to generate a recent US estimate of incidence of hATTR amyloidosis, a rare genetic, progressive, and fatal disease caused by build-up of misfolded transthyretin protein (amyloid) in organs and tissues; focusing on patients with hATTR-associated polyneuropathy and/or mixed phenotype.

Methods: We identified patients ≥18 years diagnosed with hATTR amyloidosis in Truven Health Analytics MarketScan® Commercial and Medicare Supplemental data, using a claims-based algorithm due to lack of specific medical coding. Diagnosis required ≥1 medical claim with a relevant diagnosis code for amyloidosis (ICD-10-CM: E85.0-4, E85.89, E85.9; excludes light chain and wild type) in the calendar year (CY) of 2016 and ≥1 occurrence of qualifying criteria for hATTR any time during study (2013-2017): ≥15 days diflunisal use without >30-day gap, liver transplant, or claim with code E85.1 or E85.2. All disease-free enrollees (continuously enrolled and without a diagnosis code of amyloidosis in CY2015) were included. Annual incidence was calculated as the number of new cases of hATTR patients divided by total at-risk patient years from January 1st to diagnosis (cases) or enrollment end (non-cases) in CY 2016 and reported per million person years (PMPY). Enrollment was continuous during at-risk period.

Results: Annual incidence of hATTR in 2016 was 9.0 patients PMPY. Incident cases were concentrated in older age groups (65+ years: 23.3, 55-64 years: 14.6, 35-54 years: 5.8, 18-34 years: 2.2 PMPY) and slightly more common among females than males (9.6 vs. 8.3 PMPY). Estimates in 2017 followed mostly similar patterns but were truncated due to data censoring.

Conclusions: The epidemiology of hATTR amyloidosis is not well understood or quantified. This study reveals a small but meaningful number of new patients diagnosed with hATTR in the US in 2016. Consistent with previous studies, new cases are predominately of advanced age. Future estimation of prevalence is planned.

References: None.

Keywords: Amyloidosis

Grant Support: None.
Mutations in MORC2 cause axonal neuropathy with complex features.

Carolynne Doherty¹, Menelaos Pipis¹, Andrea Cortese¹, Alexander Rossor¹, Adnan Manzur², Francesco Muntoni², Mary Reilly¹

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Introduction: MORC2 is a DNA dependent ATPase which relaxes chromatin to facilitate repair of damaged DNA. Mutations in this gene cause axonal CMT, first described in 2016.(1) We have identified three families who carry these mutations.

Case presentations: A 25-year-old male presented with painful distal tingling and hand “locking” and cramping. He first walked at 18 months. On examination there was retinal pigmentary change, pyramidal and subtle cerebellar signs and neuropsychometry demonstrated an IQ of 80. Neurophysiology confirmed an axonal motor and sensory neuropathy with severe denervation on EMG. Extensive diagnostic evaluation included targeted genetic testing and the CMT2/intermediate panels and metabolic evaluation but did not yield the diagnosis. Ultimately a p.R252W mutation was identified in MORC2 following whole exome sequencing. The proband’s 5-year-old child was found to have delayed motor and language skills, labile behaviour and axonal neuropathy. Subsequently a 27-year-old female was found to have the same mutation, with delayed motor milestones, intellectual disability, toe walking, and hearing impairment. A wheelchair is needed for mobility since age 22. A third patient (29-year-old woman) has been found to have the p.E236G mutation and has required a wheelchair since age 27, with a history of delayed motor milestones, early foot deformity, scoliosis and patchy upper limb symptoms. Her 4-year-old child is also affected with speech and language delay, an abnormal gait at 15 months and brisk lower limb reflexes, weakness of ankle dorsiflexion and marked asymmetrical varus deformity.

Discussion: A phenotypic spectrum of axonal neuropathy with associated features such as hearing impairment, retinal dystrophy, pyramidal features and neurodevelopmental abnormalities has been reported associated with MORC2 mutations. We describe the clinical features in three families identified through whole exome or mini exome sequencing and discuss the literature.


Keywords: CMTR, Human Genetics

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Poster 9

Fatigability in Children with different CMT subtypes

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OBJECTIVE: We hypothesise that severely affected children with different types of CMT will fatigue in the last minute of the 6minute walk test used in CMTPedS. BACKGROUND: Prior studies demonstrated that children with SMA walk shorter distances in the last minute of the 6MWT, and that this may also be true in CMT. Prior studies with a smaller group of children with CMT1A did not demonstrate fatigability.

METHODS: 180 children with CMT underwent the 6MWT test at the University of Iowa CMT clinic between 2013-2018. These included 78 subjects with CMT1A, 20 with CMT2A, 11 with CMT1E, 7 with CMT4C and 7 other rare types each containing only 1-3 individuals. Patients unable to ambulate or adequately follow directions were excluded. Participants were all in barefoot. Walking times were recorded for each minute of the 6MWT and z score results 1-4 were also compared to the overall CMTPedS Scores (0-44).

RESULTS: No patient with CMT1A demonstrated significant reduction in the distance walked during the 6th minute compared to the first minute of the study, consistent with our prior data. Subjects with CMT2A, CMT1B, CMT4C and most other subtypes typically had higher CMTPedS scores and walked shorter distances overall than children with CMT1A. However, these children also did not demonstrate fatigability in the 6th minute of their walk. Children evaluated over several years did not develop fatigability in follow up studies. Rare individuals with distal HMN did fatigue during the last minute; these individuals were not genetically diagnosed.

CONCLUSIONS: Ambulatory children with different subtypes of CMT did not fatigue during the last minute of the 6MWT even if their CMT was severe as defined by higher CMTPedS scales. The 6 minute walk is therefore not able to routinely demonstrate fatigability in most ambulatory children with CMT.


Keywords: CMTR, Clinical Trials

Grant Support: NCATS/NINDS, Muscular Dystrophy Association, Charcot Marie Tooth Association
Poster 10

IN VIVO MAPPING OF CORTICAL MYELINATION IN CMT1A PATIENTS

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A single previous paper has demonstrated, using brain magnetic resonance imaging (MRI), diffuse subcortical white matter (WM) abnormalities in patients with Charcot-Marie-Tooth type 1A (CMT1A) disease. Moreover, pathological examination of the brain of a patient with PMP22 gene duplication showed diffuse hypomyelination sparing the U fibres.

A novel neuroimaging method based on the ratio of T1/T2-weighted magnetic resonance images, offers a non-invasive estimate of myelin content in the cerebral cortex. Therefore, to test whether also cortical myelination was reduced in CMT1A disease we applied this technique to a cohort of patients with PMP22 duplication.

Ten CMT1A patients (5 females, age: 30.20 ± 9.40 y) and 20 healthy controls (11 females, age: 30.25 ± 10.85 y) were investigated. All patients underwent clinical assessment and brain MRI. The myelin content in the cerebral cortex was studied using the MRI analysis technique based on the ratio of T1- and T2-weighted signal intensities.

Patients showed lower T1/T2-weighted ratio values in parietal and temporal areas. The two most significant clusters appeared in the postcentral gyrus, mainly peaking in the primary somatosensory cortex, and in the superior and inferior temporal lobes.

Our study demonstrates that myelin content in the cerebral cortex is reduced in CMT1A patients. The most involved cortical areas are those that are typically more myelinated in humans.

The mechanism of CNS myelin involvement in CMT1A is not clear as well it remains to establish if the reduced myelin content in the cerebral cortex may be a primary process or secondary to cortical remodeling due to peripheral axonal loss.

References: None.

Keywords: CMTR, Clinical Trials

Grant Support: None.
Molecular and functional characterization of cellular component associated with CMT1A endo- and perinevrium

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CMT1A is a congenital dysmyelinating disorder of the PNS characterised by ultrastructural abnormalities of the myelinated fibers which account for defective neuropathology and neurophysiology. In previous studies we demonstrated the critical contribution of lipids to the abnormal CMT1A myelin that is incorrectly formed and organised since the very early stages of development. Here, MALDI-IMS analysis performed for the first time in CMT1A neuropathy, displayed an impairment of lipid architecture both in myelinated fibers and connective tissue. Indeed, the spatial resolution applied to analyse in situ the distribution of lipid species demonstrated substantial differences in the organization of CMT1A rat sciatic nerve endonevrium and perinevrium compared to age- and gender-matched controls. These chemical and structural differences were corroborated by histological studies performed on experimental and human CMT1A. To further unravel the biological rationale underlying this issue, we isolated and investigated from the molecular and functional standpoint purified Schwann cells, endoneurial fibroblasts and perineurial cells from CMT1A rats and control littermates. Overall, we found significant differences between the two genotypes for each of the analysed condition to sustain a congenital mala organization of CMT1A peripheral nerves. Since we support the need to retrieve important biological features as critical targets for CMT1A, it is our opinion that these studies will allow a better comprehension of the molecular mechanisms undelying CMT1A neuropathy, fundamental to identify effective therapeutic strategies.

References: None.

Keywords: Schwann Cell, CMTR, Metabolic

Grant Support: None.
Digitally assessed patient-reported real-world care standards for Charcot-Marie-Tooth disease in the UK and US

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Introduction:

The objective of this analysis was to examine self-reported standards of care received by people with Charcot-Marie-Tooth disease (CMT) in UK and US real-world practice.

Methods:

Adults with CMT were recruited to a two-year international observational study exploring the real-world impact of the disease. Data were collected via CMT&Me, a bespoke ‘bring your own device’ app, through which participants were asked questions about demographic, CMT-management-related and quality-of-life variables. This interim analysis examined standards of CMT management reported by UK and US participants, including promptness of diagnosis and access to appropriate healthcare professionals. Outcomes were compared against clinical guidelines.

Results:

Diagnosis and care standards were generally aligned with guidelines. Around half of study participants received their CMT diagnosis within a year of first seeking medical care; however, substantial minorities reported experiencing diagnostic delays of several years and/or did not know their CMT subtype at the time of study participation.

The majority of participants had at least yearly access to several members of a multidisciplinary care team, including family doctors, neurologists, physical/physiotherapists, orthotists, and occupational therapists, among others. However, the type and number of healthcare professionals visited varied considerably between participants. Most people visited a neurologist – the professional recommended to coordinate CMT care – at least once a year; however, a sizable minority did not. A physical/physiotherapist, another important professional with the CMT care team, was seen at least annually by only around half of participants. The majority of people visited their family doctor at least once a year for problems with their CMT.

Conclusions:

CMT care standards in the UK and US are broadly in alignment with guidelines; however, there is scope to improve time-to-diagnosis and access to appropriate healthcare professionals. This ongoing registry will provide further real-world insights into areas for the development of CMT care.

References: None.

Keywords: Other

Grant Support: None.
Two novel mutations in the FAM134B gene: expanding the clinical and genetic spectrum of HSAN

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Hereditary sensory autonomic neuropathy (HSAN) type II is a rare, autosomal recessive, early onset sensory neuropathy, characterized by severe and progressive sensation impairment, leading to ulceromutilating complications. Although sensory symptoms predominate, motor involvement can also occur. FAM134B gene mutations have been recently reported to be associated to HSAN2B. We report the clinical and neurophysiological findings of two non-related families with HSAN2B, carrying two novel mutations in FAM134B gene.

Family-I: Three sisters from a consanguineous Turkish family presented HSAN type II phenotype with variable severity. The clinical manifestations started during early-childhood with difficulty in running and jumping, feet deformities and scoliosis. At 12 years of age, ulceromutilating complications appeared. The oldest sister presented a more severe phenotype with right foot amputation. Neurological examination displayed thermo-algic and vibratory hypoesthesia with glove and stock distribution; no motor weakness. Remarkably, brisk deep tendon reflexes associated to Babinski sign were noticed. Mild dysautonomic features, such as lipothymia, were present. Nerve conduction studies (NCS) showed an axonal sensorimotor polyneuropathy. A novel homozygous mutation c.896_897delAA (p.Lys299Argfs*6) was found in the FAM134B gene.

Family-II: A Portuguese female patient with no known family history and no obvious consanguinity was submitted to corrective surgery of hallux valgus at the age of 13. This surgery was complicated by rejection reaction of the osteosynthesis material. During follow-up, she presented recurrent plantar ulcerations complicated with osteomyelitis. Neurological examination revealed decreased thermoalgic and vibratory sensation in the lower and upper limbs. Slight distal motor weakness in lower limbs and absent deep tendon reflexes were also observed. There was no dysautonomia. NCS showed an axonal sensory-motor polyneuropathy with marked sensory impairment. A novel homozygous mutation c.1426del (p.Gln476Argfs*57) was found in the FAM134B gene.

In conclusion, this report expands the clinical and genetic spectrum of HSAN2B and emphasizes the phenotype variability even within the same family.

References: None.

Keywords: CMTR

Grant Support: None.
A fast low-cost protocol to obtain motor neurons from iPSc by Sedimentation Field Flow Fractionation

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Human induced pluripotent stem cells (hiPSc), generated for the first time in 2007, show the same properties as embryonic stem cells, with the advantage that they can be obtained from any differentiated cell types. Thanks to this feature, iPSc are widely used to create cellular lines that can not be directly taken from living patients, like motor neurons. Several protocols have been developed to differentiate iPSc into motor neurons: most of them are long and costly, requiring specific growth factors and cell culture media. We have already described a new method to obtain neural progenitors from iPSc using the Sedimentation Field Flow Fractionation (SdFFF) (1). This strategy of cell sorting enables to separate the neural fraction only on the basis of physical criteria, like size, density, or shape, avoiding labeling cells with antibodies or using expensive culture media. Furthermore, this approach helps to decrease the culture time so that we were able to obtain a cellular population enriched in neural progenitors in only 10 days. Here we report our last studies about the potential application of the method. After obtaining neural progenitors by SdFFF, we verified if they are capable to finalize the differentiation process up to motor neurons stage. SdFFF is a versatile, low-cost and noninvasive technique of cell sorting. Motor neurons derived from IPS cells and enriched by SdFFF could represent a good and easy to obtain cellular model for the study of peripheral neuropathies.


Keywords: CMTR

Grant Support: Région Nouvelle Aquitaine, University of Limoges
Hereditary Sensory Autonomic Neuropathy (HSAN) is a rare group of inherited peripheral neuropathies caused by at least 15 different types of mutations and characterized by disproportional sensory impairment with different degrees of autonomic and motor involvement. A 68-year-old man reported a history of simultaneous onset of numbness in the feet and hands in his 40s (denied any symptoms during childhood or adolescence), gradual loss of fingerprints, followed by mutilations/deformities in his hands and feet due to multiple injuries, such as burning (see attached photo). He gave written consent for this report. He also complained of burning feet and cold intolerance, generalized itching, arthritis and decreased hearing. He denied taste or olfactory impairment. He also reported that his father died at age 86, had worse deformities than him and had been diagnosed with leprosy. His neurological exam revealed absent ankle jerks and generalized hyporreflexia, high sock pain and vibration loss and decreased vibration in the hands. His EMG revealed a demyelinating sensorimotor neuropathy and work-up for acquired causes of neuropathy was negative, including a negative nerve biopsy to rule out leprosy. Genetic testing revealed 2 unreported mutations: C>A chr3.38.926.843 heterozygous for gene SCN11A and C>T chr2:167.133.677 heterozygous for gene SCN9A. No knock-out mice or gene function study was conducted to evaluate the mutations. In summary, this is a novel, predominantly severe sensory neuropathy phenotype (HSAN) resulting from an yet unidentified altered function of SCN9A and/or SCN11A genes. Further studies are necessary to evaluate the clinical phenotype in the relatives and evaluate the mutation effect in animal models of the disease to further understand the neurobiology of the new mutations observed.


Keywords: Human Genetics, Axonal Biology, Small Fibers, CMTR, Pain

Grant Support: CNPq
**Poster 17**

**Impact of Patisiran, an RNAi Therapeutic, on Diarrhea Symptoms in Patients with Hereditary Transthyretin-Mediated Amyloidosis**

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**Introduction**: hATTR amyloidosis is a rapidly progressive disease often resulting in wasting, weight loss, and reduced quality of life. This is due in part to debilitating diarrhea caused by amyloid deposition in the gastrointestinal tract and autonomic nerves. Inanition associated with progressive peripheral or autonomic neuropathy is a leading cause of death among these patients. In the Phase 3 APOLO study, patisiran demonstrated improvements on dysautonomia as measured by COMPASS-31 and Norfolk QOL-DN. This analysis further evaluates the impact of patisiran on diarrhea.

**Methods**: APOLO was an international, randomized (2:1), double-blinded, placebo-controlled study of patisiran 0.3mg/kg or placebo IV q3W in patients with hATTR amyloidosis with polyneuropathy (NCT01960348). Change in presence and severity of diarrhea symptoms was evaluated descriptively using question-level analyses from COMPASS-31 and Norfolk QOL-DN.

**Results**: APOLO enrolled 225 patients: median age 62 years, 74% male, 43% V30M, FAP Stage 1 (46%) and 2 (53%). At baseline, two-thirds reported mild to severe bouts of diarrhea in the prior year on COMPASS-31. After 18 months, patisiran treated patients were 3.5-fold more likely to report improvement in diarrhea compared to placebo patients (18% vs 5%, respectively). Patients treated with patisiran were also more likely to remain stable in their diarrhea severity than those receiving placebo (54% vs 42%, respectively). On Norfolk QOL-DN, more placebo-treated patients progressed to moderate or severe diarrhea and/or loss of bowel control at 18 months vs baseline (43% vs 33%, respectively); fewer patisiran-treated patients had moderate or severe symptoms at 18 months vs baseline (27% vs 34%, respectively).

**Conclusions**: Following 18 months, patisiran was more likely to improve or stabilize diarrhea at a lower-grade severity than placebo based on question-level analyses of patient-reported questionnaires. These data reinforce the clinical benefit of patisiran in addressing the debilitating autonomic symptoms of hATTR amyloidosis.


**Keywords**: Amyloidosis

**Grant Support**: None.
PXT3003 pleotherapy improves neuromuscular dysfunction in Charcot-Marie-Tooth type 1A

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The most common type of Charcot-Marie-Tooth disease (CMT1A) is caused by a duplication of PMP22, leading to dysmyelination, axonal loss and progressive muscle weakness. No therapy is currently available. PXT3003, a low-dose combination of baclofen, naltrexone and sorbitol, is a novel polytherapeutic approach reported to slow disease progression in the Pmp22 transgenic rat model of CMT1A. This effect was even more striking after early postnatal short-term administration that improved PI3K-AKT/MEK-ERK signaling dysbalance, axonal diameter distribution and partially prevented disease manifestation in CMT1A rats. Distal motor latencies (DML) correlated with the clinical improvement of CMT1A rats (Prukop et al., 2019). However, the synergistic effect of the single components of PXT3003 remained elusive. Thus, using a DRG co-culture system derived from transgenic rats we first found that PXT3003 exhibited a superior activity on myelination when compared to its single and dual components. We then applied a clinically relevant study design with late-onset therapy start in phenotypically affected CMT1A rats at multiple PXT3003 dosages and dual components for 3 months. In line with the in vitro data, PXT3003 treated animals exhibited a superior performance in contrast to single components when examining clinical endpoints. In order to address the effect of PXT3003 on the motor unit-beyond Schwann cell pathology, we then examined the neuromuscular junctions (NMJ) and muscle pathology in treated CMT rats. PXT3003 protected the number of functional NMJs in CMT1A rats. Moreover, in isolated muscles of CMT1A rats, we observed a shift in favor of fast contracting fibers after PXT3003 treatment. We thus conclude that baclofen, naltrexone and sorbitol contribute to the effect of PXT3003. We hypothesize that PXT3003 supports axonal function, improves the function of NMJs and consecutive muscle innervation which may contribute to the improved motor function observed in CMT1A rats.


Keywords: Pre-clinical Studies, Schwann Cell, Axonal Biology

Grant Support: This trial was supported by Pharnext.
Homozygosity for the Glu89Gln mutation in hATTR: first report of an Italian family

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Introduction. Hereditary transthyretin amyloidosis (hATTR) is related to different point mutations in the 127-amino acid TTR gene. In most of these, inheritance is autosomal dominant; homozygosity has been reported in V30M and V122I mutations. Patients homozygous for the V30M mutation do not appear to suffer from more severe disease (Holmgren et al., 1992), and asymptomatic homozygous V30M gene carriers have been described (Ikeda et al., 1992). A more recent study reported the largest homozygous V122I cohort, demonstrating an association with earlier onset. We describe the first case of ATTR homozygous for the amyloidogenic Glu89Gln mutation with an early onset and rapid course of disease.

Patient and Results. A 39-year-old man had a 2-year history of dyspnea and hypertrophic cardiomyopathy with diffuse left ventricular wall thickening. Because of cardiac worsening, he underwent cardiac transplantation. 2 years later he complained mainly of impotence. He then manifested others features of progressive and severe autonomic involvement (orthostatic hypotension, constipation alternating with diarrhea). He sudden died at 48 years. Family history was positive for heart failure: the mother and three of her brothers. 2/4 died at 53 to 63 years of age, and onset of symptoms had been at 45 to 56 years of age. The other two are heterozygous. His father died at 84 years. Conclusions. In our single-center experience in Sicily, Glu89Gln mutation is characterised by 5th - 6th decade onset, neuropathy as presenting symptoms with heart dysfunction. Homozygosity for the Glu89Gln mutation is associated with an earlier onset and rapid course of disease with severe cardiac and autonomic disturbances. Transthyretin analysis should be considered in young patients with heart disease mainly in presence of autonomic features such as impotence, hypotension and gastrointestinal dysmotility

References: None.

Keywords: Amyloidosis

Grant Support: None.
The biological significance of exploring CMT1A hypercellularity in peripheral nerves

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The prevalent feature of CMT1A neuropathy is dysmyelination associated with an abnormal remodelling of the whole peripheral nerve. Although the number of myelinated axons is reduced in CMT1A due to an impasse of Schwann cells (SC) differentiation program, abnormal proliferation is also a well-known aspect of pathological nerves both in animal models and human patients. Several cell types other than SC have been proposed to mediate this process in CMT1A. However, the role of most of these cells is still unclear. In an experimental model of CMT1A, we confirmed a remarkable increase of cell nuclei and DNA, by immunofluorescence and Sybr-Green assays, either in motor and sensitive peripheral nerves. Interestingly, this increase was evident starting from 30 days after birth and deeply grew over time. Since we aimed at identifying a molecular determinant paralleling this progressive increase of cells, we performed real time qPCR starting from a transcriptome profiling already performed in our lab. We found a significant overexpression of genes still underexplored in CMT1A but whose role is well known in cell proliferation, glial differentiation, tissue remodelling and monocyte differentiation. Interestingly, these genes are strongly and early modulated following crush injury to suggest a role in peripheral nerve plasticity. In our opinion, in peripheral nerves it is present a not well defined cellular type with specific undescribed function that is overexpressed in CMT1A and participate in the development of neuropathological abnormalities specific of this neuropathy.

References: None.

Keywords: CMTR, Schwann Cell

Grant Support: None.
Poster 21

Cardiopulmonary Exercise Test Performance and Predictors of Aerobic Capacity in Charcot Marie Tooth Disease 1A

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**Background:** Investigations of people with Charcot-Marie-Tooth disease (CMT) found reduced activity than the general population (1–3) and de-conditioning, as measured by exercise testing in seven participants (4). The objective of this study was to report in detail the cardiopulmonary response during maximal cycling exercise in a larger cohort of patients with CMT 1A. A second objective was to explore potential predictors of aerobic capacity with measures of physical impairment and functional performance.

**Methods:** Twenty-two people with CMT1A were recruited. Participants underwent maximal cardiopulmonary exercise testing (CPET) using a semi-recumbent cycle ergometer. During the test, on-line gas exchange was measured. Data were analysed to determine the peak O₂ consumption (VO₂ peak), anaerobic threshold (AT), maximum heart rate (MHR), ventilatory equivalent for CO₂ slope (VE/VCO₂) and Respiratory Exchange Ratio (RER). Impairment, functional and patient reported measures were also recorded. Predicted CPET variables were calculated based on published normative data for age, gender and weight (5,6).

**Results:** There was a significant difference in VO₂ peak compared to predicted values (CMT: 21.6 ±4.6 ml/kg/min, predicted: 28.0 ±5.2 ml/kg/min; p<0.01), AT (CMT: 12.1 ±2.1, predicted: 15.4 ±2.2; p<0.01) and MHR (CMT: 134.2 ±17.7, predicted: 176.2 ±14.5; p<0.05). There was no difference in ventilatory efficiency (VE/VCO₂) and RER was 1.10 indicating that participants were working maximally. Linear regression analysis demonstrated that VO₂ peak is related to body fat percentage (R²=0.37, p<0.01) and six minute times walk distance (R²=0.34, p<0.01).

**Conclusion:** Lower than predicted CPET variables were observed that were not explained by cardiopulmonary limitations or reduced effort. This indicates that peripheral factors maybe limiting the exercise bike task, e.g. quadriceps strength. The regression analysis implied prediction of VO₂ peak by body fat percentage and 6 minute walking distance, but may not be causative. Six minute walk distance could be a potential proxy measure of cardiopulmonary fitness.


**Keywords:** CMTR, Clinical Trials

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ESCOR-TTR: A National patient support program to monitor patients treated for hereditary transthyretin-mediated amyloidosis (hATTR)

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Introduction

hATTR amyloidosis is a progressive, life-threatening disease caused by a mutation in the TTR gene where amyloid fibrils accumulate in multiple tissues, including nerves and the heart. Due to its rapid progression, patients require close follow-up. Our objective was to create a patient program, ESCOR-TTR, to support both patients and their treating physicians in French centers.

Methods:

A group of French hATTR experts (neurologists and cardiologists) and patient representatives gathered to define the best approach to monitor hATTR symptoms between two routine consultations, including patients ‘and experts’ needs. The workshop was facilitated by an independent observer and followed up by several expert meetings.

Results:

The ESCOR-TTR program was initiated in February 2019 and is expected to run for a minimum of 1 year. Nurses were trained to identify disease progression according to criteria established by the experts. All patients receiving treatment for hATTR are eligible to enroll in the program which consists of an inclusion call and four follow-up calls (months 3, 6, 9 and 12) conducted by a trained nurse. The nurse monitors the course of the patient’s disease and helps the patient to prepare visits with the neurologist at 6 and 12 months and to complete self-assessment questionnaires. In the case of rapid disease progression, she may send an alert to the neurologist. Call content and questionnaires are securely logged and forwarded to the referring neurologist. A nurse helpline is also available for patients who wish to call spontaneously with basic questions.

Conclusion:

ESCOR-TTR first global program designed to answer the unmet need of the follow-up of the patients between their visits. The program combines distance monitoring provided by nurses ensuring a closer follow-up of the disease course and standardized national face to face evaluation by physicians. The program has been endorsed by NERF, Fibromus, and Amyloidosis Patient Association.

References: None.

Keywords: Amyloidosis, Other

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Sensitivity of Clinically Assessed Measures of Balance and Computerized Dynamic
Posturography in Pediatric CMT

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We aimed to identify sensitive clinical outcome assessments (COA) and adaptive strategies used to maintain balance in pediatric CMT. Eight participants (11.1±3.3 y/o) (4 male) with CMT 1A completed CMT Pediatric Scale (CMTPedS), Y-Balance test, and computerized dynamic posturography (CDP) Sensory Organization Test (SOT), evaluated utilization of visual/vestibular/somatosensory feedback for postural control, and Motor control tests (MCT), evaluated motor response time. Data was converted to z-scores. Impairment was described as z-score ≥ 2 s.d. below mean, and CMTPedS was used to classify disease severity. CMTPedS score was (12.75±5.92), five participants mild and three moderate disease severity. Dorsiflexion strength (2.59±0.95), sensation (4/8 participants decreased pinprick/vibratory sensation), and BOT-2 Balance subtest (-3.52±3.88) were impaired. Y-balance (0.60±0.89) and CDP composite SOT (-0.17±1.11) didn’t detect impairment; however progressive decrement was observed in conditions with <3 systems available. Participants performed best in static condition with all systems available (0.57). Conflicting visual stimuli negatively impacted performance (-0.14), and performance was the worst (-0.51) with vision occlusion, conflicting somatosensory stimuli, and only vestibular input available. MCT showed increased latency times (176.5ms ±19.27; normal latency < 150-160ms) for motor response. Anterior (COG) was present in 6/8 participants, consistent with limited dorsiflexion range. Increased forward latency responses were evident over backwards translations. Participants with CMT1A demonstrated ability to compensate for decreased somatosensory input and distal weakness on both the Y-Balance and SOT tests with visual compensation and adaptive postural strategies. Anterior COG allowed utilization of strong plantar flexors for support during static and dynamic-static tasks; however they were unable to utilize their weak dorsiflexors to recover from perturbations pushing them backwards. The BOT-2 balance subtest was the most sensitive balance assessment and should be used in assessment of patients with CMT1A as its items provide dynamic movement challenges, visual occlusion, and varied stances that decrease base of support.

References: None.

Keywords: CMTR

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Severe distal motor involvement in a non-compliant adult with biotinidase deficiency

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Biotinidase deficiency (BD) is an autosomal recessive disorder in which affected neonates are unable to recycle biotin and present hypotonia, seizures, ataxia, developmental delay or sensorineural hearing loss. When diagnosed by screening and treated by biotin supplementation outcome is excellent.

We report a young adult BD patient diagnosed by newborn screening who was asymptomatic while on therapy. Six months after voluntary interruption of biotin, he developed a progressive bilateral drop foot and inability to put on tiptoe suggestive of distal motor neuropathy. His biotinidase leukocyte residual activity was found to be null. Molecular analysis of the BTD gene showed a newly homozygous insertion c.1372_1373insT, p.C458Lfs*26. Despite biotin reintroduction, muscle weakness did not improve.

Transition to adulthood may be associated with non-compliance with therapy. The neurological findings in this adult are similar to those of other adults with biotinidase deficiency ascertained in adolescence and adulthood. Prognosis in these symptomatic older individuals may be dependent on the delay in biotin treatment.

References: None.

Keywords: Human Genetics, Metabolic

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Spinal muscular atrophy caused by an original MORC2 mutation

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Spinal muscular atrophy (SMA) and distal muscular atrophy (dSMA) are genetic disorders caused by the degeneration and loss of anterior horn cells in the spinal cord. The main gene involved in SMA is SMN1, and to date at least 20 genes have been identified in dSMA. However numerous cases remain unexplained genetically.

So far MORC2 has been described as causing axonal Charcot Marie Tooth disease type 2Z. We report the case of a patient presenting with a MORC2 mutation leading to AMS. The patient, a female of 43 years old, displayed cramps and muscular weakness since age 30. There was no familial history. Clinical examination revealed distal weakness in the upper limbs and a proximal deficit in the lower limbs, with pes cavus. Electroneuromyography (ENMG) showed neurogenic features in all four limbs, with normal motor and sensory conduction. ENMG was normal for her sister.

Screening of the SMN1 gene was normal, and no mutation was found in the dSMA genes. However, exome sequencing allowed us to identify a new original mutation in the MORC2 gene. This mutation c.1152C>A (p.His384Gln) is localized in the functional highly preserved domain S5 of the gene, where five pathogenic mutations have been previously described. It is predicted as pathogenic itself. Sequencing of the MORC2 gene of her mother and sister (both asymptomatic) was normal. Her father was deceased hence no DNA was available.

This observation broadens the genotypic spectrum of SMA, and is the first to report an original MORC2 mutation in such a phenotype.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: None.
Efficacy of a videogame intervention in Charcot-Marie-Tooth on balance and gait training

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Charcot-Marie-Tooth disease (CMT) is the most common neuromuscular disease. Patients with CMT neuropathy have often weakness and loss of sensitivity to lower limbs. The feet dysfunction and deformities strongly influence the disability and the quality of life of patients with CMT and, to date, there is not an effective pharmacological therapy to ameliorate the symptoms or to slow the progression of neuropathy. The aim of this project is to further evaluate the efficacy of different rehabilitative protocols and to demonstrate the safety and the efficacy of a rehabilitative protocol with a play station that is easy to transport at home, thinking about an "at home rehabilitation" with an easy to use and cheap instrument, available on the market.

We are recruiting 30 patients with diagnosis of CMT and we are performing the following evaluation with a blind operator before the treatment: strength (MRC), equilibrium (Berg's balance scale), walk (10 meters walk test and 6 meters walk test) and gait analyses. Patients have been invited to fill a questionnaire about the limitations perceived (walk-12).

We then randomized the patients in 3 groups: Stretching and proprioceptive exercises (previously, we have demonstrated the efficacy of this protocol), Nintendo Wii with balance board and a sham-group (massage). Every physiotherapist had to strictly follow the times and the sequences of the exercises of the protocol. They have been blindly re-evaluated at the end of rehabilitation.

Currently, we have the final data of 8 patients. As expected, we found that performances of CMT patients at the balance board are lower compared to normal controls. Spe and Wii treatments showed an better improvement comparing to massage in all evaluations, particularly Spe improves the quality of gait, Wii seems to improve the balance. More data are needed to complete the statistical analyses (at the end of the treatments).

References: None.

Keywords: Other

Grant Support: None.
Expanding the clinical manifestations of the DNAJB2 c.352 + 1GA mutation

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Background: DNAJB2 gene is almost exclusively expressed in neuronal cells and has been associated to several types of hereditary neuropathies. The homozygous DNAJB2 c.352 + 1G>A mutation seems to be associated not only to dHMN and CMT2 but also to Parkinson's disease and cerebellar ataxia.

Aim: To present a Brazilian patient with the DNAJB2 c.352 + 1G>A mutation in homozygosis presenting a complex clinical phenotype.

Case report: In a screening study using NGS, we identified the c.352 + 1G>A mutation in homozygosity in a patient followed in our outpatient clinic. He was first seen at the age of 18 years complaining of weakness and walking problems since he was 15. There was no sensory manifestation. He was the only affected member of his family. There was no consanguinity. On examination there was distal weakness and decreased ankle and wrist reflexes. Sensory examination, coordination, cranial nerves and speech were normal. His disease progressed, and on his last evaluation at the age of 29 his weakness and atrophy worsened significantly. He needs support to walk, has severe proximal weakness, vibration is decreased distally, his tendon jerks are absent but on plantar stimulation toes go up and there is triple flexion. EMG shows now a motor and sensory axonal neuropathy (CMAP: R-Peroneal = 0.13 mV, 32.9 m/s; R-Posterior tibial = 0.14 mV, 32.2 m/s; SNAP: R-sural 2.78 uV, 43.8 m/s).

Discussion/Conclusion: This presentation seems to indicate that the DNAJB2 c.352 + 1G>A mutation may also involve the corticospinal tract.


Keywords: Human Genetics, Other, Other, Other, Other

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Application of unbiased molecular datasets and machine learning for discovery of novel dHMN-associated genes

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A single causative disease gene cannot be identified for many distal hereditary motor neuropathy (dHMN) patients, despite advances in genomic technology. The use of combined annotation datasets to predict pathogenic variants has been shown using the mitochondrial proteome prediction tool, MitoMiner. This approach is hindered for dHMN, however, by a lack of unbiased datasets relating to the peripheral nerve. Therefore we used experimental datasets to train a predictive model to identify novel dHMN-causing genes and variants.

dHMN-causative variants were compiled by using ClinVar alongside control variants generated from ExAC. These variants were annotated using variant-level annotations, such as protein pathogenicity scores, alongside gene-level annotations, including values from experimental datasets. These annotated files were used as positive and negative training sets to train a random forest machine-learning model. This model was optimized and tested against exome data from patients with known mutations causing dHMN and can effectively distinguish disease-causing variants from a large proportion of other mutations. We used the model to make predictions of pathogenic variants for a cohort of unsolved neuropathy cases.

We have found the use of experimental datasets—especially those relating to the axonal transcriptome—effective in identifying dHMN genes. We see unexpected features being used by the model, such as minimal levels of gene expression in non-neural tissues. The model's accuracy can be improved by adding more non-biased datasets relating to the peripheral motor neuron, and the generation of these data should be encouraged. Our bioinformatic tool applies a systematic non-biased approach to identifying novel dHMN variants appropriate for the next generation sequencing era.

References: None.

Keywords: Axonal Biology, Human Genetics, Other

Grant Support: None.
A novel mutation c.941AG in WARS gene was identified in a Chinese dHMN family

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Distal hereditary motor neuropathy (dHMN) is a clinically and genetically heterogeneous group of inherited neuropathies that share the common feature of progressive distal muscle weakness and wasting without sensory abnormalities. To investigate the clinical and genetic features of dHMN caused by WARS mutations in mainland China, we performed Sanger sequencing of the coding regions of WARS in 160 unresolved CMT patients. We detected a rare heterozygous WARS variant, c.941A>G (D314G), in the proband of an autosomal dominant dHMN family. This variant segregated with the phenotype in 5 affected family members in 3 generations. The clinical features included adolescence to adulthood onset (15~23y), mild to moderate distal weakness and muscle wasting, and minimal sensory findings. Nerve electrophysiological studies indicated motor axonal degeneration. D314G was not present in gnomAD and 250 healthy controls from China. The variant was predicted to be ‘damaging’ or ‘probably damaging’ by in silico prediction tools and as ‘likely pathogenic’ according to the ACMG guidelines. Although this variant is located at the second nucleotide of exon 8, RNA analysis ruled out altered splicing. Structural analysis showed that the p.D314G substitution is located in a deep ‘Trp- and ATP-binding’ pocket, and might have an influence on the recognition, binding and activation of Trp. Our report expands the clinical and mutational spectrum of WARS to a mild and later onset phenotype.

References: None.

Keywords: Human Genetics

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THE PATH TO DIAGNOSING CHARCOT-MARIE-TOOTH DISEASE: THE PATIENT EXPERIENCE

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OBJECTIVES: Charcot-Marie-Tooth (CMT) patients cite a long path to obtaining an accurate diagnosis of their disease, even with a family history of CMT. This study assessed the path to diagnosis experienced by CMT patients, considering family history of disease, initial presentation of symptoms, and length of time to obtain a diagnosis.

METHODS: Hereditary Neuropathy Foundation, in association with Hannah’s Hope Fund, created the Global Registry for Inherited Neuropathy (GRIN), to capture detailed Inherited Neuropathy (IN) patient history via an online, IRB approved patient survey from 2013Q1-2019Q1. IN patients (N=2,195) engaged in an eight question survey regarding family history of CMT and diagnosis.

RESULTS: 76% of CMT patients have a history of the disease in their family. Overall, 59% of patients take over one year to get an accurate diagnosis of CMT, with 23% of patients taking five years or more to get diagnosed. 42% present symptoms of age 15 years or younger, with 26% of patients being 30 years or older. 30% of patients were the first to notice their CMT symptoms, while 27% of patients were first identified by a healthcare practitioner (HCP). Neurologists were overwhelming identified at the HCP who first diagnosed CMT at 33%; other practitioners were noted with de minimis results. Genetic testing was the leading method for obtaining an accurate diagnosis at 24%, with electrodiagnostic studies (EDX) next at 15%.

CONCLUSIONS: CMT patients can present symptoms early in life, yet it can still take several years to obtain a definitive diagnosis, even with a family history of the disease. While HCP’s early identification of patient symptoms is sizably represented, given the large cohort of youthful manifestation of the disease coupled with the length of time it takes to obtain a definitive diagnosis, increase symptom awareness across the spectrum of HCP’s is indicated.

References: None.

Keywords: Other

Grant Support: None.
Neuropathy-Related Disease Burden in Hereditary Transthyretin Amyloidosis Relative to Diabetic Neuropathy

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Introduction: Hereditary transthyretin amyloidosis (hATTR) is a rare and fatal disease resulting in progressive polyneuropathy and cardiomyopathy. Polyneuropathy symptoms and outcomes associated with hATTR amyloidosis resemble those of diabetic neuropathy (DN). An instrument designed to capture multiple dimensions of quality of life (QOL) in patients with DN – the Norfolk QOL-DN – has been validated with patients with hATTR amyloidosis. It is possible to examine the relative QOL burden of hATTR amyloidosis by comparing Norfolk QOL-DN scores from this population with scores observed for patients with DN.

Methods: The Norfolk QOL-DN captures QOL in patients who suffer from neuropathy with scores ranging from -4 to 136 (higher scores represent lower QOL). In addition to a total score, five domains can be assessed: physical functioning/large-fiber neuropathy (PF/LPN; range -4-56 points), symptoms (0-32), activities of daily living (ADL; 0-20), autonomic neuropathy (0-12), and small-fiber neuropathy (SFN; 0-16). Norfolk QOL-DN scores observed across three published studies of hATTR patients1,2,3 were compared to scores observed in a cross-sectional survey4 of 25,000 patients with diabetes, with or without DN, and with or without ulceration, gangrene or amputation.

Results: Patients with hATTR amyloidosis reported Norfolk QOL-DN total scores of approximately 50 points, with scores at about 25 points for PF/LPN, 10 for symptoms, 7 for ADL, 6 for SFN, and 3 for autonomic neuropathy. These scores are roughly 40% higher than patients who self-reported diabetes with DN; however, they closely match scores from patients who self-reported diabetes with DN accompanied by at least one episode of ulceration, gangrene, or amputation.

Conclusions: The QOL burden of patients with hATTR amyloidosis exceeds that for patients with DN and no complications, but closely matches that of patients with DN accompanied by ulceration, gangrene, or amputation.


Keywords: Amyloidosis, Clinical Trials

Grant Support: None.
**Poster 34**

**Sensory Neuron-derived IGF-1 Augments Neurite Outgrowth And This Autocrine/paracrine Pathway Is Suppressed in Diabetes**

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The level of insulin-like growth factor 1 (IGF-1) in serum of diabetic patients and animal models with type 1 and 2 diabetes declines significantly as the disease progresses. Recently, IGF-1 has been used for treatment of neurodegenerative disorders including Alzheimer’s disease and amyotrophic lateral sclerosis. We hypothesized that impaired autocrine/paracrine IGF-1 in dorsal root ganglia (DRG) was a contributing factor to progressive neurodegeneration and impaired nerve regeneration in diabetic sensory neuropathy. DRG neuron cultures and tissues from age-matched control or streptozotocin (STZ)-induced type 1 diabetic rats were used for in vitro and in vivo studies. Despite no difference in IGF-1 receptor level, IGF-1 protein and mRNA levels in liver and DRG tissues were significantly (P<0.05) lower in type 1 diabetic rats vs age-matched control rats. DRG neurons derived from control rats secreted a higher amount of IGF-1 into the culture media compared to cultures from diabetic rats (P<0.05). IGF-1 mRNA was expressed in neurons of the DRG and brain rather than in glial cells or sciatic nerve tissue as determined by RNA-FISH and Northern blot analysis. The hyperglycemic state suppressed IGF-1 mRNA expression in DRG neurons after 2 days which was relieved by treatment with (10nM) IGF-1 or an aldose reductase inhibitor, Sorbinil (blocks polyol pathway activity under high [glucose]). Bioinformatic screening and chromatin immunoprecipitation assay revealed NFAT1 and CEBP-β functional binding sites on the IGF-1 gene promoter in rat DRG neurons. In growth factor-free media, either IGF-1 neutralizing antibody or two IGF-1-targeting encapsulated siRNAs (in cationic nanoparticles) downregulated IGF-1 receptor and Akt S473 phosphorylation, and lowered background neurite outgrowth in cultured DRG neurons. In conclusion, downregulation of endogenous IGF-1 in DRG neurons in diabetes may contribute to pathogenesis of progressive distal dying-back neurodegeneration and up-regulation of neuronal IGF-1 at the mRNA level may be a promising target for therapy.

References: None.

Keywords: Axonal Biology, Axonal Regeneration, Other

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Distal Symmetric Polyneuropathy is Likely the First Neurologic Complication of Obesity

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Previous studies suggest that the metabolic syndrome (MetS) is associated with distal symmetrical polyneuropathy (DSP), and that diabetes and obesity are the main metabolic drivers. The aim of this study is to investigate the association of MetS components with retinal and cognitive function in a bariatric surgery cohort prior to surgery. Patients were recruited from the Bariatric Surgery Clinic at the University of Michigan and lean controls from a research website (no MetS components based on NCEP/ATPIII definition). Participants underwent extensive metabolic phenotyping including a glucose tolerance test and fasting lipid profile. DSP was defined using the Toronto consensus definition of probable clinical neuropathy. Retinal function was measured with frequency doubling technology perimetry (mean deviation), and cognitive function with the NIH Toolbox (composite score). Multivariable linear regression models were used to evaluate the association between MetS components and retinal/cognitive function. We recruited 138 bariatric surgery participants and 46 lean controls. The DSP prevalence was 2.2% in lean controls, 12.1% in normoglycemic, 7.1% in pre-diabetic, and 40.8% in diabetic bariatric participants (p<0.01 for trend). Retinal function was -0.4 (2.8), -0.4 (2.7), -2.1 (4.02), and -1.4 (4.4) (p=0.04 for trend), and cognitive function was 116.9 (13.7), 105.0 (17.4), 105.1 (17.8), 101.6 (18.7) (p<0.01 for trend) for these same groups. Pre-diabetes (-1.8, 95%CI: -3.6,0.0) was the only MetS component associated with retinal function. Systolic blood pressure (2.2, 95%CI: 0.1, 4.3) and waist circumference (-1.4, 95%CI -2.3,-0.5) were associated with cognitive function. Obesity alone may be sufficient to cause DSP and cognitive decline. Similar to previous data for DSP, pre-diabetes and obesity are associated with retinal and cognitive function respectively. Interestingly, while clinical DSP is common in this population, clinical retinopathy and dementia are not, indicating that DSP may be the first metabolic complication in the morbidly obese.

References: None.

Keywords: Metabolic, Diabetes

Grant Support: The project described was supported by Grant Number P30DK020572 (MDRC) from the National Institute of Diabetes and Digestive and Kidney Diseases.
Distribution of obesity is a key differentiator of neuropathy status

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While much is known about diabetes and neuropathy, much less is known about the relationship between obesity and neuropathy. Therefore, we aimed to determine the prevalence of neuropathy stratified by glycemic status to evaluate whether obesity alone is a potential cause of neuropathy. We also aimed to determine the association between the distribution of obesity, using extensive anthropometric measurements, and neuropathy. We performed a cross sectional, observational study in patients attending a bariatric surgery clinic prior to intervention. We also recruited lean controls from a research website. Neuropathy was defined by the Toronto consensus definition of probable neuropathy. Diabetes and pre-diabetes were defined according to the Expert Committee on the diagnosis and classification of diabetes mellitus, and the metabolic syndrome by NCEP/ATPIII criteria. We compared nine anthropometric measurements between obese participants with and without neuropathy. We used multivariable logistic regression to explore associations between these measures, and other metabolic risk factors, and neuropathy. We recruited 138 obese individuals and 46 lean controls. The mean age (SD) was 45.1 (11.3) in the obese population (76% female) and 43.8 (12.1) in the lean controls (82% female). The prevalence of neuropathy was 2.2% in lean controls, 12.1% in obese participants with normoglycemia, 7.1% in pre-diabetes, and 40.8% in diabetes (p=<0.01). waist circumference was the only anthropometric measure that was larger in those with neuropathy (139.3 cm vs. 129.1 cm, p=0.01). Hip-thigh (71.1 cm vs. 76.6 cm, p<0.01) and mid-thigh (62.2 cm vs. 66.3 cm, p=0.03) circumferences were smaller in those with neuropathy. waist circumference (OR=1.07, 95%CI 1.02-1.12), systolic blood pressure (OR=2.89, 95%CI 1.49-5.61), and triglycerides (OR=1.31, 95%CI 1.00-1.70) were significantly associated with neuropathy. Normoglycemic obese patients have a high prevalence of neuropathy indicating that obesity alone may be sufficient to cause neuropathy. Central obesity, but not general obesity, is significantly associated with neuropathy.

References: None.

Keywords: Metabolic, Diabetes

Grant Support: The project described was supported by Grant Number P30DK020572 (MDRC) from the National Institute of Diabetes and Digestive and Kidney Diseases.
Deletion of SARM1 has a Protective Effect for High-fat Diet-induced Peripheral Neuropathy and Glucose Intolerance

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Introduction: Recently, SARM1 has been highlighted as a critical factor causing axon degeneration both in acute neuronal injury and subacute/chronic conditions such as chemotherapy-induced peripheral neuropathy. Here, we evaluated the effect of SARM1 deletion for the development of distal neuropathy and glucose intolerance after the high-fat diet (HFD).

Methods: SARM1 knockout (KO) mice and wild-type (WT) littermates were fed with normal diet or HFD for 12 weeks. Analysis of thermal test, sensory nerve conduction study (NCS) and intra-epidermal nerve fiber density (IEND) at the hind paws were carried out after diet for the assessment of distal neuropathy. We also measured fasting blood glucose level every week and performed glucose tolerance test, insulin tolerance test, insulin secretion test and innervation of pancreas at the end-point for evaluation of glucose/insulin homeostasis. Results: WT mice with HFD developed thermal hypoalgesia and significant loss of IEND compared to WT with the normal diet. However, in SARM1 KO mice with HFD, the development of thermal hypoalgesia and the loss of IEND were prevented. There were no significant differences for sensory NCS between groups. Although both SARM1 KO mice and WT littermates showed increased fasting blood glucose level when fed HFD, SARM1 KO mice had significantly lower fasting blood glucose level than WT at the end of the study. Moreover, SARM1 KO mice fed HFD showed less insulin resistance compared to WT on the insulin secretion test and had preserved innervation of the pancreatic islet cells. Conclusions: This study reveals SARM1 as a potent regulator of distal axonal degeneration and dysfunctional glucose/insulin metabolism induced by HFD. The further research uncovering precise molecular mechanisms will be needed.

References: None.

Keywords: Pre-clinical Studies, Axonal Biology

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Plasma Deoxydihydroceramides are Elevated in People with Diabetic Neuropathy and Correlate with Neuropathy Severity

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Diabetic neuropathy (DN) is a debilitating condition that affects up to 50% of people with diabetes. Altered sphingolipid metabolism in diabetes may lead to an accumulation of atypical, neurotoxic deoxysphingolipids (dSLs) associated with neuropathy. dSLs can arise from reduced availability of the amino acid L-serine and/or the presence of excessive L-alanine. Studies have not investigated which dSL molecules are relevant to DN. We hypothesized that dSLs are elevated with DN. We examined dSL species using LC/MS/MS in plasma samples from a university based weight management program from age and HbA1C matched subjects with obesity (0, n=19), obesity with Type 2 Diabetes (T2D) (OD, n=18), obesity with T2D and DN (ODN, n=19), and lean controls (LC n=19). Sample means for the majority of deoxydihydroceramides (1-deoxyDHCer) for the four groups followed the same order from lowest to highest: LC, O, OD, ODN. Adjusting for pair-wise comparisons, mean levels of most 1-deoxyDHCer species were higher in the ODN as compared to the LC groups (0.527 vs. 0.226 pmol/100 µl for C16 1-deoxyDHCer, p=0.0021; 1.129 vs. 0.385 pmol/100 µl for C18 1-deoxyDHCer, p=0.0002; 1.136 vs. 0.492 pmol/100 µl for C20 1-deoxyDHCer, p<0.0001; 2.461 vs 1.585 for C22 1-deoxyDHCer, p=0.0496; 0.181 vs. 0.932 pmol/100 µl for C24:1 1-deoxyDHCer, p=0.0073). Mean levels of C20 1-deoxyDHCer were higher in the ODN group than the O group (1.136 vs. 0.733 pmol/100 µl, p=0.0350). No significant difference was observed between OD and ODN groups. Further analysis demonstrated that L-alanine was higher and L-serine lower in ODN versus LC (326.2 vs. 248.0, p=0.0086 and 70.2 vs. 89.8, p=0.0110), consistent with a causal contribution to the observed dSL profiles. 1-deoxyDHCer correlated inversely with nerve fiber density across all groups. These novel findings indicate that 1-deoxyDHCer are elevated in individuals T2D and DN and may be important biomarkers and/or mediators of DN.

References: None.

Keywords: Diabetes, Metabolic

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Early Parallel Progression Of Peripheral And Cardiac Autonomic Nerve Dysfunction In Recent-Onset Type 1 Diabetes

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Purpose: We previously demonstrated an early parallel involvement of small and large fibers in recent-onset type 2 diabetes. Here we hypothesized that this pattern may also be pertinent to type 1 diabetes (T1D).

Methods: Motor and sensory nerve conduction velocity (MNCV, SNCV), vibration perception thresholds (VPT), thermal detection thresholds (TDT), intraepidermal nerve fiber density (IENFD), and heart rate variability (HRV) were assessed in participants with T1D from the German Diabetes Study (GDS) at baseline (diabetes duration £1 year) and in glucose-tolerant controls: CON/T1D-B: n=96/360; age [median (1st; 3rd quartile)]: 34.5 (26.0; 46.8)/34.6 (26.5; 45.3) years; male: 72/58%; BMI: 25.0 (22.9; 28.3)/24.0 (22.0 (22.0; 27.0) kg/m²; diabetes duration: -/173 (114; 173) days; HbA1c: 5.1 (5.0; 5.3)/6.4 (5.9; 7.2)%; M-value (hyperinsulinemic-euglycemic clamp): 11.6 (9.1; 13.6)/8.2 (6.5; 10.4) mg*kg⁻¹*min⁻¹.

Results: T1D-B showed lower peroneal MNCV ([mean±SEM]: 45.8±0.2 vs 47.0±0.3 m/s), median MNCV (55.1±0.2 vs 56.0±0.7 m/s), and IENFD (10.0±0.5 vs 11.2±0.5 fibers/mm) than CON (P<0.05). In T1D, a deterioration from baseline to 5 years (n=151) was noted for ulnar and median MNCVs and SNCVs (e.g. ulnar MNCV: 57.4±0.4 vs 56.3±0.3 m/s), malleolar VPT (0.76±0.07 vs 1.12±0.12 µm), and HRV indices (e.g. standard deviation of normal RR intervals (SDNN): 69.3±2.4 vs 62.0±2.1 ms; root mean square of successive differences (RMSSD): 42.8±2.3 vs 34.7±2.0 ms) (all P<0.05). Peroneal MNCV, sural SNCV, and TDT remained unchanged. The decline in MNCV was associated with an increase in HbA1c (e.g. median nerve: β=-0.316, P=0.004) and the deterioration in HRV with decreasing M-value (e.g. SDNN: β=0.246, P=0.041).

Conclusions: Within the first 5-6 years of type 1 diabetes despite good glycemic control, the deterioration in median and ulnar MNCV was related to worsening HbA1c levels, while cardiac autonomic dysfunction progressed in relation to increasing insulin resistance.

References: None.

Keywords: Small Fibers

Grant Support: This work was supported by the Ministry of Culture and Science of the State of North Rhine-Westphalia and the German Federal Ministry of Health. This study was supported in part by a grant from the German Federal Ministry of Education and Research to the German Center for Diabetes Research (DZD).
Oxidative Stress and Human Diabetic Neuropathy: Role of NADPH Oxidase 5

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Diabetic Neuropathy (DN) is a common complication of diabetes. The underlying pathophysiological mechanisms of DN are not clear. However, reactive oxygen species (ROS) appear to play a key role in the cellular and molecular injury observed in DN. NADPH oxidase (NOX) enzymes generate ROS and of the 5 isoforms of NOX (1-5), NOX5 is present only in man. The aim of this study was to investigate a role for NOX5 in DN in cutaneous nerve fibers and sural nerve biopsies of subjects with DN.

Cellular localization of NOX5, myelin basic protein (MBP) and protein gene product (PGP) 9.5 were determined in cutaneous nerve fibers of non-diabetic controls and subjects with DN. NOX5 methylation status, gene expression and protein levels were assessed in subjects with DN that were divided into two groups based on changes in sural nerve myelinated fiber density: regenerators (showing significant nerve regeneration) and degenerators (showing significant nerve degeneration).

Our preliminary findings show that NOX5 is present in diabetic myelinated cutaneous nerve fibers, but absent in control fibers. Genome-wide DNA methylation analysis revealed that the NOX5 promoter, enriched with CpG sites, is hypomethylated in sural nerve biopsies of the degenerator cohort compared to the regenerator. Focused qPCR array revealed alteration of gene profiles in the oxidative and antioxidative pathways of the degenerator sural nerves compared to regenerators. In particular, NOX5 was increased at both the mRNA and protein levels in the degenerator cohort. The increase in NOX5 protein expression in degenerator sural nerves was accompanied with a decrease in MBP levels relative to the regenerator group.

Overall, our results point to a potential epigenetic and mechanistic role for NOX5 in DN, although further mechanistic studies are needed to provide more insight into the contribution of NOX5 to DN pathogenesis.

References: None.

Keywords: Diabetes

Grant Support: None.
Neuropathy is the most prevalent complication of type 2 diabetes (T2D) and prediabetes. The progression of neuropathy in prediabetic and T2D patients correlates with dyslipidemia characterized by elevated levels of circulating saturated fatty acids (SFAs). Recent studies indicate that dietary replacement of SFAs with monounsaturated fatty acids (MUFAs) improves the metabolic health of prediabetic and T2D patients; however, the differential effect of dietary SFAs and MUFAs on neuropathy is unknown. This study examined the impact of SFAs and MUFAs on nerve function.

Three groups of mice were fed diets with varying fatty acid composition from 6 to 24 weeks including a standard diet (SD), a SFA-rich high fat diet (HFD), and a SFA-rich HFD until 16 weeks followed by a MUFA-rich HFD (HFD-MUFA) until 24 weeks. At 24 weeks, both HFD and HFD-MUFA groups exhibited impaired glucose tolerance, increased body weight, and higher body fat mass compared to the SD group. Despite equivalent metabolic dysfunction in HFD and HFD-MUFA groups, the HFD-MUFA mice exhibited a complete restoration in sural and sciatic nerve conduction velocity. In parallel, intraepidermal nerve fiber density was significantly increased in HFD-MUFA mice compared to HFD mice.

To identify molecular changes underlying the restoration of sensory function in HFD-MUFA mice, we next evaluated the effect of SFA palmitate and MUFA oleate on mitochondrial dynamics in cultured dorsal root ganglion (DRG) sensory neurons. Diabetic concentrations of palmitate impaired mitochondrial transport and function in DRG axons. Supplementation of palmitate treatments with oleate prevented the impairment of axonal mitochondrial transport and restored mitochondrial membrane potential and ATP production in DRG neurons.

Together, these results support the contention that the development of neuropathy in prediabetes is related to mitochondrial dysfunction induced by SFAs, and that MUFAs reverse the progression of neuropathy by protecting mitochondrial function and dynamics in DRG neurons.

References: None.

Keywords: Metabolic, Diabetes, Axonal Biology

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Poster 42

Altered Nerve Triglycerides in Mouse Models of Diabetes with Neuropathy.

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Lifestyle changes, including dietary reversal (DR), can ameliorate peripheral neuropathy (PN) in patients with prediabetes and type 2 diabetes (T2D) however the mechanisms remain unclear. Our objective was to identify the contributions of altered nerve lipid profiles in PN development using mouse models of diabetes that underwent DR. 5wk old mice were fed a standard (10% kcal fat; SD) or high fat diet (60% kcal fat; HF) and at 12wk, a subset of HF mice were injected with STZ to induce a more diabetic-like phenotype. To simulate DR, subsets of HF and HF-STZ mice were placed on the SD from 16-24wk. At study conclusion, untargeted and targeted lipidomic profiling, complemented with RNAseq gene expression analysis, was performed on sciatic nerve (SCN) tissue. Compared to HF and HF-STZ mice, PN was corrected in HF-DR and HF-STZ-DR animals. Untargeted lipidomics revealed that triglycerides were increased in HF and HF-STZ SCN tissue but decreased in SD and DR groups. Quantitative targeted lipidomics validated these findings with an increase in triglycerides containing saturated fatty acids being observed in HF mice. Gene expression analysis revealed numerous differentially expressed genes that were dysregulated in HF and HF-STZ SCN but reversed by DR while KEGG enrichment indicated that lipid metabolism pathways were enriched. The lipidome and transcriptome datasets were integrated and identified a biologically relevant correlation between lipid levels and genes involved in triglyceride regulation. In parallel, DGAT2 expression, the enzyme required for triglyceride synthesis, was increased in sural nerve biopsies from hyperlipidemic diabetic patients with PN. We demonstrate that DR in HF and HF-STZ mice can restore PN that coincides with restoration of nerve lipid homeostasis. Collectively, these findings strengthen the hypothesis that abnormal nerve-lipid signaling is a key player in peripheral nerve dysfunction and suggest that lipid centric therapeutic interventions are needed for PN.

References: None.

Keywords: Diabetes, Pre-clinical Studies, Metabolic, Other, Other

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Poster 43

Risk Factors for the Development of Chemotherapy Induced Peripheral Neuropathy: A Retrospective Study

Noah Kolb, John Singleton, Joan Skelly, Summer Karafaith, Alpert Smith
Introduction: The objective of this study was to assess frequency, severity and risk factors for chemotherapy induced peripheral neuropathy associated (CIPN) with paclitaxel treatment.

Methods:
A natural language processing tool was utilized to perform retrospective chart review on paclitaxel treated breast cancer patients at the University of Utah between 1999 and 2015. CIPN risk factors were determined via time stamped ICD9/10 records while progress notes were reviewed for CIPN diagnosis and NCI CTCAE severity. Stepwise logistic modeling was used to determine the significant risk factors for the development of CIPN.

Results:
The mean age of the 549 patients was 52±12 with 99.6% female, and 57.9% weekly and 42.1% dose dense paclitaxel. Mean total paclitaxel dose (mg/m2) of those with vs. those without CIPN was 754±231 vs. 738±.256 p=0.49.

At the conclusion of chemotherapy: 74% had CIPN: 32% grade 1, 35% grade 2, 4% grade 3, <1% grade 4 or 5 neuropathy. At 2 years after chemotherapy: 36% had CIPN: 20% grade 1, 15% grade 2, <1% grade 3, 4 or 5, 14% CIPN still present but unable to determine severity. There was no significant difference in the percent with CIPN between dose dense and weekly dosing (75.5% vs 71.9%, p=0.31)

Result of stepwise regression modeling:
Significant risk factors for the development of CIPN: pre-existing non-diabetic/non- hereditary neuropathy (OR=12.0 (95%CI: 5.72-25.28)) and hyperlipidemia (OR=1.91 (1.13-3.21)). Risk factors for persistent CIPN at 2 years: Non-diabetic/non-hereditary neuropathy (OR=4.42 (2.94-6.63)), diabetic polyneuropathy (OR=3.46 (1.11-10.79)) and hypertension (OR=1.95 (1.33-2.86)).

Conclusions:
Approximately 75% of breast cancer patients treated with paclitaxel develop CIPN and it frequently persists 2 years later. Regression modeling demonstrates that pre-existant neuropathy, hyperlipidemia and hypertension may represent important risk factors for CIPN development and persistence.

References: None.

Keywords: Other

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Depleted Systemic Markers of Neuroinflammation And Growth Factors In Type 2 Diabetes Patients With Polyneuropathy

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Purpose: The determinants and mechanisms contributing to diabetic sensorimotor polyneuropathy (DSPN) remain unclear. Since inflammation and altered nerve regeneration have been implicated in the pathogenesis of both DSPN and neuropathic pain, we hypothesized that the corresponding biomarkers could be associated with DSPN and may have the potential to discriminate between the painful and painless DSPN entities.

Methods: We measured 92 serum biomarkers including pro- and anti-inflammatory cytokines, chemokines, and growth factors (GF) using the Proseek Multiplex INF I assay (OLINK Proteomics) in 304 individuals with type 2 diabetes and polyneuropathy (DSPN+), defined by the Toronto Consensus Criteria (2011), as well as in 158 individuals with type 2 diabetes without DSPN (DSPN-) and 354 individuals with normal glucose tolerance and without DSPN (NGT) (DSPN+/DSPN-/NGT [mean±SD]: age: 68±9/71±6/69±5 years; male: 76/59/41%; BMI: 30.8±5.3/30.8±4.4/26.9±3.7 kg/m²; diabetes duration: 13.5±9.6/7.6±5.8/– years; HbA1c: 7.4±1.3/6.6±1.0/5.5±0.3%). Within DSPN+, 161 participants suffered from neuropathic pain.

Results: After adjustment for multiple testing and sex, age, BMI, HbA1c, and smoking, the serum levels [normalized protein expression values] of 17 biomarkers including four cytokines (e.g. tumor necrosis factor ligand superfamily-12 (TNFSF12): 9.06±0.35 vs 9.30±0.32 and 9.45±0.29), five chemokines (e.g. C-C motif ligand-4 (CCL4): 7.93±0.68 vs 8.36±0.64 and 8.18±0.57), and four growth factors (e.g. Neurotrophin-3: 0.87±0.40 vs 1.00±0.33 and 1.03±0.34) were lower, while the level of one chemokine was higher in DSPN+ (CCL20: 5.79±1.23 vs 5.24±1.11 and 4.91±1.18) compared to DSPN- and NGT (P<0.05). No differences in biomarker levels were found in DSPN+ individuals with or without neuropathic pain. In diabetes, six biomarkers were associated with measures of peripheral nerve function (e.g. TNFSF12 with sural sensory nerve conduction velocity: r=0.259, P<0.0001).

Conclusions: Deficits in systemic cytokines, chemokines, and growth factors promoting nerve regeneration in type 2 diabetes are linked to polyneuropathy in general but not specifically to the painful or painless entity.

References: None.

Keywords: Inflammatory, Pain
Grant Support: The study was funded in part by grants from the European Union Seventh Framework Programme FP7/2007-2013 (PROPANE consortium; grant no. 602273), the German Center for Diabetes Research, and from the German Diabetes Association (Deutsche Diabetes-Gesellschaft, DDG). This work was also supported by the Ministry of Culture and Science of the State of North Rhine-Westphalia and the German Federal Ministry of Health. This study was supported in part by a grant from the German Federal Ministry of Education and Research to the German Center for Diabetes Research (DZD). Helmholtz Zentrum München – German Research Center for Environmental Health is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. Research was supported within the Munich Center of Health Sciences (MC-Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ.
Introduction: Vitamin D deficiency is closely related with diabetic polyneuropathy. However, there is no report of peripheral neuropathy associated with vitamin D deficiency in non-diabetic patient. Methods: We describe a 55-year-old woman with vitamin D deficiency presenting with progressive gait ataxia and paresthesia. Results: Neurological examination showed hypoactive deep tendon reflexes and proprioceptive sense impairment. Nerve conduction studies revealed sensory polyneuropathy. Serum 25 (OH)D3 and 1,25(OH)2D3 levels were 1.9 ng/mL (normal range; 9.5~55.5) and 1.4 pg/mL (19.6~54.3), respectively. Serum total calcium and vitamin B12 values were 5.5 mg/dL (8.6~10.0) and 185.9 pg/mL, respectively. Serial nerve conduction studies were performed for 1 year, while she received treatment for vitamin D deficiency. There was progressive clinical improvement, but electrophysiological findings were not improved. Conclusion: To my knowledge, this is the first report of sensory polyneuropathy associated with vitamin D deficiency. It is interesting to note that the sensory polyneuropathy associated with vitamin D deficiency state was developed in non-diabetic patient.

References: None.

Keywords: Metabolic

Grant Support: None.
Poster 47

Liability Of The Voltage-Gated Potassium Channel SK3 Repeat Polymorphism To Acute Oxaliplatin-Induced Peripheral Neurotoxicity

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Aim: Thus far, there are conflicting results on the causal role of potassium channels in the pathogenesis of acute Oxaliplatin-Induced Peripheral Neurotoxicity (OXAIPN). As such, we tested the hypothesis that the voltage-gated potassium channel SK3 repeat polymorphism confers liability to acute OXAIPN.

Methods: DNA from 151 Oxaliplatin-treated patients for colorectal cancer was extracted. Genotyping was performed with DNA fragment analysis by capillary electrophoresis of PCR products. The frequency of the 11 most common hyperexcitability symptoms associated with the acute OXAIPN was assessed by a descriptive questionnaire (yes/no response format), while the severity of acute OXAIPN was scored basing on the number of symptoms reported by the patients at each clinical assessment. The increased number of acute symptoms was considered as being suggestive of an increased severity of acute OXAIPN.

Results: A total of 130/151 (86.1%) patients developed any grade of acute OXAIPN. Grade I neurotoxicity was revealed in 43 (28.5%) patients; grade II in 34 (22.5%) and grade III in 53 (53.1%) patients. Genotyping revealed alleles carrying 11 to 20 CAG repeats. The majority of patients was heterozygous (131; 89.4%). The most common numbers of CAG repeats were 15 (n=46), 16 (n=53) and 17 (n=89). Patients carrying alleles with either 15-17 CAG repeats (p=0.601) or 17 repeats (p=0.161) did not experience a higher incidence of grade III (treatment-emergent) acute OXAIPN. Likewise, no increased incidence of acute treatment-emergent OXAIPN was noted in heterozygous patients carrying either two short alleles (< 19 CAG repeats) or one short and one long (≥ 19 CAG repeats) allele (p=0.701).

Conclusion: Our study failed to provide evidence to support a causal relationship between the SK3 repeat polymorphism and acute OXAIPN.

References: None.

Keywords: Other

Grant Support: None.
Poster 48

The Relationship Between Changes in Orthostatic Blood Pressure and Symptoms in Patients with Orthostatic Hypotension

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Background: Orthostatic hypotension (OH) is a cardinal feature of the autonomic peripheral neuropathy. Patients with OH can present with a wide range of symptoms, although often without clear link to blood pressure (BP).

Objective: To define the relationship between changes in BP on orthostatic symptom development in patients with OH.

Methods: In this retrospective study we reviewed 1037 charts of patients for autonomic testing from January 2016 to March 2018. Systolic, diastolic and mean arterial pressures were recorded continuously and each minute of testing. Change in blood pressures was compared to baseline values after supine rest, prior to testing. BP measures included the lowest BP in the first 3 minutes of tilt, the absolute BP value on tilt vs the lowest and the orthostatic BP-drop. Subjects were questioned about symptoms of orthostatic intolerance at baseline and two times during the first ten minutes of tilt.

Results: Eighty-nine patients (57% male, mean age 69 years) with OH were included in the final analysis. All patients completed the symptom questionnaires during tilt table testing. Supine hypertension was present in 59%. The majority (78/89) of patients had OH related to neurodegenerative disease or peripheral neuropathy, with lightheadedness and dizziness the most common symptoms. There was no relationship between magnitude of blood pressure fall and maximum symptoms ($R^2=0.0$, $P=NS$) or total symptoms ($R^2=0.04$, $P=NS$). There was no relationship between absolute lowest blood pressure and maximum symptoms ($R^2=0.02$, $P=NS$) or total symptoms ($R^2=0.05$, $P=NS$).

Conclusions: These results suggest a poor relationship between the magnitude of the orthostatic blood pressure fall, the absolute orthostatic blood pressure and symptoms. Many patients are asymptomatic despite substantial BP falls and low orthostatic blood pressures. These findings have implications for clinical care of patients with OH and clinical trials to treat patients with OH.

References: None.

Keywords: Small Fibers, Other

Grant Support: None.
Poster 49

Enhanced Schwann cell and Axonal Regeneration during M. leprae infection following Intracutaneous Axotomy in Armadillos

Gigi Ebenezer¹, Maria Pena², Richard Truman³, Linda Adams², Kelly Wagner¹, Michael Polydefkis¹
Nine–banded armadillos develop peripheral neuropathy after experimental *M. leprae* infection that closely recapitulates human lepromatous leprosy neuritis. We used the armadillo model to determine whether *M. leprae* infection alters cutaneous nerve regeneration following intracutaneous axotomy to further understand the pathogenesis of *M. leprae* associated peripheral neuropathy.

15 naïve and 18 *M. leprae*-infected armadillos underwent 3mm excisional skin punches in abdominal skin at 12, 13 and 14 months post-*M. leprae* inoculation. 4mm concentric punches, overlapping the previous 3mm excision punch sites yielded samples that were 30, 60 and 90 days post-axotomy. 3mm skin punches were obtained at the distal leg at 16 months. 50µm sections were immunostained with the panaxonal marker PGP9.5, and anti-p75, the Remak Schwann cell marker. Axonal and Schwann cell growth rates were assessed by measuring changes in epidermal innervation over time, expressed as mean±SE.

Both collateral sprouting and vertical regenerative axon regrowth from the deeper dermis led to complete reinnervation of the epidermis at the axotomy site by 60 days post axotomy. The axonal growth rate was significantly (*p*=0.01) higher in infected animals (naïve: 21.9±2.5, *M. leprae*: 30.6±2.8 mm/day) at the early 30 day post axotomy time point. Later timepoints had similar growth rates. There was a similar trend towards increased Schwann cell nuclear proliferation (cells/day, naïve: 118±14, *M. leprae*: 137±13) at 30 days. At the distal leg, epidermal nerve fiber density was reduced in infected animals compared to controls (14.3±2.8 vs. 9.5±1.2 fibers/mm, *p*<0.04) while Schwann cell number remained elevated in infected animals (*p*=0.02).

These results suggest that *M. leprae* infection leads to increased and persistent Schwann cell proliferation in response to injury. This is initially associated with enhanced axonal regeneration that slows over time and is ultimately associated with distal axon loss.

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**Keywords:** Axonal Regeneration, Schwann Cell, Small Fibers

**Grant Support:** Health Resources and Services Administration (HRSA), National Hansen’s Disease Programs
In the acute motor axonal neuropathy (AMAN) variant of Guillain-Barré syndrome (GBS), autoantibodies against gangliosides damage peripheral nerve axons by activating the classical complement cascade. In mouse models, anti-ganglioside antibodies (AGAbs) plus a complement source are used to target the distal motor nerve terminal (mNT), outwith the blood-nerve barrier. In large nerve bundles (spinal roots, nerve trunks), macrophage infiltration into the periaxonal space is a key early feature of AMAN, potentially acting as both executors of axonal injury and assisting in essential debris clearance. At the presynaptic mNT, perisynaptic Schwann cells (pSCs) overlying the terminal axonal membranes respond rapidly to mNT injury, and have been implicated in debris clearance. In this study, we have evaluated the relative responses of macrophages and pSCs to distal nerve injury in our AMAN model.

Three days after AGAb and complement-mediated injury, injured and control diaphragms from MacGreen mice (expressing EGFP in monocytes and macrophages) were analysed for macrophage content and activation state. In parallel, ex vivo nerve-muscle preparations were used to investigate the role of pSCs in mNT injury. In vivo, we show macrophage numbers are not elevated in the diaphragm, nor do they shift to pro- or anti-inflammatory phenotype. However, there is a redistribution of macrophages towards the vicinity of the mNT, indicating that tissue-resident macrophages are attracted to the injury. As the mNT regenerates rapidly, these macrophages are unlikely involved in continued nerve damage. We are currently investigating whether they are critical for debris clearance to allow regeneration. In contrast, observations from ex vivo mNT injury studies demonstrate pSCs do rapidly become phagocytic and engulf axonal debris from the injured mNT.

In conclusion, pSCs are important for clearance of debris and subsequent axonal regeneration. Tissue-resident macrophages are also attracted towards the mNT after localised injury, and their role is being investigated.

References: None.

Keywords: Axonal Biology, Axonal Regeneration, Inflammatory, Schwann Cell

Grant Support: Wellcome Trust
Introduction: In Guillain-Barré syndrome (GBS), two thirds of patients are reported to have antecedent infections up to four weeks prior to the onset of weakness. The profiles of antecedent infections vary geographically. In Southeast Asia, arthropod-borne viruses are common and dengue, specifically, is hyperendemic. In this case-control study, we aim to determine the association of a recent dengue infection and GBS in a Malaysian population. Methods: Consecutive patients presenting with features supportive of GBS were recruited between 2010 and 2018. The frequency of dengue virus infections was determined by dengue IgM antibodies. The sera of neurological controls with a similar distribution in age, gender, and period of sampling were obtained. Sera from patients with GBS were obtained before treatment. Results: A total of 95 patients with GBS were recruited. Evidence of recent dengue infection was present in 20.0% of GBS patients compared to 7.4% of neurological controls (19/95 vs 5/68, OR 3.2, 95% CI 1.1-8.9, p = 0.025). On univariate analysis, GBS patients with dengue IgM were associated with diarrheal symptoms (p = 0.027), severe disease at nadir (Medical Research Council sum score: p = 0.009; GBS disability score: p = 0.018), need for ventilation (p = 0.002), facial palsy (p = 0.004), absence of anti-ganglioside antibody (p = 0.022) and acute inflammatory demyelinating polyneuropathy (AIDP) subtype on electrophysiology (p < 0.001). AIDP subtype (p = 0.008) was the only independent associated factor on multivariate analysis. The presence of dengue IgM antibodies in patients with GBS was not associated with age, gender, disease progression, sensory deficits, cerebrospinal fluid albuminocytological dissociation or clinical outcome at 6 months. Conclusions: A recent dengue infection is significantly associated with GBS in Malaysia. Dengue-associated GBS patients were more likely to have AIDP on electrophysiology.


Keywords: Inflammatory

Grant Support: Dr. CY Tan receives research grant from the University of Malaya (BK074-2017).
Poster 52

Pure Motor Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in 17 Patients: Clinical Characteristics, Electrophysiological Study

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Introduction: Pure motor Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is a rare and poorly described form of CIDP.

Methods: Patients with definite or probable CIDP with pure motor clinical form, in a polyneuropathic distribution with abnormalities in sensory conductions studies in electrodiagnostic (EDX) studies (Pure Clinical Motor CIDP, PCM-CIDP) or without (Pure Motor CIPD, PM-CIDP) were included.

Results: 17 patients (prevalence of 2%) were included, with male predominance (71%), and a median age at onset of 48 years. At peak of severity, patients had upper and lower limb weakness (94%), with distal and proximal weakness in four limbs in 8 patients (53%). Clinical course was progressive in 12 patients. 6 patients had an associated disease including 3 patients with paraneoplastic CIDP (B-cell lymphoma, lung cancer and palate cancer), one patient with HIV, one patient with HCV and Sjögren syndrome and one patient with Inflammatory bowel disease. 12/16 and 4/5 patients had response to intravenous immunoglobulin (IVIg) and corticosteroids respectively. In EDX study, conduction block (CB) (82% of patients) and F abnormalities (88%) were frequent. Antiganglioside antibodies were positive in 3 patients (20%) including 2 patients with GM1+. The CSF protein was mildly elevated (>50mg/dl) in 11 patients (79%). During the follow-up, 4 of 10 patients in PCM-CIDP developed mild sensory symptoms, none in PM-CIPD group. Patients with PM-CIDP seem to have poorer outcome at the last follow up (median ONLS 4 versus 2, p = 0.03).

Conclusion: Beyond the previously reported features of pure motor CIDP including the low prevalence, response to IVIg, frequent CBs and F waves abnormalities in EDX study; our study revealed progressive clinical course in majority of patients, frequent associated paraneoplastic disorders and sensibility to corticosteroid therapy. In contrast to PCM-CIDP patients, PM-CIDP patients seem to have poorer outcome and did not develop sensory symptoms during follow-up.

References: None.

Keywords: Inflammatory

Grant Support: None.
CIDP with antibodies to CNTN1 is associated with HLA-DRB11 haplotype

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Introduction: CIDP is a heterogeneous autoimmune disease affecting the peripheral nerves. IgG4 antibodies to contactin-1 (CNTN1) are associated with a specific CIDP subtype. Risk factors associated with the appearance of these antibodies have not been described. HLA class II haplotypes strongly associate with several IgG4-mediated diseases, including anti-NF155-associated CIDP. This study describes the human leukocyte antigen (HLA) class II allele frequencies in chronic anti-CNTN1 positive patients.

Methods: 15 anti-CNTN1 positive and 51 anti-CNTN1 negative CIDP patients were included in the study. The frequencies of the HLA-DRB1 and HLA-DQ alleles were analyzed in all patients and compared with the allele frequencies of the general population obtained from the Allele frequencies database. In silico HLA-peptide binding and CNTN1 antigenicity predictions were performed to analyze overlap between presented peptides and antigenic regions.

Results: When comparing anti-CNTN1+ patients with the normal population: DRB1*11:01 alleles were present in 5 of the 15 anti-CNTN1+ (33.3 vs 14.6%; OR = 3.8, CI = 1.26 to 11.47), DRB1*11:02 alleles were founded in 2 anti-CNTN1+ (13.3 vs 2.84%; OR = 5.87, CI = 1.27 to 27.02) and 1 anti-CNTN1+ patient had the DRB1*11:03 allele (6.67 vs 1.97%; OR = 6.7, CI = 0.82 to 53.63); in contrast, none of the anti-CNTN1+ patients presented the DRB1*11:04 allele (0 vs 9.4%; OR = 1.2, CI = 0.07 to 20.98).

Overall, DRB1*11 alleles appeared in significantly higher proportions in anti-CNTN1+ patients than in normal population (53.33 vs 28.8%; OD = 3.3, CI = 1.14 to 9.56); even though the DRB1*11:04 is more frequently expressed in the general population. DRB1*11 alleles were predicted to present the same peptides and can be considered functionally homologous.

There were no statistically significant differences between the HLA II alleles in anti-CNTN1+ patients and seronegative CIDP patients.

Conclusion: HLA-DRB11 alleles are associated with CNTN1-antibodies in CIDP patients.

References: None.

Keywords: Human Genetics

Grant Support: None.
Poster 54

Clinical and serological investigations in CIDP patients with antibodies against CNTN1/Caspr1 complex.
Introduction:

Autoantibodies against paranodal proteins are useful biomarkers for diagnosis and treatment decision-making in patients with CIDP. Among them, antibodies against contactin-1 (CNTN1) and against contactin-associated protein-1 (Caspr1) were described in small subsets of patients with CIDP. Also, antibodies targeting the paranodal CNTN1/Caspr1 complex (but not CNTN1 alone) were described in one patient with an aggressive CIDP. However, the clinical-immunological features associated with antibodies against the CNTN1/Caspr1 complex have never been described.

Methods:

Eight CIDP patients with antibodies against CNTN1/Caspr1 complex were enrolled for characterization. Antibodies were tested by cell-based assays using HEK293 cells cotransfected with CNTN1 and Caspr1, or transfected with CNTN1 alone. We collected clinical, neurophysiological, laboratory and treatment response data.

Results:

We identified eight patients (5M, 3F) aged between 40 and 75. Patients’ sera showed reactivity only when CNTN1 and Caspr1 were cotransfected, but not when CNTN1 was transfected alone. All patients fulfilled EFNS/PNS definite diagnostic criteria for CIDP. They presented with an aggressive CIDP, with predominantly motor involvement. Half of them were initially diagnosed of Guillain-Barré syndrome due to a subacute onset. Neurophysiological studies showed findings of acquired demyelination in all patients, and acute denervation in at least two of them. Complete response to IVIg or steroids was not observed in any patient, while the response to rituximab in four treated patients was excellent.

Conclusion:

Antibodies against CNTN1/Caspr1 complex are present in a subset of patients with aggressive CIDP with poor response to first line treatments. We recommend screening antibodies against the CNTN1/Caspr1 complex as they will help guide the management. Experiments to elucidate the specific target of the autoantibodies of these patients are undergoing.

Keywords: Inflammatory, Node

Grant Support: None.
Poster 55

Serum Contactin-1 Levels In Chronic Inflammatory Demyelinating Polyneuropathy – A Pilot Study

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Purpose:

Biomarkers assessing disease activity in CIDP are needed to make informed treatment decisions in everyday care. Contactin-1 (CNTN1) is a paranodal axonal adhesion protein. Paranodal and juxtaparanodal proteins, including CNTN1, are targets for autoimmunity in subsets of CIDP patients. We hypothesized that serum CNTN1 levels reflect disease activity in CIDP.

Methods:

Three prospective cohorts of CIDP patients were studied: 1) patients starting induction treatment (IT cohort, N:27) measured at baseline and six months after starting treatment; 2) patients on maintenance treatment starting IVl g withdrawal (MT cohort, N:24) measured at baseline and six months after IVl g withdrawal or at time of relapse and 3) patients in long-term remission without treatment (N:26). Serum CNTN1 was measured using Luminex® assay. Age matched healthy controls (N:33) were used for comparison. Treatment response was defined as improvement by at least the minimal clinical important difference (MCID) on the I-RODS; and/or an increase of ≥8 kPa on grip strength. Relapse was defined as any deterioration requiring retreatment.

Results:

CNTN1 levels were lower in the IT cohort (median 10.2 ng/ml; IQR 8.9-12.5) compared to the MT cohort (12.0; IQR 10.4-15.0), patients in remission (14.2; IQR 11.3-17.7) and healthy controls (13.0; IQR 11.2-14.9; p<0.01 overall). After induction treatment, 2/8 (25%; follow-up sample missing for 1 patient) of the non-responders showed an increase in CNTN1 compared to 12/18 (67%) of the responders (p:0.09). After treatment withdrawal, 5/15 (33%) of patients with a relapse showed a decrease in CNTN1 compared to 7/9 (78%) of the patients without relapse (p:0.09).

Conclusion:

In this pilot study, CNTN1 levels in untreated CIDP patients with active disease were lower compared to patients stable on maintenance treatment, patients in remission and healthy controls. Changes in CNTN1 levels in relation to treatment response should be investigated in a larger cohort.

References: None.

Keywords: Inflammatory

Grant Support: None.
Background: Treatment in chronic inflammatory demyelinating polyneuropathy (CIDP) mainly consists of corticosteroids or intravenous immunoglobulins (IVIg). Remission is an important long term outcome. Corticosteroid therapy possibly increases the chance of long term remission. We aim to assess duration of treatment and compare remission rates following treatment with corticosteroids (monotherapy or in combination with IVIg) and IVIg.

Methods: Patients fulfilling the EFNS/PNS 2010 criteria for CIDP were prospectively enrolled in the ICOS and treatment data were systematically collected. A preliminary analysis was conducted in treatment naïve incident cases from two tertiary centers with a follow-up period of at least one year. For comparison, we grouped patients based on treatment type: corticosteroids (monotherapy or with IVIg) or IVIg monotherapy. We assessed treatment persistence at one year. In addition we assessed remission rates, defined as sustained improvement after discontinuation of treatment.

Results: 31 patients were included of which 22 (71%) received corticosteroids and nine (29%) IVIg monotherapy at baseline. In the corticosteroid group, six received pulsed high-dosed dexamethasone (during six months) and 16 received a combination of IVIg and methylprednisolone (every three weeks during four months). At one year nine (41%) patients in the corticosteroid group were still treated and five (56%) in the IVIg group. In the IVIg group, withdrawal was attempted in seven patients. Remission at one year was achieved in 13 patients (59%) patients treated with corticosteroids compared to four (44%) patients treated with IVIg.

Conclusion: Overall about half of patients were treated at one year. Based on this preliminary data, 59% of patients who received corticosteroid monotherapy or the combination therapy were in remission at one year compared to 44% of patients receiving IVIg. At the conference we will present the treatment results of all incident cases in ICOS, including a cohort of patients from a third tertiary center.

References: None.

Keywords: Inflammatory
INTRODUCTION. The Medical Research Council (MRC) scale is an outcome measure of strength, routinely used in neurological examinations. Previous research reported limitations of the MRC scoring system, proposing a collapsed 0-to-3-point scale. We aimed to assess the clinimetric properties of the original 0-to-5-point MRC scoring system and its sensitivity for GBS patients, using data from the International GBS Outcome Study (IGOS)-1300 cohort. METHODS. MRC scores were assessed at entry bilaterally for: shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and foot dorsiflexion. Rasch analysis was conducted to assess the suitability of the MRC 0-to-5-option response format, individual item fit, local dependency and dimensionality. Discriminative ability was determined by comparing scores to disability level [GBS Disability Score (GBS-DS)]. RESULTS. Data were available from 1099 patients (mean age 49±19 years, 40% female). The cohort comprised 76% (n=838) severely affected patients (GBS-DS≥3). No disordered thresholds were observed, supporting use of the 0-to-5 point response format. It was necessary to combine bilateral measurements to overcome local dependency caused by high inter-item correlations (>0.8). The foot dorsiflexion item required removal from the sum-score to achieve fit to the Rasch model. Rasch-derived MRC sum-scores (0-100, higher values indicate increasing strength) were generated for patients (mean 56.7±25.5). Sum-scores differentiated between patients with mild (mean score 79.3±17.3) versus severe (mean score 49.8±23.6, p<0.001) disability levels. Foot dorsiflexion raw scores (bilateral measures, out-of-10) independently discriminated between disease severity (mild: mean score 8.8±1.5 vs. severe: 5.7±3.4). CONCLUSION. For clinical use, MRC scores in their original format require no adjustment for GBS patients. For research purposes, Rasch-derived MRC sum-scores should be generated, and bilateral measurements combined to account for the symmetrical nature of GBS. Further, we recommend to assess foot dorsiflexion separately, as it may be an important individual indicator of disease severity that cannot be summarized by sum-scores.

References: None.

Keywords: Inflammatory

Grant Support: None.
Diagnostic Delay and Work-Up of CIDP in the International CIDP Outcome Study (ICOS) cohort

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Introduction

The diagnostic challenges in the spectrum of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are related to the variation in clinical presentation, electrophysiology, treatment response, and differential diagnosis of CIDP. CIDP is a treatable disorder and an early and correct diagnosis is essential to prevent secondary axonal damage and improve clinical outcome. We aim to describe the diagnostic work-up, identify factors related to diagnostic delay, and investigate the impact on clinical outcome in CIDP.

Methods

A preliminary analysis was conducted in 179 patients included in the International CIDP Outcome Study (ICOS).¹ For comparisons the median duration to CIDP diagnosis was used to separate patients in an ‘early’ and a ‘late’ diagnosis group.

Results

The time from onset of first symptoms until CIDP diagnosis was median 9 months (interquartile range 4-24, range 1-233 months) and more than 12 months in 70 patients (41%). The diagnostic work-up included nerve conduction studies (100%), lumbar puncture (82%), nerve biopsy (3%), nerve ultrasound (30%), magnetic resonance imaging (33%) and somato-sensory evoked potential (1%). Patients with a late compared to an early diagnosis more frequently had asymmetric CIDP variants (26% vs 8%) and nerve ultrasound examinations (39% vs 19%). Patients with an early diagnosis more frequently had cerebrospinal fluid examinations (94% vs 74%) and more often had elevated CSF protein levels (92% vs 75%).

Conclusions

Based on preliminary analysis, this study confirms the presence of diagnostic delay in CIDP and the first possible related clinical and diagnostic factors have been identified. At the conference, ICOS will be expanded by an additional cohort of treatment naïve CIDP patients and results of the full CIDP cohort regarding diagnostic delay in CIDP, including data on (initial) misdiagnosis, EFNS/PNS classification and possible related impact on clinical outcome.


Keywords: Clinical Trials, Inflammatory

Grant Support: None
Poster 59

Ultrastuctural Mechanisms of Macrophage-Induced Demyelination in Guillain-Barré Syndrome

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Introduction: Although recent advances in the identification of anti-ganglioside antibodies have significantly contributed to clarifying the pathogenesis of Guillain-Barré syndrome, particularly acute motor axonal neuropathy, the mechanism of classical macrophage-induced demyelination in acute inflammatory demyelinating polyneuropathy (AIDP) remains unclear.

Methods: Longitudinal sections of sural nerve biopsy specimens from 11 patients with AIDP exhibiting macrophage-associated demyelinating lesions were examined using electron microscopy. A total of 1205 nodes of Ranvier, with middle sections that were cut perpendicularly, were examined to determine the relationship of the macrophage-associated demyelinating lesions with the nodal regions.

Results: Overall, 252 macrophage-associated demyelinating lesions were identified in the longitudinal sections. Of these, 40 lesions exhibited complete demyelination with no association with the lamellar structures of myelin. In 183 lesions, the macrophage cytoplasm was located at the internodes without association with the nodes of Ranvier or paranodes. In particular, these internodal lesions were more frequent in one patient (152 lesions). Focal unraveling of the myelin layers apposed to the macrophage cytoplasm was frequently seen at the Schmidt-Lanterman incisures, where uncompaction of the myelin lamellae is observed under normal conditions as well. In the remaining 29 lesions, the involvement of nodal regions was obvious. Invasion of the macrophage cytoplasmic processes into the space between the paranodal myelin terminal loops and axolemma from the node of Ranvier was observed in three patients. Immunohistochemistry suggested complement C3d deposition in the areas with initial macrophage-associated demyelinating lesions in patients who underwent biopsy during early disease phase.

Conclusions: The initial macrophage-associated demyelinating lesions were located not only at the internodes but also at the paranodes. The sites at which the macrophages initiated phagocytosis of myelin might be associated with the location of complement deposition in certain patients with AIDP.

References: None.

Keywords: Inflammatory, Node, Schwann Cell

Grant Support: None.
Poster 60

Antibody- and macrophage-mediated internodal demyelination in CIDP: clinical, electrophysiological, immunological and pathological correlations

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a heterogeneous disorder considered an auto-immune disease involving both cellular and humoral immunity. IgG fixation on the outer surface of the Schwann cell has been described in patients’ nerve biopsies, suggesting that autoantibodies may be implicated in the demyelination process, and antibodies against specific nodal and paranodal junction components have been recently identified. In a cohort of 178 French CIDP patients we found that 31% of patients’ sera presented an IgG reactivity toward the node and paranode of mouse sciatic nerve. Interestingly, 18% of the patients presented a strong IgG or IgM reactivity against the internodal compact myelin. We report here the clinical, electrophysiological, immunological, and microscopic features of six of these CIDP patients in whom sural nerve biopsies were available. Five over six patients fulfilled the EFNS/PNS electrophysiological criteria for definite CIDP. These five patients showed increased (1.6 to 5.1 times) duration of proximal compound muscle action potential in at least two nerves. Electron microscopy of sural nerve biopsies showed normal paranodes and nodes, but demonstrated the presence of macrophage-mediated demyelination restricted to the internode. Immunolabeling for Nav channels, MPZ, and neurofilament-H confirmed the presence of segmental demyelination and remyelination. However, the nodal region appeared unaffected in these patients. Altogether these results indicate that CIDP patients with antibodies to internodal myelin or nodal/paranodal components show differential morphological features and pathogenic mechanisms.

References: None.

Keywords: Schwann Cell, Inflammatory, Other, Other, Other

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Poster 61

Prognostic features for death and progression in patients with POEMS syndrome

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Background

POEMS syndrome is a rare multisystem disorder with favourable long term prognosis if appropriately treated. A proportion of patients appear resistant to treatment, some relapse and few die. Ascertaining prognostic factors will assist with identifying high risk patients likely to require more frequent monitoring or more aggressive or alternative therapeutics.

Aim

To evaluate individual risk factors and produce a predictive model for risk of progression or death in POEMS syndrome.

Methods

We retrospectively analysed 100 patients with newly diagnosed POEMS syndrome at our institute from 1998 to present day. We performed univariate and multivariate regression analysis to identify statistically significant risk factors leading to poor outcome.

Results

A binomial logistic regression was performed which ascertained the effect of Haematological non-response (hNR), VEGF non-response (vNR), low glomerular filtration rate (GFR), low albumin at presentation and treatment with autologous stem cell therapy (vs other forms of treatment) on the likelihood of progression or death. The regression model was statistically significant, $X^2 = 50.117$ ($p<0.005$). The model explained 54% (Nagelkerke $R^2$) of the variance in progression or death and correctly classified 87% of cases. Sensitivity was 70%, specificity 95%, positive predictive value was 88% and negative predictive value 86%.

Conclusion

Haematological non-response (hNR), VEGF non-response (vNR), low glomerular filtration rate (GFR), low albumin at presentation and treatment with autologous stem cell therapy (vs other forms of treatment) are significant risk factors in outcome (progression or death) in POEMS syndrome.

References: None.

Keywords: Inflammatory

Grant Support: Dr Keddie is funded by ABN and Guarantors of Brain
Axon degeneration accounts for poor recovery in patients with Guillain-Barré syndrome (GBS), but there are no first-line treatments to target this key stage in pathogenesis. Animal models of the acute motor axonal neuropathy (AMAN) variant have demonstrated that injury to the nerve is caused by autoantibodies to axonal antigens activating the complement cascade, culminating in the formation of a pore. Uncontrolled influx of water and ions, including calcium, through the pore results in conduction block and structural disruption through activation of the calcium-dependent cleavage enzyme calpain. We assessed the potential of calpain inhibition as an axon protective therapy using transgenic mice that over-express the endogenous calpain inhibitor calpastatin (hCAST). Axonal integrity was compared between wild type (WT) and hCAST mice (n=4/group) in our established ex vivo and in vivo injury models of AMAN. Immune-mediated injury was induced at distal axons by administering monoclonal anti-ganglioside antibodies and complement. Neurofilament, a known calpain substrate, was used as a marker of axonal structural integrity. As the diaphragm is the target in our in vivo model, respiratory function was measured by whole-body plethysmography as a functional output. Axon integrity (neurofilament immunolabeling) is significantly protected in ex vivo injury preparations from hCAST compared to WT mice, while nodal integrity is partially protected. In vivo, both WT and hCAST mice acutely develop weakness, and respiratory dysfunction. Distal axonal neurofilament immunolabeling was significantly reduced in WT mice, and in contrast was protected in hCAST mice. In summary, calpain inhibition can protect the axonal integrity of the nerve in an in vivo injury paradigm, but not the acute loss of function, as expected from the effects of uncontrolled ion flux. These studies provide proof of principle that calpain inhibition can protect axons in vivo and lays the foundation for further animal and clinical study using exogenous calpain inhibitors.

References: None.

Keywords: Axonal Biology, Node Biology, Pre-clinical Studies, Inflammatory

Grant Support: Wellcome Trust
Optimizing electrodiagnosis for chronic inflammatory demyelinating polyneuropathy with automated analysis and machine learning

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Background: Diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) is based on consensus guidelines in which interpretations of nerve conduction studies (NCS) have a major role. Automated analysis could improve interpretation of findings to fit into the current electrodiagnostic criteria, which could lead to better diagnostic accuracy. In addition, machine learning is able to detect complex relationships in datasets, which are not visible to the human eye or simple statistical models.

Objectives: to evaluate the diagnostic accuracy of the current EFNS/PNS electrodiagnostic criteria with adaptations and to explore the diagnostic accuracy of machine learning algorithms.

Methods and results: NCS data from patients suspected of subacute or chronic immune mediated neuropathies were extracted from our NCS database in the period between 2009 and 2018. Automating the electrodiagnostic criteria (EFNS/PNS 2010) (85 CIDP patients and 180 patient controls) showed a relatively high sensitivity and moderate specificity. Adaptations to the electrodiagnostic criteria were implemented to explore changes in diagnostic accuracy, such as: exclusion of known pressure segments, the allowed amount of temporal dispersion in the leg nerves, the implementation of CMAP area instead of amplitude, and defining minimal distal CMAP amplitude to allow the criteria to be valid. Especially exclusion of the distal CMAP duration criterion led to an improved specificity. Subsequently, we explored a machine learning model: a Random Forest Classifier algorithm. This algorithm uses the input parameters to create random dichotomous decision trees and then averages the outcomes, thereby creating a robust model for classification. Preliminary results showed that the performance of this random forest classifier was higher than the current EFNS/PNS electrodiagnostic criteria.

Conclusions: Implementing adaptations of the current consensus-based electrodiagnostic guidelines for CIDP improve the diagnostic accuracy in our hospital. A data-driven approach using machine learning algorithms may further improve diagnostic performance.

References: None.

Keywords: Inflammatory

Grant Support: None.
Dengue, a Mosquito-borne Flavivirus infection is endemic in Sri Lanka, with a cumulative reported cases of over 180,000 during the past two years [1]. Neurological complications of dengue occur as a result of metabolic disturbance, viral invasion or immune reaction [2]. Guillain-Barré syndrome (GBS) is a rare post infectious immune mediated complication. We report a case series of GBS subtypes following dengue hemorrhagic fever (DHF). The first case is a 24 year old man, who had acute ascending flaccid paralysis with global areflexia and bifacial palsy for four days after 10 days of dengue critical phase. Clinical diagnosis of GBS was made and started on intravenous immunoglobulin (IVIg). Nerve conduction showed acute inflammatory demyelinating polyradiculoneuropathy (AIDP) subtype. The patient fully recovered in 14 days. The second case is a 17 year old woman, who presented with back pain, acute flaccid paralysis and worsening lower limb pain with areflexia for 5 days after 12 days of dengue critical phase. She later developed respiratory paralysis. Her nerve conduction showed acute motor-sensory axonal neuropathy (AMSAN) subtype. She was treated with IVIg. She was extubated in 7 days and fully recovered in 6 weeks. The third case is a 19 year old man, who had ascending acute flaccid paralysis with areflexia for 6 days after 9 days of dengue critical phase. His nerve conduction showed acute motor axonal neuropathy (AMAN) subtype. He was treated with IVIg and he improved rapidly. All 3 cases were diagnosed as DHF with a positive nonstructural protein 1 antigen and Dengue IgM antibodies. Day 10 Cerebrospinal fluid examination revealed albuminocytologic dissociation in all patients. This case series highlights that post dengue infection GBS can exhibit either demyelinating or axonal forms. High degree of clinical suspicion and timely management is crucial. Duration of recovery may vary according to the subtype.


Keywords: Inflammatory, Other

Grant Support: None.
Poster 65

Types and treatment practices in GBS in a tertiary care center in Sri Lanka

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Introduction

The recommended mode of treatment in Guillain-barre (GBS) is either intravenous immunoglobulin (IV IG) or therapeutic plasma exchange (PEX). However, in the presence of delayed recovery, repeated cycles of IV IG and PEX is a practice under debate.

This study aimed at evaluation of types of GBS and modes of therapy used upon Sri Lankan patients. The number of patients encountered was 25, with an age distribution from 17 to 86 years with 13 males and 12 females.

On initial nerve conduction, 13 were of AIDP, 4 were AMAN and rest had nonspecific F wave abnormalities. All the patients were treated with either IV IG or PEX. The 8 patients who showed delayed recovery indicated by a persistent GBS disability score (DS) of 4 or 5 at 2 weeks were given a second course of therapy.

Out of the 25 patients, 8 patients received more than one cycle of treatment and 1 received 3 cycles and 1 received 4 cycles. (IV IG + IVIG -4, IV IG + PEX - 2, IV IG + TPE + TPE – 1, IV IG + IV IG + TPE + TPE - 1) The mean duration of onset of the second cycle of therapy is 15.7 days and the third cycle is 26 days. The mode of the second cycle was decided depending on the facilities available and clinicians preference. Among the 6 patients who received 2 cycles only, improvement by at least 1 DS had occurred within 18 to 30 days.

The patient who received 3 cycles, improved up to DS 2, within 36 days.

The patient who received 4 cycles didn’t show major improvement.

Conclusion

In the presence of delayed recovery, repeating the second cycle of IVIG or PEX seems to give favorable outcomes which need further studies.

References: None.

Keywords: Inflammatory, Clinical Trials

Grant Support: None.
Effectiveness And Tolerance Of Subcutaneous Immunoglobulin In CIDP – A Substudy Of INCbase

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Introduction

Subcutaneous immunoglobulin (SCIg) has recently been shown to be an efficacious maintenance therapy for chronic inflammatory demyelinating polyneuropathy (CIDP). Questions remain however concerning long-term effectiveness, tolerability and the optimal switching regimen from intravenous immunoglobulin (IVIg) to SCIg. A specific module will be incorporated within INCbase, a prospective international registry, to provide real-life answers to these questions.

Methods

CIDP patients fulfilling the definite or probable CIDP criteria who are currently stable on treatment with IVIg or SCIg and new patients starting on SCIg (Hizentra; CSL Behring, King of Prussia, PA, USA) will be included in a multicenter study. Standardized data that includes outcome measures and treatment data will be collected at baseline and every 6 months for 2 years. In the event of deterioration unplanned study visits will be conducted to capture interval outcomes and treatment data. The primary outcome is the proportion of patients who are persistent with SCIg treatment after a 1-year follow-up. Persistence is defined as the absence of (a) discontinuation of or (b) switch from initial SCIG treatment. Main secondary outcomes include relapses (both attributed and not attributed to tapering/withdrawal of treatment), treatment withdrawal not attributed to relapse, changes in disability, impairment and quality of life between the start of treatment and after 1 and 2 years of follow-up, proportion of patients tapered off SCIg and adverse events. In an exploratory analysis, we will assess the impact of different SCIg switching regimes. In addition, we will collect data on reasons for switching from IVIg to SCIg and vice versa, and the rationale for the choice of the initial dose and titration schedule will be determined. We will include at least 150 patients on SCIg treatment and 150 patients on IVIg treatment. First results are expected in June 2023.

References: None.

Keywords: Inflammatory

Grant Support: This INCBase substudy is supported by CSL Behring.
Association Of IgM Antiglycolipid Antibodies With Clinical Features In Fisher Syndrome And Related Disorders.

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In Guillain-Barré syndrome (GBS) and Fisher syndrome (FS), molecular mimicry is a main mechanism of antiglycolipid antibody generation. However, the pattern of IgG antibodies (IgG-abs) is often different from that of IgM antibodies (IgM-abs), even in anti-GQ1b-associated FS that shows homogeneous features. The discordance between IgG and IgM antibody patterns is not fully explained by molecular mimicry or class-switching. Objective: To clarify characteristics of patients with FS or its related disorders who show the discordance between IgG and IgM antibody patterns. Methods: Sera from 61 patients with FS, 14 with Bickerstaff brainstem encephalitis (BBE), and 12 with FS-GBS overlap (FGO) were used for antiglycolipid antibody screening. Antibody pattern and clinical findings of patients with the discordance between IgG and IgM antibodies were compared with those of patients with only IgG-abs. Results: Seventy-two patients had some IgG-abs, 47(FS31, BBE10, FGO6) of whom had IgG-abs to GQ1b and/or GT1a without IgM-abs (G group), 12(FS7, BBE2, FGO3) had IgG and IgM antibodies to GQ1b and/or GT1a and IgM-abs to other glycolipids (partial discordance, M1 group), and 13(FS9, BBE1, FGO3) had IgG-abs to GQ1b and/or GT1a and IgM-abs to other glycolipids (partial discordance, M2 group). Mean age at onset was 49.6 years old in a group G, 38.1 in M1 and 32.8 in M2. Antecedent respiratory infection was 83% in G, while gastrointestinal infection was 42% in M1 and 54% in M2. Mean Hughes grade was 3.1 in G, 2.7 in M1 and 1.8 in M2. Class-switching of IgM-abs to GalNAc-GD1a, GM2, or GM1 seldom occurred. Conclusion: Patients in groups M1 and M2 were characterized by younger onset, antecedent gastrointestinal infection, and milder disability, with statistical significance. Antecedent infection may regulate production of IgM antiglycolipid antibodies, while class-switching may be influenced by the type of antiglycolipid antibodies or age of onset.

References: None.

Keywords: Inflammatory

Grant Support: None.
Introduction: Little is known about the long-term health-related quality of life (HRQoL) outcomes of chronic inflammatory demyelinating polyneuropathy (CIDP) patients treated with subcutaneous immunoglobulin (SCIG). Long-term HRQoL data from patients treated with SCIG IgPro20 (Hizentra®, CSL Behring, King of Prussia, PA, USA) in the 48-week open-label PATH extension study are presented.

Methods: Subjects started with 0.4 g/kg IgPro20 weekly and switched to 0.2 g/kg weekly after 24 weeks. In case of CIDP relapse, 0.4 g/kg was re-initiated. After a study amendment, subjects started on 0.2 g/kg weekly with dose increase at CIDP relapse. General QoL (EQ-5D), treatment satisfaction (TSQM) and work productivity (WPAI-GH) were assessed at Baseline, Week 25 and study completion.

Results: Relapse rates by INCAT (Inflammatory Neuropathy Cause and Treatment) score were 10% (during treatment with 0.4 g/kg, n=72) and 48% (during treatment with 0.2 g/kg [n=73]; 89% of whom recovered within 4 weeks upon switching to 0.4 g/kg). Across all EQ-5D domains, the health status in non-relapsers was more likely to be maintained or improved than in relapsers. This was most notable for ‘usual activities’ (92% vs 75%, respectively). Maintenance/improvement rate in non-relapsers was ≥90% for all domains in both doses; for relapsers this was 60–80% for 0.2 g/kg and 75–88% for 0.4 g/kg depending on the domain. Most TSQM assessments remained stable (except in ‘convenience’ which improved regardless of relapse and ‘side effects’ which improved in non-relapsers). WPAI-GH remained stable apart from ‘work productivity loss’ and ‘absenteeism’, both of which got better in relapsers.

Discussion: HRQoL, treatment satisfaction and work productivity were generally maintained or improved in CIDP patients treated with SCIG for up to 72 weeks. Relapse had limited impact, possibly

References: None.

Keywords: Inflammatory

Grant Support: This study was supported by CSL Behring.
The Guillain-Barré syndrome (GBS) is a rare, but potentially fatal, immune-mediated disease of peripheral nerves and nerve roots that is usually triggered by infections. GBS can be a complex disorder to manage, as clinical presentation is heterogeneous and prognosis varies widely between patients. Managing GBS can be especially challenging in outbreak periods, as was most recently seen during the Zika virus epidemic in French Polynesia and Latin America. In absence of an international clinical guideline for GBS, we developed a consensus guideline for the diagnosis and management of GBS. This guideline aimed for general applicability in all clinical environments, irrespective of specialist capabilities or availability of resources, and was developed by an international team of neurologists with support from representatives of the GBS-CIDP Foundation International. The guideline is based on current literature and expert consensus and has a 10-step approach to facilitate its use in clinical practice. These steps cover: early recognition, diagnosis, intensive care unit admission, treatment indication and selection, monitoring and treatment of disease progression, prediction of clinical course, and long-term management. To make sure this guideline remains clinically applicable, we will continue to actively seek feedback and make updates based on results from ongoing and future research. This consensus guideline will also form the basis for the development of online information resources and teaching courses to further improve the world-wide management of GBS. These resources will be directed towards clinical neurologists, other healthcare workers, and patients with GBS and their relatives.

This consensus guideline can help improve the management of GBS world-wide, and is the first step towards the development of up-to-date, consensus-based information and training material for GBS.

References: None.

Keywords: Inflammatory

Grant Support: Horizon 2020, ZikaPLAN Grant Agreement No. 734584
Purpose: To evaluate the predictive power of electrophysiological measures of axonal loss for the clinical long-term outcome in patients treated for chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods: A hospital-based long-term electrophysiological follow-up study was conducted in 2018 in patients studied for the first time between 1985 and 2006. The clinical status in 2018 was evaluated using the Inflammatory Rasch-built Overall Disability Scale (I-RODS). Motor and sensory nerve conduction studies were carried out in nerves in the arm and leg.

Results: Fourteen CIDP patients were included, five of whom were in remission. The median time since onset of CIDP was 17.5 years (range 12.0 – 30.0) and the median time elapsed between the initial and the follow-up electrophysiological studies was 14.2 years (range 11.4 – 24.2). Twelve patients walked independently, one needed ambulatory support and one had no walking function. The I-RODS was 74.5 (range 28.0 – 100.0) at follow-up. The median combined electrophysiological z-score of motor and sensory action potential amplitudes was -4.7 (range -11.5 – -1.6) at time of diagnosis and -3.4 (range -12.6 – -0.3) at follow-up (p=0.08, not significant). There was a significant association between initial and current axonal loss following univariate regression analysis, the p-value and coefficient of determination (R^2) being 0.01 and 0.42 respectively. Univariate regression analysis also revealed a highly significant association between initial axonal loss and current I-RODS, the p-value and R^2 being <0.0001 and 0.73 respectively. There was a significant reduction in current demyelination compared to initial demyelination (p=0.03) as indicated by the change in conduction velocity z-scores.

Conclusion: The axonal loss at the initial diagnostic electrophysiological examination was predictive for the long-term disability and for the axonal loss at follow-up. In addition, the axonal loss did not worsen throughout the disease course.

References: None.

Keywords: Inflammatory

Grant Support: None.
Objective: To describe the diagnose and the treatment in patients with chronic inflammatory demyelinating polyneuropathy who harbored antibodies against NF155.

Methods: Sera from 32 CIDP patients, 29 with other neuropathies in our clinical were collected for anti-NF155 antibody measurement by Cell-based assay(CBA). To characterize the clinical features, nine additional CIDP outpatients presented with tremor and distal acquired demyelinating symmetric phenotype were included. Clinical information, electrophysiology and response to treatment were obtained in patients with anti-NF155 immunoglobulinG4(IgG4) antibody positive CIDP.

Results: 6 patients(18.75%) with IgG4 autoantibodies against NF155 from 32 CIDP patients, no patients with other neurologic disorders were positive. 4 patients(44.4%) with IgG4 autoantibodies against NF155 from 9 additional CIDP outpatients presented with tremor and distal acquired demyelinating symmetric phenotype. Anti-NF155 antibody positive CIDP were associated with younger onset age, tremor, distal limb weakness and high frequency of gait disturbance, deep and superficial disturbance. Higher cerebrospinal fluid protein levels and longer F-wave latencies than anti-NF155 antibody negative patients. Treatment with rituximab were added in 2 patients, they all improved dramatically. Plasma exchange were given in 2 patients, rapid and effective improvement were observed.

Conclusion: Anti-NF155 antibody positive CIDP patients occur in a special subgroup of CIDP patients with younger onset age, tremor, distal acquired demyelinating symmetric phenotype, higher cerebrospinal fluid protein levels and longer F-wave latencies. Plasma exchange and rituximab were effective for patients with anti-NF155 IgG4 antibody-positive CIDP.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Increased Effector B cells in Peripheral Blood of Chronic Inflammatory Demyelinating Polyneuropathy Patients

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OBJECTIVE: Although, autoantibodies that target node/paranode of Ranvier proteins were identified in a small subset of CIDP patients, disease-specific autoantibodies linked to CIDP remain unknown in most patients. This study aimed to analyze peripheral B-cell homeostasis, and investigate the differences of B-cell phenotypes among patients with typical, and atypical CIDP, also investigate its value as a biomarker.

METHODS: The study included 25 typical CIDP (15 male, 10 female, 34.3±16.9), 18 MADSAM (12 male, 6 female, 27.8±11.6), 7 DADS (2 male, 5 female, 32.6±17.1) patients who fulfilled the 2010 EFNS/PNS diagnostic criteria for definite (n=49) or probable (n=1) CIDP. Twenty-five age-matched healthy donors (HC) (13 male, 12 female, 33.0±8.0), 19 patients with multiple sclerosis (MS) (11 male, 8 female, 34.9±6.9), and 13 patients with CMT1A (7 male, 6 female, 38.9±13.3) served as disease controls.

Peripheral blood mononuclear cells (PBMCs) were isolated through ficoll density gradient centrifugation, and were stained with anti-human monoclonal CD3-FITC, CD16/CD56-PE, CD45-PerCP, CD19-APC, CD27-FITC, IgD-APC/Cy7, CD138-PE, CD24-PerCP, and CD38-Alexa fluor 700 conjugates (BD FACS AriaII). Acquired T, NK, B-cells, and subgroups of B-cells (immature, naive, memory, regulatory B-cells, plasmablasts, and plasma cells) were analyzed using FlowJo software.

RESULTS: No differences were found in B-cells, T-cells, and natural killer cells percentage in groups of typical, and atypical CIDP, MS, CMT 1A, and HC. However, we detected significant reduction in naive B-cells (CD19+IgD+CD27-) (p<0.01), B10 cells (CD19+CD27+CD24+) (p<0.05), and an elevation in switched memory B-cells (CD19+IgD-CD27+) (p<0.01) in CIDP patients compared to HC. Also, CIDP group had significantly higher naive (p<0.001), and switched memory B-cells (p<0.01) than MS group. Plasmablasts (CD19+CD38++CD138-) were reduced in CIDP patients (p<0.05), and showed a tendency to decrease compared to MS.

DISCUSSION: Decreased plasmablasts, and fully developed nonproliferating plasma cells were thought to be the result of immunomodulating treatment as reported in previous studies. Also, elevated numbers of antibody secreting cells in peripheral blood indicate an overactive humoral immune system, and represent a typical signature in both typical, and atypical CIDP, which is downscaled after clinically successful IVlg administration. According to our results, increase in frequency of memory B-cells in peripheral blood with a reciprocal decrease of still-dividing precursor cells (naive B-cells) give an impression of a chronic antigen exposure, and overactive humoral immune system.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Poster 74

Diagnostic yield and clinical utility of nerve biopsy in evaluation of neuropathy

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Background: Nerve biopsy is a diagnostic test used in selected cases for evaluation of acquired neuropathy. The pathologic findings may confirm or change the clinical diagnosis, and help guide treatment. However, it is an invasive procedure with known side effects. To prove its diagnostic value, studies evaluating the diagnostic yield and clinical utility are needed.

Methods: We performed a retrospective review of the clinical information, laboratory data, electrodiagnostic studies, and pathology report of 115 nerve biopsy cases from a single institution. Four categories were defined: 1) Definite diagnosis reached and concordant with the clinical diagnosis; 2) Definite pathologic diagnosis reached but discordant with the clinical diagnosis; 3) Nonspecific (e.g. perineurial chronic inflammation) or unremarkable pathologic findings concordant with the clinical diagnosis, and 4) Nonspecific or unremarkable findings discordant with the clinical diagnosis.

Results: Among the 115 cases of nerve biopsies, 90 cases (78.3%) had a concurrent muscle biopsy. The pathologic findings were abnormal in 81.7% of the cases. A specific diagnosis was established in 27.0% of the cases. Of note, a specific diagnosis was made in 9 additional cases as a result of the muscle biopsy (7.8%). 27.0% of the cases had a definite pathologic diagnosis concordant with the clinical diagnosis, whereas 6.1% had a definite pathologic diagnosis discordant with the clinical diagnosis. 52.2% demonstrated nonspecific pathologic findings but they were concordant with the clinical diagnosis. 14.8% had nonspecific pathologic findings which were discordant with the clinical diagnosis. Overall, the concordance rate between the clinical impression and pathologic findings was 79.1%.

Conclusions: Biopsy altered the diagnosis in more than 20% of the suspected neuropathy cases, and therefore its diagnostic utility should not be overlooked. A concurrent muscle biopsy is strongly encouraged, given our finding that approximately 8% of the cases had unexpected myopathy.

References: None.

Keywords: Inflammatory, Other

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Poster 75

Characterization of a Relapsing/Remitting, Disease Course for Corticosteroid- Responsive Small-Fiber Neuropathy

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Introduction: Small-fiber polyneuropathy (SFN) is an often-painful axonopathy of small-diameter nerve-fibers. There is increasing evidence that disordered inflammation/immunity underlies some acute monophasic and chronic cases initially thought idiopathic.¹⁻³

Methods: With IRB-approval, we collected Small-Fiber Symptom Survey (SSS) data throughout 2017-2019 and reviewed medical records.⁴

Results: 14 days after upper-respiratory infection (URI), an otherwise-healthy 30-year-old rapidly developed first-ever erythromelalgia comprising heat-induced paroxysms of paresthesias, itch, reddening, and 6-8/10 pain in her feet and hands, worsening with heat or exercise, with minor nose symptoms. Medical history revealed only mild scalp psoriasis and CIDP in a cousin. Examination identified minimal toe and finger weakness. Nerve-conduction, electromyography, and lumbar puncture were normal; autonomic function testing (AFT) was borderline with reduced right-foot sweating. Oral prednisone 60 mg initiated 3 months post-onset gave rapid improvement and was tapered off during 3 months. Remission lasted 3.5 years during which the patient noted only small patches of reduced sensation in fingers and toes in the cold. Then, symptoms returned 10 days post-URI and 4 days after influenza immunization. On day 2, prednisone 80 mg gave major improvement during rapid then slow taper with SSS scores decreased from 27/136 on d6 to 7 on d45. First 0/10 pain was d73; first 0/136 SSS was d208. On d21 lower-leg PGP9.5-immunolabeled skin biopsy was borderline (191 neurites/mm² skin surface area, at 10.7 centile of predicted). Day-26 examination documented tachycardia, toe-erythema and mild finger-abduction weakness; d30 AFT was normal. Day-26 complement C3 and C4 were normal.⁵ She remained symptom-free for 6 months until 2 weeks post-URI when symptoms returned (d2SSS 16/136). Prednisone 50 mg was immediately resumed while planning transition to immunoglobulin treatment.

Conclusions: We document a case of relapsing/remitting, corticosteroid-responsive SFN distinct from previously reported monophasic and chronic courses. The temporal link to URIs suggests molecular mimicry may be triggering recrudescences.


Keywords: Inflammatory, Pain, Small Fibers

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Next generation sequencing in idiopathic sensory neuronopathies.

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Introduction: Sensory neuronopathies (SN) are characterized by asymmetric sensory deficits and sensory ataxia. This distinctive pattern emerges from the dorsal root ganglia damage. Its recognition represents a window of opportunity to the investigation of associated diseases. Nonetheless, even with an extensive workup nearly half of the SN patients remain labeled as idiopathic (iSN). NS-like pattern in a broader neurological phenotype is present in several inherited conditions. However, iSN as an isolated manifestation has not been addressed yet through next generation sequencing technics (NGS).

Objective: To investigate possible genetic etiology for iSN.

Methods: We enrolled consecutively all patients with iSN followed in a neuromuscular clinic. Patients were diagnosed following the criteria proposed by Camdessanché and cols in 2009. Patients were labeled as iSN after an extensive workup resulted negative. Peripheral blood samples were used to obtain leukocyte DNA that had the exoma sequenced through NGS. The identified variants were then filtered by the terms: “sensory ataxic neuropathy”, “distal peripheral sensory neuropathy”, “sensory neuropathy” and “peripheral neuropathy”. The resulting variants were than classified according to the ACMG criteria and those “likely pathogenic” or “pathogenic” were reviewed.

Results: Twenty-two iSN patients were enrolled. Male/female proportion was 9:13 with a mean age of 9.5±7.5 years. None of these iNS patients had a family history of peripheral neuropathy. Most patients had asymmetric sensory deficits and a SN evolving in a chronic fashion (77% and 54% respectively). None of the iSN had definite genetic diagnose identifiable by NGS. Four patients had heterozygote variants in suspected genes (CUBN; POLG; FXN and FLVCR1).

Conclusion: Despite that NGS was not able to identify a monogenetic cause for the iSN patients of this cohort, some hypothesis regarding the disease pathology may be raised: NGS may be not able to identify them or alternatively iSN may behave as complex neurological disease.

References: None.

Keywords: Human Genetics, Inflammatory, Other

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Acute small fibre neuropathy: a neglected condition?

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Background: Small fibre neuropathies (SFN) constitute a disorder involving thinly myelinated Aδ-fibres and unmyelinated C-fibres. Causes are various and often remain unknown. SFN are typically chronic length-dependent polyneuropathies. However, some patients report an acute onset.

Aim: To describe a series of patients with an acute small fibre neuropathy (ASFN).

Methods: To be included, patients must present with sensory manifestations involving at least two limbs, an exclusive impairment of pain and/or heat sensation on clinical examination and neurophysiological investigation, and a progression phase of less than 4 weeks. Patients with associated large fibre involvement were excluded. We collected their clinical, neurophysiological, and biological data.

Results: From November 2017 to February 2019, we prospectively included 11 patients with ASFN (7F:4M, median age: 43.7 [23.5-59.2]). Ten patients reported neuropathic pains. Nine patients presented a non-length-dependent profile. Orthostatic hypotension was present in 3 patients. Ten patients had at least abnormal results of laser-evoked potentials, warm detection thresholds or electrochemical skin conductance. Standard immunological blood tests were normal. AntiFGFR-3 antibodies were positive in 3 patients (6 tested). Cerebrospinal fluid was normal in 4 patients. A precipitating potential event was present in 7 patients: 3 infections, 2 vaccinations, and 2 treatment intolerances. Disease course was characterized by a complete remission in 2 cases, recurrent episodes in 5 cases, and chronicity in 4 patients.

Discussion: Few cases of ASFN have been reported, usually with a favourable prognosis. However, the present series shows a variable disease course. The evidence of a precipitating factor in two-thirds of cases and the presence of antiFGFR-3 antibodies support an immune dysfunction, as it was previously suggested with the transient detection of antibodies directed against small fibres. Early immunomodulating treatment is worth to be discussed.

Conclusion: ASFN appears as a potential inflammatory neuropathy with an important clinical impact and a variable disease course.


Keywords: Small Fibers, Inflammatory, Pain

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Analysis of 193 whole genome sequencing data to understand neuropathic pain disorders.

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Extreme pain phenotypes, such as erythromelalgia and insensitivity to pain, caused by rare high impact genetic variants, offer us insight into mechanisms that may apply to more common causes of neuropathic pain. The aim of our study was to identify singleton patients and families with extreme pain phenotypes to determine whether variants/mutations were present in genes known to cause neuropathic pain. We included participants with: congenital insensitivity to pain; painless sensory neuropathy; chronic pain caused by erythromelalgia, small fibre neuropathy, and sensory neuropathy. NeuPSIG grading criteria for neuropathic pain were used to stratify the cohort. A total of 219 participants were recruited from secondary care clinics across the UK. Neuropathic pain was classified as: not present (n=9, 4.1%), definite (n=125, 57.1%), probable (n=62, 28.3%), possible (n=12, 5.5%) or unlikely (n=1, 0.5%). Ten participants were unaffected family members. Whole genome sequencing data, acquired using next generation sequencing technology, were available for 193 participants. Previously characterised pathogenic variants in SCN9A, the gene encoding the sodium channel (Nav) 1.7, were identified in 11 participants. For example, the SCN9A pathogenic variant, c.2543T>C (p.Ile848Thr), was identified in a pair of sisters diagnosed with erythromelalgia. Novel uncharacterised variants, predicted through in silico analysis to be pathogenic and confirmed in multi-disciplinary team meetings, were identified in SCN9A, SCN10A, SCN11A and SPTLC1 genes. We have demonstrated that a meticulous phenotyping approach combined with next generation sequencing provides a powerful platform to explore pathophysiological mechanisms of chronic neuropathic pain.

References: None.

Keywords: Pain, Human Genetics, Small Fibers

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SCN11A Arg225Cys mutation causes nociceptive pain without detectable peripheral nerve pathology.

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OBJECTIVE: The SCN11A gene encodes the NaV1.9 sodium channel found exclusively in peripheral nociceptive neurons. METHODS: All enrolled participants were evaluated clinically by electrophysiologic studies, DNA sequencing, and punch skin biopsies. RESULTS: All affected family members are afflicted by episodes of pain. Pain was predominantly nociceptive, but not neuropathic in nature, which led to a diagnosis of fibromyalgia in some patients. All patients had normal findings in nerve conduction studies for detecting large nerve fiber neuropathies and skin biopsies for detecting small nerve fiber pathology. CONCLUSIONS: Unlike those patients with missense mutations in SCN11A, small fiber sensory neuropathy, and neuropathic pain, the Arg225Cys SCN11A in the present study causes predominantly nociceptive pain with minimal features of neuropathic pain and undetectable pathophysiologic changes of peripheral neuropathy. This finding is consistent with dysfunction of nociceptive neurons. In addition, since nociceptive pain in patients has led to the diagnosis of fibromyalgia, this justifies a future search of mutations of SCN11A in patients with additional pain phenotypes such as fibromyalgia to expand the clinical spectrum beyond painful small fiber sensory neuropathy.

References: None.

Keywords: Human Genetics, Pain, Small Fibers

Grant Support: None.
Poster 80

**Pregabalin for muscle cramps in patients with liver cirrhosis, A randomized, double-blind, placebo-controlled study**

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To assess the efficacy and safety of pregabalin in the treatment of muscle cramps, we performed a randomized, double-blind, placebo-controlled study with 60 patients with frequent muscle cramps (> 2 cramps/week) with liver cirrhosis of under 75 years of age. Patients who received pregabalin had a significantly greater reduction in cramp frequency. After the 4-week standard dose period, the mean change from baseline to treatment phase in cramp frequency was 33.3% for the pregabalin group, and 0% for the placebo group (p=0.015). The 50% responder rate was significantly higher in the pregabalin group compared to placebo (68.8% vs. 31.2%). There were no significant differences in the mean changes of pain intensity and number of cramps during sleep between the pregabalin and placebo groups. The scores for all SF-36 domains were higher in the pregabalin group than in the placebo group after the 5-week treatment period. There was significant difference in the “role limitations due to physical health” domain score between the pregabalin and placebo groups (p=0.023). The scores for all LDQOL domains, except the “loneliness” domains, were higher in the pregabalin group than in the placebo group after the 5-week treatment period. Additionally, we evaluated the afterdischarge (duration ≥ 2 sec, end of afterdischarge: pause ≥ 80msec) threshold as a tool of neurophysiological outcome measure before and after pregabalin treatment in 30 patients. The threshold of afterdischarge was higher in the pregabalin group than placebo group. Our clinical and neurophysiologic experience suggests that pregabalin would be helpful in the treatment of muscular cramps in patients with liver cirrhosis.

**References:** None.

**Keywords:** Clinical Trials, Pain, Metabolic, Other, Inflammatory

**Grant Support:** None.
mNIS+7 Components and Lower Limb Function Responsiveness in Inotersen Treatment of Hereditary Transthyretin Amyloidosis Polyneuropathy

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The modified Neuropathy Impairment Score +7 (mNIS+7) was developed from the NIS+7 to better represent neuropathic impairments in transthyretin amyloidosis polyneuropathy. In the 15-month phase 3 trial (NEURO-TTR; NCT01737398), inotersen, an antisense oligonucleotide inhibitor of transthyretin production, demonstrated a significant beneficial effect compared with placebo in the 2 primary outcomes of mNIS+7 and Norfolk Quality of Life—Diabetic Neuropathy questionnaire scores in patients with hereditary transthyretin amyloidosis (hATTR). The NIS is comprised of 3 major components (NIS-weakness, NIS-reflexes, and NIS-sensation loss), and the mNIS+7 is comprised of the 5 attributes of nerve conduction, somatotopic quantitative sensation testing of touch pressure and heat pain, and heart rate response to deep breathing (HRDB). In NEURO-TTR, 5 of the 7 main components of mNIS+7 showed statistically significant benefit by 15 months in patients receiving inotersen versus placebo. HRDB and touch pressure did not reach statistical significance; however, HRDB cannot be assessed in patients with active pacing or atrial fibrillation, which are common in patients with hATTR. In this analysis, we assessed the performance of the components of mNIS+7 by anatomic location (upper and lower limb) as well as the Lower Limb Function (LLF) test. The LLF test assesses 3 functional abilities: a patient’s ability to ambulate on toes, to ambulate on heels, and to arise from a kneeled position. All mNIS+7 components assessed by upper and lower limbs showed a statistically significant benefit in patients receiving inotersen versus placebo except NIS-reflexes (upper limb) and touch pressure (upper and lower limbs). Overall LLF score and each individual LLF test score showed statistically significant benefit by 15 months in patients receiving inotersen compared with placebo. These data support the beneficial effects of inotersen on muscle weakness, muscle stretch reflexes, sensation, attributes of nerve conduction of limb nerves, and lower limb function.

References: None.

Keywords: Amyloidosis, Axonal Biology, Clinical Trials, Human Genetics

Grant Support: Akcea Therapeutics
Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations
Quality of Life

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Background: Cryptogenic sensory polyneuropathy (CSPN) affects adults, causing pain, resulting in poor quality of life (QOL). The primary outcome from the PAIN-CONTRoLS study was presented at this meeting in 2018. We are now presenting the secondary outcomes.

Objective: To compare the effect of four pain medications: nortriptyline, duloxetine, pregabalin and mexiletine on QOL.

Methods: We conducted a comparative effectiveness study of 4 neuropathic pain medications in reducing CSPN pain. In this PCORI funded trial, patient advisors assisted in identifying important outcomes related to QOL. The SF-12 and the PROMIS® pain interference, fatigue, and sleep disturbance scales were used to assess QOL. Participants completed the SF-12 and PROMIS scales at baseline and weeks 4, 8 and 12. Mean T-scores were calculated for each specific medication group and the probability best for each medication was calculated.

Results: 402 patients with CSPN were enrolled in the study (nortriptyline 134, duloxetine 126, pregabalin 73, mexiletine 69 respectively). The mean T-scores for the PROMIS® pain interference is 63.1±7.0, 62.4±6.8, 63.3±5.5, 60.9±7.9; fatigue 59.6±3.4, 59.7±3.3, 59.1±53.73, 59.7±3.2; sleep disturbance is 59.1± 9.8; 60.6±8.3, 59.8±8.7, 57.0±11.4. The mean T-scores of the SF-12 physical component is 38.0±9.3, 38.5±9.3; 37.9±9.1, 41.1±10.1. The mean T-scores of the SF-12 mental component is 48.0±10.4; 46.7±10.1, 46.8±11.3; 47.2±11.1. A substantial number of patients quit in the mexiletine group. The probability best for patients who stayed in the study at week 12 for PROMIS® fatigue scores was 0.05, 0.05, 0.05, 0.93; pain interference 0.02, 0.07, 0.00, 0.91. For sleep disturbance and SF-12, there was no statistical clear separation among the drugs in the probability best at 12 weeks.

Conclusion: Overall, there is no significant difference on pain or QOL. However, patients on mexiletine, that could stay in the study for 12 weeks, had a better outcome in pain interference and fatigue scales.

References: None.

Keywords: Pain, Clinical Trials, Small Fibers

Grant Support: PCORI AWARD: University of Kansas Medical Center CER-1306-02496
SENSORY-MOTOR PACLITAXEL POLYNEUROPATHY CHARACTERIZATION IN A RAT MODEL

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PURPOSE. Paclitaxel-Induced Peripheral Neurotoxicity (PIPN) is a detrimental condition that affects cancer survivors. It is a mainly sensory, axonal, length-dependent polyneuropathy. There is no treatment for this side effect. A reason for this lack is the absence on definite data on PIPN pathogenesis. Thus, a bench-side approach is warranted to test potential neuroprotectant agents. We characterized a rat model with advanced and standard neurophysiology, as well as with behavioral tests and neuropathology in order to standardize our setting to promptly translate data in clinical trials.

METHODS. Twenty-four female Wistar rats were used. They were divided in control (CTRL) and paclitaxel (PTX, 10mg/Kg, iv, 1qw4ws) groups. Animals were tested with standard neurophysiology (sensory and motor recordings) and dynamic test at base-line and at end of treatment. Nerve Excitability Testing (NET) was assessed at 24, 48, 72 hours after the 1st administration and at end of treatment to characterize axonal properties. At end of treatment, harvesting of caudal and sciatic nerves, DRG and skin biopsy was also performed.

RESULTS. NET monitoring after the 1st administration showed in PTX group: no changes at 24 hours and minor alterations in current/threshold properties and in threshold electrotonus. At end of treatment, standard neurophysiology showed statistically significant changes compatible with a sensory-motor polyneuropathy; dynamic test was also significant for a painful behavior in PTX animals. NET monitoring at the end of treatment showed alterations mainly in threshold electrotonus.

CONCLUSION. We characterized an animal model with a multimodal assessment able to reproduce clinical evidence. We also performed NET monitoring showing early axonal dysfunction. This set of outcome measures will be the core for our future neuroprotection experiments.

References: None.

Keywords: Pain, Pre-clinical Studies, Other

Grant Support: None.
Modelling dHMNX and CMTX6 using patient derived iPSC motor neurons.

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INTRODUCTION Mutations in the copper (Cu) transporter ATP7A and in the pyruvate dehydrogenase kinase 3 (PDK3) genes cause X-linked hereditary distal motor neuropathy (dHMNX) and X-linked Charcot-Marie-Tooth type 6 neuropathy (CMTX6), respectively. Our investigations using dHMNX and CMTX6 patient fibroblasts have shed light on the pathomechanisms underlying these diseases:
- Fibroblasts harbouring the p.T994I ATP7A mutation show defective retrograde trafficking of mutant ATP7A leading to intracellular Cu dysregulation which has been reproduced in embryonic fibroblasts of a conditional knock in Atp7a mouse model for dHMNX. - CMTX6 patient fibroblasts with the p.R158H mutation show hyperactivity of PDK3 and hyperphosphorylation of the E1 subunit of the pyruvate dehydrogenase complex, a critical regulator of the energy producing Krebs cycle, leading to mitochondrial abnormalities, lactate acidosis and reduced ATP production.

METHODS To investigate how defective ATP7A trafficking and PDK3 kinase hyperactivity leads to axonal degeneration we have established two lines of induced pluripotent stem cells by re-programming fibroblasts from a dHMNX patient with the ATP7A p.T994I mutation (iPSC_dHMNX) and a CMTX6 patient harbouring the PDK3 p.R158H substitution (iPSC_CMTX6).

RESULTS Our data demonstrates the iPSC_dHMNX and the iPSC_CMTX6 lines retain pathogenic molecular phenotypes found in the dHMNX and CMTX6 patient fibroblasts, respectively. iPSC_dHMNX cells show altered ATP7A intracellular distribution. iPSC_CMTX6 cells maintain the E1-hyperphosphorylation signature and treating the patient cells with the PDK inhibitor dichloroacetate reduces the levels of phosphorylation, suggesting PDK3 is an ideal pharmacological target for the development of treatment therapies. We have successfully differentiated spinal cord motor neurons from the iPSC_dHMNX and the iPSC_CMTX6 lines and shown the patient derived motor neurons (MN_dHMNX and MN_CMTX6) display disease specific pathological features.

CONCLUSIONS Patient MN_dHMNX and MN_CMTX6 motor neurons are an ideal neuronal system to model axonal degeneration in dHMNX, CMTX6 and other neurodegenerative diseases in which Cu dysregulation and mitochondrial abnormalities occur.


Keywords: Axonal Biology, Human Genetics, CMTR, Metabolic

Grant Support: None.
Mutations in MFN2 are the most commonly identified genetic cause of Charcot-Marie-Tooth disease type 2A. While long sensory and motor peripheral nerves are the most susceptible structures to MFN2 mutations, a variety of additional phenotypes have been reported including optic atrophy, spastic paraparesis, developmental delay, myopathy, and lipodystrophy. MFN2 is an outer mitochondrial membrane protein that regulates a variety of functions including mitochondrial fusion, transport, ER interactions, and mitophagy. However, the mechanism by which the primarily dominantly inherited point mutations in MFN2 promote mitochondrial and axonal injury remains unknown. We generated induced pluripotent stem cells from two patients with CMT2A (T105M, H361Y). Additionally, we used CRISPR/Cas9 combined with single stranded oligonucleotide donors to generate isogenic control lines using homologous recombination for the T105M and H361Y lines. Subsequently we differentiated CMT2A patient iPSCs into motor neurons using established protocols, fluorescently labeled mitochondria, and used live cell imaging to examine mitochondrial dynamics in axons. Mitochondrial size was found to be smaller in iPSC-MNs from CMT2A patients compared to normal and isogenic controls. Mitochondrial also spent a greater percentage of time paused, and displayed less anterograde movement in CMT2A iPSC-MNs compared to normal or isogenic controls. Ongoing work focuses on examining diverse MFN2 functions in these models, and whether MFN1 augmentation can mitigate phenotypes observed.

References: None.

Keywords: Axonal Biology

Grant Support: None.
The Italian Registry for Charcot-Marie-Tooth disease

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The Italian Charcot-Marie-Tooth disease (CMT) Registry is fully operative at the https://www.registronmd.it website. It is a dual registry where the patient registers herself/himself, chooses a reference centre among nine spread all over Italy, where the attending clinician, in an ad hoc visit, collects a minimal dataset of information and administers the CMT Examination/Neuropathy Score, CMTES/CMTNSv2, for adults, or the CMT Pediatric Scale, CMTPeds, for children; data are entered in the Registry and encrypted.

796 CMT patients have registered thus far and have chosen one of the 9 reference centers; information has been entered in the Registry for 649 of them (337 females; mean age 47.1, range 7-89). Diagnoses are the following: 407 CMT1, 95 CMT2, 21 CMT4, 8 dHMN, 32 HNPP, 1 HSAN, 85 still unclassified. Genetic diagnosis, achieved in 556 cases, show that the most frequently mutated genes are: PMP22 (295 CMT1A, 32 HNPP, 3 CMT1E), GJB1 (66 CMTX1, 30 females), MPZ (33 CMT1B, 32 CMT2l/J), GDAP1 (7 dominant and 8 recessive cases), MFN2 (17 CMT2A), NEFL (12 cases), and SH3TC2 (12 CMT4C). Clinical score are the following: CMTES (n = 633) mean 8.4 +/- 5.2, range 0-27; CMTNS (n = 190) mean 12.5 +/- 6.5, range 0-31. Ninety-four subjects have at least one follow-up visit; 472 complain of gait difficulties, 294 use orthotics aids, 70 need support for walking (44 unilateral, 26 bilateral) or use a wheelchair (23); 123 patients have scoliosis (9 requiring surgery, 39 bracing), 11 hip dysplasia, 5 optic atrophy and 2 profound hearing loss.

Conclusions: analyses of data from the Italian CMT Registry are giving results which are important for: a) epidemiology of CMT across Italy, b) assessing disease burden to develop standards of care, c) recruiting patients in forthcoming clinical trials. The Registry will be linked to the CMT International Database.

References: None.

Keywords: CMTR

Grant Support: Supported by Telethon-UILDM grant GUP13006.
The purpose of this study was to examine differences in preferred walking speed as a function of development and CMT type in youth with CMT. The preferred walking speed of 22 youth with CMT1 (12.2 ± 3.1 years), 12 youth with CMT2 (9.8 ± 4.6 years), and 54 age matched typically developing (TD) peers (9.6 ± 3.4 years) was measured using gait analysis. Some patients were tested more than once resulting in 29 total CMT1 and 22 total CMT2 observations. Changes in walking speed with age were compared among groups using linear mixed effect models including a random intercept term to model the repeated measures for some participants. Walking speed increased with age in controls (2.2 cm/sec/year; 95% CI: 0.7 to 3.6; p=0.004), however, changed at a significantly lower rate and tended to decrease with age in CMT1 (-2.2 cm/sec/year; 95% CI: -4.9 to 0.4; p=0.097) and CMT2 (-2.4 cm/sec/year; 95% CI: -5.0 to 0.3; p=0.085). The differences in walking speed among groups were primarily due to stride length which increased with age in TD peers (4.4 cm per year; 95% CI: 3.5 to 5.4; p<0.001) but decreased with age in CMT1 (-2.1 cm/year; 95% CI: -3.8 to -0.3; p=0.02) and CMT2 (-1.8 cm/year; 95% CI: -3.4 to -0.1, p=0.38). Youth with CMT show a decline in walking speed with age compared to TD peers. This appears to be more severe and starts earlier for those with CMT2 vs. CMT1. The decline in walking speed resulted from reduced stride length, which is likely caused by reduced plantar flexor strength and increased ankle instability. Treatments that increase step length such as plantar flexor strengthening and bracing, which can also improve ankle stability in stance, are likely to improve walking speed and associated function such as keeping up with peers.

References: None.

Keywords: Other, Other, Other, Other, Other

Grant Support: Harold and Rebecca Gross Foundation
Charcot-Marie-Tooth diseases (CMT) are a heterogeneous group of hereditary genetic neuropathies. CMT1b is a rare form of CMT caused by mutations in the myelin protein zero (MPZ) gene. Phenotype is variable and heterogeneous as is the age of onset. Our purpose is to characterize genotype–phenotype correlations and establish baseline clinical data for peripheral neuropathies caused by mutations in the MPZ gene in France. It is important to make clinical trials for patients with MPZ mutations a realistic possibility, in order to reduce misdiagnosis.

We present retrospective data to define the phenotypic spectrum and clinical baseline of patients with these mutations. A cohort of patients with MPZ gene mutations was identified in 11 French reference centers for neuromuscular diseases. Patient phenotypes were quantified by the Charcot–Marie–Tooth disease examination score (CMTES). Genetic testing was performed in all patients to document mutation in MPZ gene indicating diagnosis of CMT1B. There were 80 patients with 44 different MPZ mutations with a mean age of 56 years (range 20–86 years). Childhood onset represented 7%. Twenty patients wore orthoses, twenty-six required walking assistance or support, and six required wheelchairs. There was hearing loss in seven patients, scoliosis in sixteen patients, optic atrophy in twelve patients and five patients presented with respiratory failure. Hip dysplasia was noted in one patient.

Preliminary data didn’t reveal any significant correlation between CMTES and age of onset, nor between CMTES and age. These results demonstrate that MPZ mutations can be associated with heterogeneous phenotypes, which is consistent with previous studies. Adult forms appear to be moderately severe with an average onset age of 32 and an average CMTES of 9. Data obtained from the French cohort is useful as a baseline for future clinical trials of patients with CMT1b.

References: Sanmaneechai et al, Genotype-phenotype characteristics and baseline natural history of heritable neuropathies caused by mutations in the MPZ gene, Brain, 2015

Keywords: CMTR, Human Genetics

Grant Support: None.
**Poster 89**

**Genotype and phenotype in Thai children with Charcot-Marie-Tooth Disease.**

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**Introduction**

Charcot-Marie-Tooth disease (CMT) is a group of genetically heterogeneous, despite the clinical similarities. So far, more than 100 gene mutations have been reported to be associated with different types of CMT. However, with the limitation of next generation sequencing in our country, very few studies have been done for genetic identification in CMT patients. The aim of this study is to investigate the CMT genotype and phenotype in Thai children.

**Methods**

We prospectively evaluate children with the clinical and neurophysiological diagnosis of CMT from January 2017 to October 2018. Clinical presentation, CMTNS or CMTPedS and neurophysiologic studies were documented. DNA samples were sent to Samsung Medical Center and Kongju National University in South Korea for genetic identification with next generation sequencing (NGS) technique.

**Results**

A total of 25 patients, 19 have axonal CMT and 6 have demyelinating CMT. Mutation analysis by whole exome sequencing (WES) was performed in 25 cases from 24 families. The result of WES revealed genetically confirmed in 21 patients. Patients have mutation in MFN2 (5 patients), PMP22 (3 patients), NEFL (3 patients), GDAP (3 patients), SETX (2 patients), MPZ (1 patients), GJB1 (1 patients), IGHMBP2 (1 patients), EGR2 (1 patients), HK (1 patients). For the pathogenic or likely pathogenic mutations, the mutations were confirmed by Sanger’s sequencing method.

**Conclusion**

Whole exome sequencing give a higher yield to identify genetic mutation in CMT, especially in pediatric population with higher percentage of axonal subtype CMT and also for the resource-limited country. Future collaboration is crucial for genetic function testing. Further prognosis and genetic counseling can be done after genetic abnormalities had been identified.

**References:**


**Keywords:** CMTR

**Grant Support:** None
Poster 90

Modeling Axonal Degeneration in CMT2E using Human Motor Neurons

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Mutations in neurofilament light chain (NEFL) cause autosomal dominant, axonal Charcot-Marie-Tooth disease (CMT2E). Despite advances in understanding its pathophysiology, there is no disease-modifying therapy for CMT2E. This is partially due to lack of translational models suitable for drug discovery. Our previous work using iPSC-derived motor neurospheres have identified neurofilament deposits in the axons of motor neurons from three N98S CMT2E patients, similar to what has been shown in \textit{nefl\textsuperscript{N98S}} knock in mice. We have also identified two kinase inhibitors that promoted 50% reduction in the number and area of NEFL deposits. The aim of this study was to determine whether evidence of axonal degeneration could be found in N98S CMT2E motor neurons in order to further validate this platform as a reliable disease model and to identify potential \textit{in vitro} biomarkers of axonal degeneration for use in drug discovery.

Morphological analysis of axons and measurement of neurofilament light chain protein (NEFL) in the culture supernatant of control and N98S CMT2E motor neuron cultures were performed at baseline conditions and after ascending doses of a known axonotoxic compound (Vincristine) in doses ranging from 1 to 10 nM. Despite normal axonal morphology at baseline, N98S CMT2E demonstrated increased levels of NEFL in culture supernatant when compared to controls. Furthermore, N98S CMT2E motor neurons were more susceptible to vincristine-induced axonal degeneration, as demonstrated by both increased supernatant NEFL levels as well as increased axonal beading and breakdown when compared to controls. Taken together, these findings demonstrate that iPSC-derived N98S CMT2E motor neurons are more susceptible to axonal degeneration both at baseline conditions and in response to exposure to vincristine, suggesting that this platform can reliably model CMT-associated axonal degeneration \textit{in vitro} and could be used to identify modulators of axonal degeneration with therapeutic potential for CMT2E and other axonopathies.

References: None.

Keywords: CMTR, Axonal Biology, Human Genetics, Pre-clinical Studies

Grant Support: Charcot-Marie-Tooth Association National Institutes of Health
Mutation Burden and Oligogenic Inheritance in a large Inherited Axonopathy Cohort

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Inherited axonopathies include the clinically distinct phenotypes, Charcot-Marie-Tooth (CMT) and Hereditary Spastic Paraplegia (HSP), which both cause slowly-progressing, length-dependent axonal degeneration. Both phenotypes are genetically and phenotypically diverse with close to 100 Mendelian genes involved for each thus far. Whole-exome sequencing of axonopathy patients may identify more than one rare variant within known disease genes. Occurrence of additional rare variation, also referred to as a ‘mutation burden’, has been reported in two independent CMT cohorts (n £40) supported by functional zebrafish assays. The data indicate that mutation burden may influence clinical heterogeneity and severity of disease. We sought to replicate a mutation burden across inherited axonopathies in a WES cohort 10-fold larger than the original observations (CMT cases = 357, HSP cases = 515, controls = 931). We tested the mutation burden in cases compared to controls for both non-synonymous and loss-of-function variants at ExAC MAF £0.1% and 1%. For each tested variant set, cases harbored a higher average number of qualifying variants (Mann-Whitney, p-value £0.05). The significance of this difference was further evaluated by permuting case/control status over 10,000 iterations (p-value £0.05). Next, we evaluated the possibility of di- and oligogenic inheritance within each cohort. Cases carrying a qualifying variant in ≥2 genes were classified as di/oligogenic and in ≥3 genes as oligogenic. We observed a difference in the proportion of cases and controls carrying variants for both di/oligogenic and oligogenic inheritance for non-synonymous variation (Chi-squared, p-value £0.05). Neither HSP nor CMT showed evidence of oligogenic inheritance for loss-of-function variation; however, HSP cases were enriched for digenic inheritance (Chi-squared, p-value £0.05). In this study, we provide further evidence of a mutation burden in CMT cases, demonstrate a mutation burden in HSP cases, and explore potential oligogenic inheritance patterns in a large cohort.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: None.
Hyperglycosylation of Myelin Protein Zero: from pathogenesis to therapeutic options.

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Introduction: mutations in the Myelin Protein Zero gene (MPZ), encoding P0, the major structural glycoprotein of peripheral nerve myelin, are found in 5% of Charcot-Marie-Tooth (CMT) patients. P0 variants may cause different gain of function including misglycosylation (either gain-of-glycosylation or loss-of-glycosylation), a novel pathomechanism encompassing several genetic disorders. We decided to establish a mouse model carrying the D61N mutation, a MPZ variant causing hyperglycosylation of P0 (1). Methods: the knock-in mouse model was generated using the Crispr/Cas9 system. The phenotype was characterized by behavioral, electrophysiological and neuropathological tests, at different time points. We evaluated the presence of tremor, the motor capacity, the sciatic motor nerve conduction velocity and cMAP. We performed light microscopy morphological observations, analyzing sciatic nerve semithin sections. We also decided to establish myelinating DRG cultures from wild type (WT) and Mpz D61N/+ embryos. Results: at one and three months of age, all evaluations, showed significant differences in Mpz D61N/+ mice compared with WT animals. Tremor was evident in all Mpz D61N/+ mice and correlated with a significant motor impairment on the accelerating Rotarod where mutant mice showed a reduced average latency to fall. Electrophysiological parameters also differed between the two groups: at one month of age, the average MCV was 11,8m/s ±1,2 in Mpz D61N/+ as compared with 32,88m/s ±1,3 in controls. The pathological analysis confirmed a demyelinating phenotype with a significant increase of the G-ratio in Mpz D61N/+ animals. In myelinating DRG cultures we detected fewer internodes carrying remarkable myelin abnormalities; when DRGs were treated with NB-DNJ, an immuno-sugar potentially able to reverse hyperglycosylation, the myelin defects seemed to decrease. Conclusions: we obtained an animal model expressing the P0D61N variant, a mutation causing gain-of-glycosylation in P0 which recapitulates the human phenotype of this variant and we are testing possible therapeutic strategies.


Keywords: CMTR, Schwann Cell, Human Genetics

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Neddylation plays a critical role for formation, maturation and maintenance of Schwann cell myelin sheaths

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Myelinating Schwann cells play a critical role for neuronal function and health. Defective myelination is responsible for the morbidity of a number of peripheral neuropathies, including Charcot-Marie-Tooth disease and diabetic neuropathy. Decades of research has uncovered a complex transcriptional and post-transcriptional program that drives the formation and maintenance of the myelin sheath. In contrast, much less is known about the functional role of post-translational modification (PTM) of proteins in this remarkable biogenic process.

Neddylation, a PTM that involves the conjugation of the ubiquitin-like protein Nedd8 to protein targets, has recently emerged as a central and versatile regulator of many cellular processes, including ubiquitination, protein transcription and signalling transduction. In Schwann cells, a functional role for neddylation has so far not been defined.

In this study, using various models of genetic and pharmacological inhibition of neddylation in vivo, we show that this PTM has complex and extensive regulatory functions in Schwann cells. For instance, genetic inactivation of NAE1, the enzyme that catalyses neddylation reactions, specifically in developing Schwann cells, leads to striking nerve defects that exhibit all the hallmarks of a severe neuropathy, including gait abnormalities, muscle weakness, and hindlimb clasping. Strikingly, NAE1-deficient mice lack peripheral myelin and exhibit active myelin breakdown of the few formed myelin sheaths. Mechanistically, this severe block of myelination is due to a deficiency in the ubiquitin-mediated degradation of negative regulators of myelination in perinatal nerves, which remain artificially elevated, thus blocking myelination. Notably, we also found an important function of neddylation in maturation and maintenance of myelin sheaths, and in the Schwann cell responses to nerve injury.

In summary, our study reveals that PTMs can play a central role in nerve development, and identifies neddylation as a tractable target for the development of new therapies in demyelinating disorders and for nerve regeneration.

References: None.

Keywords: Schwann Cell, Axonal Regeneration, Other

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Cell adhesion and choline-dependent metabolism in PNS myelination

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During myelination, Schwann cells up-regulate lipid biosynthesis to supply the lipid-rich (70 - 85%) mature myelin sheath. Several of these lipids are directly derived from choline-dependent metabolism, whereas the synthesis pathways of others intersect with choline derivatives. Choline-derived lipids are important both as structural components and as reservoirs of signaling molecules that have a direct implication on the initiation of myelination, the compaction and the maintenance of the myelin sheath. Little is known about the molecular mechanisms that regulate the lipid synthesis during Schwann cell myelination. It is likely, however, that axo-glial interactions are involved. Recently we identified in Schwann cells a protein complex that incorporates cell adhesion molecule Nectin-like 4 (Necl4) and Choline Transporter-Like protein 1 (CTL1). We have shown that intracellular choline homeostasis, as well as choline-dependent lipid biogenesis of phosphatidylcholine and phosphatidylinositol are disrupted in Necl4-deficient Schwann cells. To expand our in vitro data to an in vivo system, we generated a Schwann cell-specific CTL1 knockout mouse (dhhCre;CTL1fl/fl). EM analyses of developing sciatic nerves reveals PN myelination defects including delayed myelination, thinner myelin sheaths as well as myelin in-folding and out-folding. The mice also exhibit impaired motor behavioral performance and reduced nerve conduction thresholds. While choline is a vital nutrient that must be acquired though the diet, cells do have the ability to produce choline de novo through the PEMT pathway. Thought to have little to none biological role in non-hepatic tissues, we show that the PEMT enzymes are strongly expressed in developing sciatic nerves at the onset of myelination. Similar to the CTL1 knockout mice, PEMT knockout mice present numerous myelin abnormalities in the PNS. These results suggest that the regulation of choline metabolism through CTL1 and PEMT pathways is an important parameter to myelin formation.

References: None.

Keywords: Schwann Cell, CMTR

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The Integrated Stress Response Contributes to Charcot-Marie-Tooth Type 2D Peripheral Neuropathy in Mice

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Dominant mutations in glycyl-tRNA synthetase (GARS) cause CMT type 2D (CMT2D). How mutations in GARS cause neurodegeneration is unclear, but impaired translation has emerged as a potential toxic gain-of-function mechanism based on work with Drosophila. To test this mechanism in mice, we have profiled translation in motor neurons of mice with mutations in Gars that are validated as CMT2D models. In vivo, cell type-specific, fluorescent non-canonical amino acid-tagging (FUNCAT) has revealed reduced translation in motor neuron cell bodies of mutant Gars mice. To complement the protein analysis, in vivo ribosome-tagging from mutant Gars motor neuron cell bodies was used to identify mRNAs undergoing translation. This revealed an upregulation of transcripts associated with the integrated stress response, including ATF4 and several of its gene targets. Using RNAscope in situ hybridization, we show that (1) activation of the stress response occurs in approximately 70% of mutant motor neurons, (2) most gamma motor neurons do not show this response, (3) a subset of sensory neurons in dorsal root ganglia also upregulate the stress response, and (4) no other cell types in the spinal cord or dorsal root ganglia activate this response. We also find evidence of stress response activation in the spinal cords of mutant Yars-E196K mice, a model of dominant intermediate CMT type C. Genetic experiments reveal that removing GCN2, a kinase that activates the stress response, from mutant Gars mice prevents expression of the most highly upregulated ATF4 gene targets. Removing GCN2 also significantly alleviates neuropathy, resulting in increased body weight, improved grip strength, less denervation at the neuromuscular junction, increased nerve conduction velocity, and less motor axon loss. Because chronic stress response activation is detrimental to motor neurons in this disease context, inhibiting GCN2 in human patients with mutations in tRNA synthetase genes may be beneficial.

References: None.

Keywords: CMTR, Axonal Biology

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Role of the ER stress transcription factor XBP1 in Charcot-Marie-Tooth disease type 1B

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Myelin protein zero (Mpz) protein is the most abundant protein in the myelin of peripheral nerves. The mutant MpzS63del causes Charcot-Marie-Tooth (CMT) 1B disease in humans and a similar demyelinating neuropathy in transgenic mice. MpzS63del protein provokes an endoplasmic reticulum (ER) stress in myelinating Schwann cells, resulting in an unfolded protein response (UPR) characterized by activation of PERK, ATF6 and XBP1 pathways. We have previously reported that activation of CHOP and GADD34, two mediators downstream of PERK, is pathogenetic in MpzS63del mice, but the role of the other UPR branches remains to be investigated.

To unravel the role of the XBP1 pathway in CMT1B, we generated new models of CMT1 mice in which XBP1 gene is deleted or overexpressed specifically in Schwann cells and, in parallel, we exploited MpzS63del dorsal root ganglia (DRG) explant cultures in which XBP1 signaling is modulated by gain/loss of function approaches.

We have observed that the absence of XBP1 dramatically worsens hypomyelination and electrophysiological/locomotor parameters in young and adult S63del neuropathic animals. Interestingly, we observed strong upregulation of PERK and IRE1-mediated RIDD signalings in neuropathic animals lacking XBP1. This suggests that the activation of XBP1 targets plays a critical role in limiting MpzS63del toxicity, which cannot be compensated by other stress responses. In addition, we demonstrated in S63del DRG cultures that inhibition of XBP1 pathway impairs myelination while activation of XBP1 signaling ameliorates myelination.

Overall, these data demonstrate that the XBP1 pathway has an essential adaptive role in MpzS63del neuropathy and suggest that activation of this pathway is beneficial for CMT1B and possibly for other neuropathies characterized by UPR activation.

References: None.

Keywords: Schwann Cell

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NRG1 type I dependent autocrine stimulation of Schwann cells in onion bulbs of peripheral neuropathies

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In contrast to acute peripheral nerve injury, the molecular response of Schwann cells in chronic neuropathies remains poorly understood. Onion bulb structures are a pathological hallmark of demyelinating neuropathies, but the nature of these formations is unknown. Here, we show that Schwann cells induce the expression of Neuregulin-1 type I (NRG1-I), a paracrine growth factor, in various chronic demyelinating diseases. Genetic disruption of Schwann cell-derived NRG1 signalling in a mouse model of Charcot-Marie-Tooth Disease 1A (CMT1A), suppresses hypermyelination and the formation of onion bulbs. Transgenic overexpression of NRG1-I in Schwann cells on a wildtype background is sufficient to mediate an interaction between Schwann cells via an ErbB2 receptor- MEK/ERK signaling axis, which causes onion bulb formations and results in a peripheral neuropathy reminiscent of CMT1A. We suggest that diseased Schwann cells mount a regeneration program that is beneficial in acute nerve injury, but that overstimulation of Schwann cells in chronic neuropathies is detrimental.

References: None.

Keywords: CMTR, Schwann Cell

Grant Support: This work was funded by the ERA-NET for Research Programs on Rare Diseases E-RARE-3 (01GM1605)
Finely tuned calcium dynamics are essential for normal neuronal function, and excessive calcium flux has been repeatedly implicated in the pathogenesis of neurodegenerative diseases. The mechanisms that lead to neuronal dysfunction and degeneration downstream of calcium entry remain poorly defined. Mutations in the non-selective cation channel TRPV4 cause motor predominant peripheral neuropathies, including Charcot Marie Tooth disease subtype 2C (CMT2C). To investigate the role of calcium in neurodegeneration and pathological mechanisms involved in CMT2C, we explored the consequences of CMT2C-causing mutant TRPV4 expression in primary mammalian neurons and in Drosophila. Expression of mutant TRPV4 causes neuronal dysfunction and axonal and dendritic degeneration that can be prevented by genetically or pharmacologically inactivating the TRPV4 ion channel pore. While activation of both wild-type and mutant TRPV4 increases intraneuronal calcium, we demonstrate that mutant TRPV4 is more sensitive to stimulation than wild-type TRPV4 in neurons. Additionally, mutant TRPV4 causes neuronal dysfunction manifested as hyperexcitability and impaired mitochondrial transport in the absence of TRPV4 stimulation. Interestingly, acute pharmacologic activation of wild-type TRPV4 also disrupted mitochondrial transport, suggesting mitochondrial transport is regulated by TRPV4 mediated calcium influx. To investigate signaling mechanisms involved in mutant TRPV4 mediated toxicity, we performed a genetic modifier screen in the fly and identified CaMKII as a potent genetic modifier of mutant TRPV4. RNAi silencing of CaMKII prevents neuronal dysfunction and neurodegeneration. Remarkably, pharmacologic inhibition of CaMKII substantially suppresses TRPV4 mediated calcium influx, suggesting CaMKII potentiates TRPV4 activity and operates at the level of calcium entry in our models. Our data suggest that neuropathy-causing mutants sensitize the TRPV4 ion channel, resulting in CaMKII dependent calcium influx and subsequent calcium-dependent disruption of mitochondrial transport and neurodegeneration. Furthermore, they suggest that TRPV4 selective antagonists warrant further investigation as potential therapeutics for TRPV4-mediated peripheral neuropathies.

References: None.

Keywords: CMTR, Axonal Biology

Grant Support: None.
Improving Physical Function in Persons with Peripheral Neuropathy Using Sensory Neuromodulation - Clinical Trial Update

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Problems with gait and balance in persons with sensory peripheral neuropathy are well documented. A new wearable device, a lower limb sensory neuroprosthesis to substitute for lost plantar sensation, is currently used in a multi-site clinical trial (NCT #03538756). The technology is intended for individuals with sensory peripheral neuropathy associated with balance problems. The device provides gentle directional tactile cues around the lower leg reflecting changes in foot pressure distribution measured with an instrumented foot pad in the shoe. Patients react to these new sensory cues and incorporate them to improve gait and balance. The trial investigates long-term chronic use effects (52 weeks) on clinical and patient-reported outcomes of balance and gait function, quality of life, physical activity/participation and pain. The study will enroll 100 patients across multiple sites 2018-2020. Clinical outcomes include Functional Gait Assessment (FGA), Gait Speed, Timed Up&Go, Four-Stage Balance Test, Vestibular Activities of Daily Living and Activities-Specific Balance Confidence Scales. Fall-rates are monitored and compared to pre-study data. Patients for the study are diagnosed with sensory peripheral neuropathy, a loss of plantar sensation and have associated gait and balance problems. Tactile vibratory sense around the ankle where the leg unit of the device is placed is required and is tested prior to use. FGA score should be below 23, the cut-off for high fall-risk in community dwelling elderly individuals, and the test should be performed without the use of an assistive device as an indication of sufficient motor function to act on new sensory information provided by the device. This presentation will share early observations from the trial and discuss their translation into clinical practice. Results from the study will help refine prescription criteria for the device and further determine whether a short-term in-clinic response is indicative of long-term improvements.

References: None.

Keywords: Clinical Trials, Diabetes, Pain, Other

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**Poster 100**

**Variable Presentation of Hereditary Transthyretin-Mediated (hATTR) Amyloidosis: A Single Center Experience with the Patisiran PAAP**

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**Introduction:** Hereditary transthyretin-mediated (hATTR) amyloidosis is a multisystem disease that can lead to a mixed presentation. Because of this variable presentation, accurate diagnosis and treatment can be delayed.

**Methods:** This case series evaluates 8 patients at a single center between 2016 – 2018 who were ultimately diagnosed with hATTR amyloidosis. Three enrolled into the patisiran Pre-Approval Access Program (PAAP), were dosed, and had at least a 6-month assessment. The patisiran PAAP is an open-label, multicenter program, consisting of the Expanded Access Protocol (EAP) in the US (NCT02939820; now closed) and Compassionate Use in the EU. The PAAP provides access to patisiran for adults with genotype-confirmed hATTR amyloidosis and symptomatic polyneuropathy who meet eligibility criteria.

**Results:** We share a series of cases in patients ages 48-79-years who presented with a variety of symptoms, including ascending paresthesias, orthostatic hypotension, heart failure, constipation, and dyspnea. Several of these cases were initially misdiagnosed which prolonged time to correct diagnosis up to 10 years. Diagnosis of hATTR amyloidosis was definitively established after a series of multisystem exams and genetic testing. Of the 3 patients in the PAAP, 1 remained stable at 12 months (PND IIIb), 1 progressed at 6 months (PND IIIb to IV), and 1 improved at 6 months (PND II to I). Patisiran was well tolerated in these 3 patients; all AEs were mild-moderate except one severe AE that was deemed not related to patisiran.

**Conclusions:** As seen in this case series of a single center, the variable presentation and mixed nature of hATTR amyloidosis makes it a difficult disease to diagnose if there is a lack of clinical suspicion. Upon recognizing the symptoms and considering hATTR amyloidosis as a differential diagnosis, it is possible to diagnose patients earlier and provide treatment for the polyneuropathy manifestations of the disease.

**References:** None.

**Keywords:** Amyloidosis

**Grant Support:** None.
A complex inherited sensory neuropathy related to compound heterozygous mutation in the FXN gene

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Friedreich Ataxia (FRDA) is an autosomal recessive hereditary ataxia, caused by a biallelic GAA-trinucleotide-repeat expansion in FXN gene. Neuropathy is a common feature. Compound heterozygosity for an expansion and a sequence mutation are rare and can cause an atypical phenotype with later age onset and slower disease progression. We describe an 80 year old patient who developed unsteadiness and difficulties walking in his 30s. He was diagnosed with Charcot Marie Tooth (CMT) disease at 40. His mobility gradually declined over the years and he has been using a wheelchair for the last 15 years. His younger brother had a similar phenotype but earlier onset. Neurological examination showed normal cranial nerves, normal tone and coordination in the upper limbs. He had distal wasting and mild weakness in the upper limbs. In the lower limbs he had distal weakness and non-length dependent proximal weakness which had a pyramidal distribution. He was areflexic. Sensory examination showed severe loss of vibration sense and proprioception in the upper and lower limbs. Nerve conduction studies were compatible with predominant axonal sensory neuropathy. Because of the unusual features he had spinal cord MRI which revealed an intramedullary lesion in the thoracic cord at T7 vertebral level probably related to a dorsal arachnoid cyst. Next generation sequencing (NGS) CMT2 and HSN panel were negative. Further NGS identified heterozygous Gly130Val pathogenic mutation in FXN and one FXN GAA repeat expansion of approximately 350 GAA repeats in the pathogenic range on the other allele. The G130V is the most frequent missense mutation in FRDA and might account for the production of a partially functional protein and milder phenotype. This interesting case expands the phenotypic variability of FRDA due to compound heterozygous mutations and highlights the importance of considering genetic testing for FRDA in cases of complex inherited sensory neuropathy.


Keywords: CMTR

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Poster 103

The longitudinal change in nerve cross-sectional area of Charcot-Marie-Tooth disease type 1A

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Introduction: The lack of sensitive biomarkers is thought to be one of the factors that led to failures of clinical trials in Charcot-Marie-Tooth disease (CMT). Recently, muscle MRI and neurofilament light were identified as potential sensitive biomarkers of disease progression. It would be beneficial for CMT patients to demonstrate that parameters obtained by non-invasive methods could be sensitive biomarkers. In CMT type 1A (CMT1A), 2-fold to 3-fold increases in nerve cross-sectional area (CSA) is observed by using nerve ultrasound. As such, the aim of this study is to determine the longitudinal change in nerve CSA in adult CMT patients. Methods: This study included 15 patients with CMT1A patients (M:F = 10:5, mean age: 55.1 years old). The measurement of the median and sural nerve CSAs using nerve ultrasound was done 4 times (at baseline, 1, 3, and 5 years after the baseline.) by one examiner. CMT neuropathy score (CMTNS) and CMT examination score (CMTE) were also measured at each visit. Comparison of each parameter between at the baseline and 5 years after the baseline was performed. Results: Regarding nerve CSAs, there was not significant 5-year change in the median (at the wrist, forearm, and upper arm) and sural nerves, although there was a tendency that sural nerve CSA was decreasing with time (p =0.07). Mean CMTNS and CMTE significantly increased linearly over 5 years (from 15.8 to 18.9 point (p <0.01) and from 10.9 to 14.0 point (p <0.01), respectively). Conclusions: Nerve ultrasound method could not detect a 5-year change in nerve CSAs. The longitudinal change in other nerve ultrasound parameters including echogenicity should be explored in the future.


Keywords: CMTR

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Systematic Survey of Electrophysiological Findings in Myotonic Dystrophy Type 1 (DM1)

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Background: DM1 is an inherited muscular dystrophy with myotonic and myopathic changes in the muscles. We reviewed the literature of electrophysiological findings of DM1 patients to reveal preference of electrophysiological changes. Methods: all English, German and Russian articles from PubMed and EMBASE about electrophysiological findings in genetically confirmed DM1 patients were reviewed. Articles of case reports of 1 or 2 patients were excluded. Results: A data set of 363 DM1 (175 females) patients was collected. Mean age were 41 years. EMG from 229 DM1 patients showed myotonic discharges in 182 (79.5%) and myopathic changes in 128 (55.9%). From 362 DM1 patients the nerve conduction velocity studies showed neuropathic changes in 79 (21.8%). Out of 41 DM1 patients in 28 (68.3%) a demyelinating neuropathy was found. Axonal neuropathy was evident in 6 (14.6%) and mixed neuropathy in 7 (17.1%). Motor conduction block or a significant temporal dispersion was not reported. Discussion and conclusion: Our study for the first time summarizes the electrophysiological findings in adults with DM1. Beyond well-known EMG findings, about 20% of DM patients show neurographic alterations. This should prime us to include neurography as a standard element in the work-up of all DM patients.

References: None.

Keywords: Other

Grant Support: None.
Charcot-Marie-Tooth disease, Type 1A (CMT1A) is one of the most common inherited peripheral neuropathies; a demyelinating disorder caused by an additional copy of the PMP22 gene. The PMP22 gene encodes a transmembrane glycoprotein that is enriched in compact myelin but little is known about the endogenous function of PMP22. Previous work in rodents suggests that PMP22 gene dosage may affect stoichiometry of compact myelin structural components, PMP22 degradation and the expression of important myelination genes. These potential models reveal interesting candidate pathways that may be modified in CMT1A rodent models but cannot fully explain the endogenous function of PMP22 or how copy number variation of this gene leads to dysregulated myelination. We are utilizing CMT1A patient fibroblasts and iPSC-derived Schwann cells in order to study PMP22 gene dosage in the genetic background of actual patients. Our recent findings revealed increased substrate adhesion in CMT1A patient fibroblasts as compared to healthy controls. Interestingly, the increased adhesion is correlated with increased cell surface PMP22 protein levels but not total PMP22 protein levels. Additionally, gene ontology analysis of RNA sequencing on both patient fibroblasts and iPSC-derived Schwann cells revealed cell adhesion as a highly significant biological process, which included genes from multiple adhesion families. These findings suggest that PMP22 copy number variation affects adhesion directly through PMP22 surface expression and indirectly by altering expression of additional adhesion genes. Current studies are focused characterizing adhesion phenotypes in iPSC-derived Schwann cells and identifying dysregulated genes in both cell types that contribute to the dysfunctional adhesion by performing rescue experiments. Results from these studies will significantly advance our understanding of PMP22 function, help uncover CMT1A pathomechanisms and reveal targets for novel therapeutics.

References: None.

Keywords: CMTR, Schwann Cell

Grant Support: The Foundation for Peripheral Neuropathy and the Johns Hopkins University Provost’s Postdoctoral Diversity Fellowship
Two Independent Cases of de novo GARS(p.Gly327Arg) Mutation that Causes a Predominantly Motor Axonal Neuropathy

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Proband 1 is an 18-year-old woman who developed pain while walking and weakness in her hands at age 10. When examined at age 14, she had diminished strength in the distal muscles of her legs and arms, pinprick loss below the ankles, and normal vibration. Her CMT Examination Score (CMTES) was 10 (out of 28). Proband 2 is a 22-year-old woman who developed weakness in her hands and feet around age 13. Her initial exam at age 22 showed weakness in the distal muscles of her legs and arms, as well as normal pinprick and vibration sensation. Her CMT Neuropathy Score was 10 (out of 36). Clinical neurophysiology showed a predominately (proband 1; age 12) or exclusively (proband 2; age 22) motor neuropathy. A clinical gene panel on DNA isolated from proband 1 identified a previously unreported variant in GARS (c.979G>A/p.Gly327Arg). This is a de novo variant as it was absent in both parents. Whole-exome sequencing of proband 2 identified the same GARS mutation, which was not present in the proband’s mother or sister. Through the GENESIS platform, the clinicians who evaluated the two probands became aware of each other’s findings. To determine the functional consequences of the p.Gly327Arg GARS mutation, yeast complementation assays were performed by modeling the variant in both the yeast and human GARS genes. In both cases, the p.Gly327Arg mutation failed to rescue yeast growth, showing that it is a loss-of-function mutation. Based on these results, the finding of a previously unreported GARS variant that is likely de novo in two, unrelated families, and the results of the yeast complementation assay, we believe the p.Gly327Arg GARS mutation is the underlying cause of the neuropathy in these two individuals, both of whom have a motor > sensory neuropathy; which is typical for GARS mutations.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: None.
Poster 107

Resolving a multi-generational neuromuscular mystery

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Introduction: Valosin containing protein (VCP) mutations have been reported to present with a high degree of variability and can be present in patients even if they may have an initial normal work up. Methods: A middle aged proband was labeled as "normal" and "pain medication seeking" after an unrevealing work up of clinical, laboratory, electrodiagnostic, radiographic, pathologic, and genetic testing. Repeat work up and further genetic testing revealed a pathogenic VCP mutation. Results: The proband presented with chronic neck pain, but had variable features of scapuloperoneal atrophy, which was also seen in her family. The patient and her family were found to have a known pathogenic c.464G>A, p.Arg155His (R155H) mutation in the VCP gene. Conclusion: Despite traditional thinking of attempting to localize neurological syndromes, VCP mutations are difficult to localize as they can present with significant clinical heterogeneity including a scapuloperoneal syndrome with variable neuropathic and myopathic features.

References: None.

Keywords: Human Genetics, Pain

Grant Support: None.
Objective: To report our experience with transthyretin (TTR) knockdown therapy in patients with hereditary TTR amyloidosis (hATTR) who failed liver transplantation. Background: Patients with hATTR amyloidosis, especially those with non V30M mutations, can continue to have disease progression and reduced survival despite early liver transplant. This is thought to be related to wild type ATTR deposition (wtATTR). Newly approved TTR knockdown therapies (Patisiran and Inotersen), significantly suppress the production of both mutated ATTR (mATTR) and wtATTR. Methods: Two patients with hATTR amyloidosis who continued to have disease progression despite liver transplantation were started on Inotersen. Results: The first patient is a 49 year-old man with TTR-Arg50 mutation and the second patient is 64 year-old man with T32C TTR mutation. Both patients underwent liver transplantation 2 years after symptoms onset and both had symptomatic improvement which lasted for 2 years before their disease progressing again. Both patients were started on Inotersen. The first patient was treated for 5 months and stopped because of thrombocytopenia. During treatment, his Neuropathy Impairment Score (NIS) remained stable (124 to 121.5). After stopping treatment, patient’s NIS increased to 140 and he started using a scooter. The second patient has been on the drug for 6 months, and his NIS improved from 124 to 98.5 with no significant side effects. Conclusion: Progression of disease following liver transplant in patients with hATTR amyloidosis is difficult to manage and is probably related to wtTTR. TTR knockdown therapy which suppresses the progression of both mTTR and wtTTR could be a promising treatment for patients with hATTR amyloidosis who continue to have disease progression despite liver transplantation.

References: None.

Keywords: Amyloidosis, Human Genetics

Grant Support: None.
A Novel Pathogenic Variant of NEFL responsible for Deafness associated with Peripheral Neuropathy

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Neurofilaments are neuron-specific intermediate filaments essential for the radial growth of axons during development and the maintenance of axonal diameter. Pathogenic variants of NEFL are associated with CMT1F, CMT2E, and CMTDIG and have been observed in less than 1% of CMT cases, resulting in the reporting of 35 variants in 173 CMT patients to date. However, only six variants have been reported in 17 patients with impaired hearing. No genotype-phenotype correlations have yet been established. Here, we report an additional case: a 69-year-old female, who originally presented with axonal sensory and motor neuropathy at the age of 45, associated with moderate sensorineural hearing loss, with a slight slope at high frequencies. NGS identified a novel pathogenic variant: c.269A>G, p.(Glu90Gly). Hearing impairment is often linked to CMT due to pathogenic variants of NEFL, especially p.(Glu90Lys) and p.(Asn98Ser), and in our case p.(Glu90Gly). These pathogenic variants are all located at hot spots, in the head domain and the two ends of the rod domain of the protein.

References: None.

Keywords: Human Genetics

Grant Support: None.
Poster 110

Electrophysiological features of hereditary ATTR amyloidosis misinterpreted as chronic inflammatory demyelinating polyneuropathy

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Purpose: To clarify the electrophysiological demyelinating features in patients with hereditary ATTR amyloidosis that may cause a misdiagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods: We retrospectively reviewed records of 102 patients with hereditary ATTR amyloidosis (85 Val30Met and 17 non-Val30Met; 37 and 65 from endemic and non-endemic areas) and investigated results of motor nerve conduction studies (MNCSs) with a 2-Hz low-cut filter in the unilateral ulnar and tibial nerves. MNCS parameters were evaluated whether they fulfilled the demyelinating values in the European Federation of Neurological Societies/Peripheral Nerve Society electrodiagnostic (EFNS/PNS EDX) criteria for CIDP. Distal compound muscle action potential (DCMAP) duration is influenced by low-cut filter settings. Therefore, DCMAP duration was analyzed using not only EFNS/PNS EDX criteria but also the cut-off value from the 2-Hz low-cut filter proposed by Mitsuma et al. (2015).

Results: Thirteen of 102 patients (13%) satisfied the definite EFNS/PNS EDX criteria for CIDP with low compound muscle action potential (CMAP) amplitude in the tibial nerve (0.7 ± 0.7 mV) and prolonged DCMAP duration in the ulnar nerve. There were no significant differences in clinical backgrounds between patients with and without the definite EFNS/PNS EDX criteria. Abnormal temporal dispersion and prolongation of distal latency in the tibial nerve were observed in 5 of 13 patients. Only one of 13 patients presented with reduction of motor conduction velocity in each nerve. No patient exhibited conduction block in any nerve. When using the upper value proposed by Mitsuma et al, 10 of 13 patients with definite CIDP criteria were downgraded as those with possible CIDP.

Conclusion: Severe axonal degeneration causes electrophysiological demyelinating features without conduction block in patients with hereditary ATTR amyloidosis. Analysis of DCMAP duration considering low-cut filter settings would be needed to minimize misinterpreting hereditary ATTR amyloidosis as

References: None.

Keywords: Amyloidosis

Grant Support: None.
A novel HINT1 mutation identified in two Norwegian patients with peripheral neuropathy

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Introduction

Recessive mutations in the histidine triad nucleotide binding protein 1 (HINT1) are known to cause axonal CMT neuropathy mostly presenting with neuromyotonia. To date 16 disease causing mutations have been published. To our knowledge, no Norwegian individuals with HINT1-neuropathy have been described previously.

Methods

A panel of 99 peripheral neuropathy genes including HINT1 was examined by next-generation sequencing. Parental samples, available for the 12-year old boy, were examined by Sanger sequencing. Knock-out HeLa cells expressing the p.(Arg95Gln) allele were examined by western blotting. The growth of Hnt1 deficient yeast expressing the HINT1 orthologue carrying the same mutation was monitored in a complementation assay under restrictive conditions (39C, galactose-containing medium).

Results

A 12-year old boy and a 33-year old male were independently referred for genetic analysis of peripheral neuropathies. Genetic testing revealed in both of them two identical heterozygous mutations in the HINT1 gene, NM_005340.6:c.110G>C p.(Arg37Pro) and NM_005340.6:c.284G>A p.(Arg95Gln). Parental testing in the 12-year boy showed that his variants were situated in trans. The p.(Arg37Pro) variant is a known pathogenic founder mutation in Europe. The p.(Arg95Gln) variant has not previously been reported, but it was predicted pathogenic and targeted an amino acid residue at the dimer interface. The novel HINT1 substitution was further modelled in HINT1 knockout HeLa cells and HNT1 knockout yeast. Functional studies showed that the p.(Arg95Gln) mutant did not cause protein degradation in both HeLa and yeast cells. However, the p.(Arg95Gln) mutant was unable to rescue the growth deficiency of a Hnt1-KO strain in yeast complementation assays.

Conclusion

This study reports a novel HINT1 variant identified in two Norwegian patients. These are the first reported Norwegian individuals diagnosed with HINT1-neuropathy. p.(Arg95Gln) is the second pathogenic HINT1 mutation demonstrated to not cause protein degradation but still resulting in a loss of function phenotype.

References: None.

Keywords: Human Genetics

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Compound Heterozygous Mutations of SH3TC2 in Charcot-Marie-Tooth Disease Type 4C Patients

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SH3TC2 mutations cause autosomal recessive Charcot-Marie-Tooth disease type 4C (CMT4C), characterized by spine deformities and cranial nerve involvement. This study identified four CMT4C families in 504 Korean demyelinating and intermediate CMT patients with compound heterozygous SH3TC2 mutations: p.G310E and p.E944G in FC523 and FC657 families and p.G310E and p.G1091V in FC703 and FC1080 families. The mutations were located at the highly conserved regions and several in silico analyses suggested pathogenic prediction of the mutations. The CMT4C frequencies were calculated to 0.33% in total Korean CMT cohort (n = 1,222), and 0.79% in demyelinating and intermediate patients (n = 504). The frequency in the Korean cohort study was relatively lower than other ethnic groups: 0.8% in a large USA CMT cohort, 1.7% in Germany, and 0.47% in Japan. Moreover, no homozygous mutation was found in the Korean patients. The reasons for low CMT4C frequency and no patients with homozygous mutation may be partly due to a strict legal prohibition of consanguineous marriage. Clinically, our patients showed less severe symptoms with no spine deformities, compared with other CMT4C patients. This study will be the first report of Korean CMT4C families with SH3TC2 mutations.

References: None.

Keywords: CMTR, Human Genetics

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Examining Mutation-Specific Impact on the Long, Distal Motor Axon in ALS using iPSC-derived Motor Neurons

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Amyotrophic Lateral Sclerosis (ALS) is a devastating motor neuron disease that is characterized by progressive dying back of motor axons and death of motor neurons that eventually leads to muscle wasting and death. Distal axon degeneration, dying-back, is a hallmark of motor neuron diseases that precedes symptom onset and motor neuron death both in human patients and animal models.1-4 There is no generally accepted explanation for the selective vulnerability of motor neurons in ALS. The longest axons tend to be the most susceptible to degeneration; therefore, the pathobiology of the long, distal motor axon in motor neuron disease is an area that must be explored thoroughly in order to understand ALS pathology and discover potential novel interventions for patients.

While motor neurons derived from human iPSCs (hMNs) hold promise for advancing ALS research,5-7 the length of axons, regenerative capacity, and mutant-specific innervation of neuromuscular junctions (NMJs) by these human neurons is not characterized. hMNs cluster into circular groups as they grow, and extend axons to other clusters, confounding quantification of axon outgrowth from individual hMNs. To address this, we have cultured hMNs from ALS patients and controls in custom microfluidic devices, and sequestered neuronal cell bodies in the main channel that extended processes through microgrooves into adjacent axonal compartments. We determined that dual-chamber devices with ample room in the axonal compartment are appropriate for examining axonal outgrowth, and allow for individual tracing of axons that are millimeters in length. This system lays the groundwork for introducing relevant cell types and gathering electrophysiological data from myocytes innervated by hMNs. We are now exploring the introduction of relevant cell types, such as myelinating Schwann cells and myocytes, into the axonal compartment in order to study ALS mutation-specific effects on structural and functional innervation of NMJs.


Keywords: Axonal Regeneration, Axonal Biology, Pre-clinical Studies

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Characterising Neurophysiological Findings in Charcot-Marie-Tooth Disease caused by Frameshift Mutations in NEFH

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Neurofilaments form an important part of the axonal cytoskeleton in both the central and peripheral nervous system. They are categorised into light (NEFL), medium (NEFM) and heavy (NEFH) chains and are essential in maintaining neuronal structure. Frameshift mutations in the NEFH gene have been associated with dominantly inherited CMT2, with translation of an abnormally elongated, amyloidogenic amino acid sequence. Clinically, patients typically present with motor-predominant symptoms between the 2nd and 5th decade with early falls and walking difficulties, but known associated features can include relatively early proximal muscle wasting, early ankle plantar-flexion weakness and pyramidal signs. Neurophysiology has been reported to show a motor and sensory axonal neuropathy largely affecting lower limbs, with EMG demonstrating non-length dependent neurogenic changes. We analysed neurophysiology obtained from 6 patients of 4 unrelated families seen at our centre, all of whom had frameshift NEFH mutations. 15 separate studies were performed on these patients. In the context of clinical information on these patients, we aim to further characterise the spectrum of neurophysiological features that can be seen in these patients. Analysis of nerve conduction studies demonstrated broadly symmetrical and length-dependent attenuation of sensory and motor amplitudes. There was isolated attenuation of only two motor responses as exceptions to this pattern. Additional features included consistent Tibial more than Peroneal muscle involvement, as well as mild Median forearm conduction slowing (42-47m/s) in the context of normal Median-APB amplitudes. EMG showed chronic or active neurogenic changes, which were often not clearly length-dependent. In summary, neurophysiology of 6 patients with frameshift NEFH mutations predominantly showed a length-dependent, axonal, sensory and motor neuropathy on NCS, but EMG shows disproportionate proximal muscle involvement. Preferential Tibial muscle involvement and mild slowing of the Median motor forearm segment were also frequently associated features.

References: None.

Keywords: CMTR

Grant Support: None.
Peripheral neuropathies are typically characterized by weakness of the extremities; however respiratory complications have also been documented in Charcot-Marie-Tooth disease type 1A (CMT1A) and Dejerine-Sottas disease (DSS) patients. Trembler J (TrJ) mice carry a point mutation in peripheral myelin protein 22 (PMP22) and serve as a model of DSS. Studies of the neuromuscular junction (NMJ) between the phrenic nerve and diaphragm of homozygous TrJ mice suggest that neuromuscular deficits contribute to respiratory complications in neuropathic patients. We hypothesized that phrenic nerve degeneration leads to destabilization of the NMJ and contributes to respiratory dysfunction. Quantifying multiple morphological parameters from the phrenic nerve of wild type (Wt) and heterozygous TrJ mice revealed highly significant (p<0.0001) demyelination and axonal atrophy in affected samples. Analyses of muscle atrophy gene transcript levels, including Atrogin-1 and MuRF-1, detected a significant down-regulation in affected animals by ~27.7% and 37.9%, respectively. However, protein levels for the same muscle atrophy markers remained stable, suggesting impaired protein turnover. Indeed, diaphragms from TrJ mice showed upregulation of the ubiquitin-proteasome and autophagy pathways compared to Wt, paralleling a phenotype seen in Schwann cells of neuropathic mice. Unexpectedly, we identified significant enlargement of myofiber cross-sectional area in the diaphragm from TrJ vs. Wt mice (974.8 µm² vs. 717.8 µm²). Our findings suggest that severe phrenic nerve neuropathy contributes to NMJ degradation in neuropathic animals, causing detectable, possibly compensatory changes in myofibers of the diaphragm. We also examined breathing patterns using whole body plethysmography, and the results suggest possible changes in the control of breathing in TrJ mice. Specifically, the rate of breathing in TrJ mice is significantly impaired (p=0.0138 vs. WT) when exposed to an acute hypercapnic/hypoxic respiratory challenge. Further elucidating the mechanisms contributing to respiratory dysfunction in neuropathic models will identify appropriate tissue targets for treatments to improve patient quality of life.

References: None.

Keywords: Schwann Cell, Axonal Biology, CMTR, Human Genetics, Axonal Regeneration

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Use of GAITRite system to investigate walking ability in Charcot Marie Tooth patients

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Here we present the results of the GAITRite system assessment, used in a multicenter randomized, single blind, controlled study to investigate the possible improvements on gait ability in 24 CMT subjects that underwent a rehabilitative treatment.

All subjects were evaluated with clinical scales investigating walking and balance abilities, and an instrumental gait assessment by means of the GAITRite system, an electronic portable walkway able to measure the temporal and spatial gait parameters. Subjects were asked to walk on the carpet for one minute at normal speed (NW), at fast speed (FW), during a cognitive dual task (DT) and overcoming obstacles in height or length (OB). The clinical measures were compared between T0 and T1 using unpaired t-test. Pearson’s correlation coefficients were calculated between all continuous characteristics, Spearman’s correlation coefficient for ordinal outcomes.

We compared both instrumental and clinical data with a control group of healthy age-matched subjects, finding significant differences in both spatial and temporal parameters. Also comparing the NW and FW gait, we found significant differences in both spatial and temporal gait parameters; analyzing DT data, no significant differences were found, hence confirming that in these patients the cognitive performance has no repercussions on the gait. At the OB task temporal and spatial parameters were significant worse respect to NW.

Moreover, we investigate the possible correlations between the clinical assessment and the instrumental data at the NW, finding a strong negative correlation between speed and 10MWT and CMTES and a strong positive correlation between speed and balance tests and with 6MWT.

The present data allow us to suggest the use of the GAITRite system as a useful and rapid tool in the walking evaluation of CMT subjects.


Keywords: CMTR, Clinical Trials

Grant Support: None.
Efficacy of Patisiran in Patients with hATTR Amyloidosis and Prior Tafamidis Use: Analysis of APOLLO

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Introduction: hATTR amyloidosis is a multisystem, life-threatening disease. Patisiran, a RNAi therapeutic, and tafamidis, a TTR tetramer stabilizer, are approved treatments for certain patients with hATTR amyloidosis with polyneuropathy. In the Phase 3 APOLLO study, patisiran demonstrated significant improvement in polyneuropathy and quality of life (QOL) from baseline to 18-months compared to placebo. The impact of patisiran on patients with previous tafamidis treatment prior to enrolling in APOLLO was evaluated.

Methods: APOLLO was a randomized, placebo-controlled study of patisiran in patients with hATTR amyloidosis with polyneuropathy (NCT01960348). Tafamidis-treated patients who entered APOLLO were required to discontinue tafamidis ≥14 days before study entry; discontinuation reason was recorded. Post-hoc analyses evaluated results for mNIS+7, a composite measure of neuropathy, and Norfolk QOL-DN, a measure of QOL, in patients who had received prior tafamidis treatment.

Results: APOLLO enrolled 225 patients of which 74 (32.9%) reported prior tafamidis use. Average (SD) length of time on tafamidis was 17.4 (16.1) months; 25 (33.8%) of these patients discontinued tafamidis due to disease progression and 46 (62.2%) discontinued to participate in APOLLO. Patients with prior tafamidis use who received patisiran demonstrated significant improvement in mNIS+7 and Norfolk QOL-DN from baseline to 18-months (n=45 for both endpoints) compared with placebo (n=15 for mNIS+7 and n=14 for Norfolk QOL-DN) (mNIS+7 LS mean change (SEM): -6.2 (2.4) vs. 20.8 (3.8); Norfolk QOL-DN LS mean change (SEM): -0.8 (2.8) vs 15.1 (4.4), respectively).

Conclusions: Approximately one-third of patients enrolled in the randomized, placebo-controlled APOLLO study were previously treated with tafamidis. These patients who received patisiran treatment for 18 months experienced a significant improvement from baseline in their neuropathy and QOL, compared to placebo, similar to that experienced by the overall patisiran-treated population.


Keywords: Amyloidosis

Grant Support: None.
Charcot-Marie-Tooth disease type 2N Patients with AARS Mutations

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Alanyl-tRNA synthetase (AARS) gene encodes a ubiquitously expressed class II enzyme which catalyzes the attachment of alanine to the cognate tRNA. It is known that AARS mutations are usually responsible for autosomal dominant Charcot-Marie-Tooth disease type 2N (CMT2N). The AARS gene encodes alanyl-tRNA synthetase. Each of the amino acid synthetases catalyzes the attachment of their respective amino acids to the appropriate tRNA. The AARS gene encodes alanyl-tRNA synthetase. Each of the amino acid synthetases catalyzes the attachment of their respective amino acids to the appropriate tRNA.

This study identified two CMT2N families in 318 axonal CMT patients with heterozygote AARS mutation: p.Q855R in FC612 family and p.R329H in FC1065 family. The mutations were located at the highly conserved regions and several in silico analyses suggested pathogenic prediction of the mutations. The p.R329H was previously reported as the pathogenic mutation of CMT2N, whereas the likely-pathogenic p.Q855R was unreported novel mutation. The FC1065 patient with p.R329H was clinically and electrophysiologically similar to previously reported patients, but onset age was somewhat different (7 yrs : 25 yrs). The CMT2N frequencies were calculated to 0.19% in total Korean CMT cohort (n = 1,035), and 0.63% in axonal CMT patients.

References: None.

Keywords: CMTR, Human Genetics

Grant Support: None.
Poster 119

Greater auricular nerve amyloidoma as a presenting manifestation of AL amyloidosis with underlying lymphoplasmacytic lymphoma

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Amyloidoma is a rare soft tissue tumour and has been reported peripheral nerves as well as in viscera such as GI tract and lung. Amyloidoma can be a presenting manifestation of AL amyloidosis.

A 57-year old female presented with profound fatigue, bilateral painful paresthesia in the hands, palpitations and transient right facial weakness. Examination revealed a mobile right neck mass. There was no clinical or neurophysiological evidence of peripheral neuropathy.

Imaging demonstrated a right greater auricular nerve mass. Biopsy was consistent with an amyloidoma demonstrating amorphous strongly congophilic deposits with patchy apple green birefringence. AL amyloid was confirmed by mass spectrometry. Additional investigations including SAP scintigraphy excluded cardiac and visceral amyloid.

Serological tests were abnormal with beta-2 microglobulin 3.5 mg/l (1.2-2.4), raised free kappa light chains 65.8mg/L (3.3-19.4) and raised kappa/lambda ratio but no paraprotein. CSF examination was unremarkable.

Whole body FDG PET-CT identified widespread FDG avid subcutaneous nodules and a prominent focus in right tibia. Right tibial biopsy was similar to the nerve biopsy. Biopsy of the subcutaneous nodules demonstrated lymphoplasmacytic lymphoma. Bone marrow was unremarkable. A breast lesion biopsied subsequently confirmed amyloid.

The patient developed progressive painful neuropathic symptoms and was commenced on bendamustine-rituximab followed by BEAM autologous stem cell transplant and is currently on maintenance rituximab.

Florbetaben PET-CT performed after treatment demonstrated widespread amyloid deposition in the tibial bone marrow consistent with known pre-treatment deposition.

This case demonstrates an atypical neurological presentation of AL amyloidoma associated with an underlying lymphoplasmacytic lymphoma. Despite presenting with localised disease this warranted systemic therapy to control symptoms.


Keywords: Amyloidosis

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Increased rate of pregnancy complications and occasional worsening of Charcot-Marie-Tooth (CMT) during pregnancy have been reported, but there are no large systematic studies.

Through an ad hoc online questionnaire, we investigated pregnancy and neuropathy course in CMT women adhering to the CMT Italian Registry. Controls were recruited among friends and unaffected relatives.

We collected data on 140 CMT women (aged 20-73 yrs) with detailed information on 194 pregnancies from 86 women. Results were compared to 31 age-matched controls and 59 pregnancies in 24 women. Age at pregnancy was 17-43 years (mean 28.7) for CMT patients and 17-41 years (mean 29.5) for controls. Complications occurred in 69 pregnancies (36%) for 30 CMT women (35%) and 10 pregnancies (16.9%) for 6 controls (26%) (p<0.05). Utero-placental hemorrhage occurred in 10% of CMT pregnancies vs 1.7% among controls (p=0.04); placenta previa occurred during 5 pregnancies in 5 CMT women and in no control (p=0.21). Delivery occurred in 158 cases for CMT (81.4%) and 46 for controls (78%) after a mean of 38.6 gestational weeks (range 26-44) vs 38.9 (range 32-42) for controls, with natural delivery in 93 CMT (16 of them with induction) vs 31 controls (similar figures in controls). There were two post-partum hemorrhages in CMT patients. Nine newborns (6.3%) from CMT pregnancies had icterus vs one control (2.2%). CMT status worsened during 16 out of 194 pregnancies (8.25%) in 12/86 patients (14%), with no recovery in 11/16 instances. After pregnancy, three more patients needed assistance for walking and two patients needed new assistive devices.

Although pregnancy course and delivery are overall regular in CMT, we observed a relatively higher frequency of haemorrhages in CMT than controls. Worsening of CMT is not infrequent and occurs not only in CMT1A. Pregnant CMT women need to be monitored with particular care.

References: None.

Keywords: CMTR

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The nerve echogenicity assessment in Charcot-Marie-Tooth disease type 1A

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Introduction: Charcot-Marie-Tooth disease (CMT) is a heterogenous group of slowly progressive hereditary neuropathies. It is challenging to detect small changes in disease activity over a few years. This is thought to be one of the reasons why clinical trials are failed in CMT. Recently, quantitative nerve ultrasound assessment is increasingly used in neuropathies. Nerve echogenicity is one of quantitative parameters. Fisse et al. reported that nerve echogenisity of the arm could be a prognostic marker in chronic inflammatory demyelinating polyneuropathy (CIDP). The aim of this study is to elucidate changes in nerve echogenicity of patients with CMT type1A (CMT1A).

Methods: This study included 15 patients with CMT1A (M:F= 10:5, mean age: 55.1 years old) and 15 age-matched normal controls (M:F = 9:6, mean age: 55.4). Nerve ultrasound examination was performed in CMT1A patients twice (at the baseline and 5 years after the baseline) and in controls once. Nerve echogenicity in the median (at the wrist, forearm and upper arm) and sural nerves was measured in each stored image using a semiautomated and quantitative method by ImageJ(provided by NIH). Comparison of nerve echogenicity between CMT1A patients and normal controls at baseline was performed, and change from the baseline to the 5 years after the baseline was analyzed.

Results: Nerve echogenicity at the forearm of the median nerve was lower in CMT1A (fraction of black: 66.2±7.9%) than in controls (57.1±8.0%) (p =0.0023), whereas there were no differences at the other sites. Regarding a longitudinal change in CMT1A patients, echogenicity of the sural nerve decreased over 5 years (p =0.016).

Conclusions: Hypoechoic change at the forearm of the median nerve was a remarkable finding in CMT1A patients when compared with controls. Additionally, echogenicity of the sural nerve may change along with the disease progression in CMT1A.


Keywords: CMTR

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Poster 122

OPA3-related autosomal dominant optic atrophy and cataract (ADOAC) plus syndrome.

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Background: Mutations in the OPA3 gene, which encodes a putative mitochondrial pro-fission protein, cause autosomal recessive 3-methylglutaconic aciduria and autosomal dominant optic atrophy and cataract (ADOAC). Neurological features have been reported in some patients with ADOAC; in one of them, peripheral neuropathy (PN) was confirmed by nerve conduction studies (NCS). The aim of this study is to describe the phenotype in individuals with OPA3-related ADOAC and PN. Methods: Two probands with several affected relatives and one sporadic case were referred for evaluation of a PN. Their phenotype was determined by clinical assessment and NCS. Neuropathologic evaluation of the sural nerve was performed in one individual. All probands underwent exome sequencing. Results: The main clinical features in one sporadic case and one family consisted of early-onset cataracts, gastrointestinal dysmotility symptoms, and PN. Impaired vision was an early-onset feature in another family, in which affected individuals had a variable combination of cataracts, gastrointestinal dysmotility symptoms, and PN. Other features among all affected individuals were hearing loss, symptoms of autonomic dysfunction, and recurrent pancreatitis. A subclinical PN, sensory-predominant PN, or motor and sensory PN were confirmed by NCS in five individuals. In one patient, sural nerve biopsy revealed loss of myelinated fibres without demyelinating features. Exome sequencing identified heterozygous OPA3 variants in all probands, including a novel missense variant and a known pathogenic mutation. Variant validation and cosegregation analyses were performed by Sanger sequencing. Conclusions: We confirm that dominant OPA3 mutations may be associated with a syndromic form of ADOAC (ADOAC plus) in which axonal PN and gastrointestinal dysmotility symptoms are common clinical features.

References: None.

Keywords: Human Genetics

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Neuropathic Pain and Clinical Characteristics in Charcot-Marie-Tooth Disease Subtypes

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Introduction

Charcot-Marie-Tooth (CMT) disease is inherited neuropathy usually affecting both - motor and sensory peripheral nerves. There are two main CMT disease subtypes - CMT1 (demyelinating form) and CMT2 (axonal form). CMT1 subtype has mutations affecting the PMP22 gene (17p11.2 duplication) and it is the most common subtype of CMT. Few researches focused on pain in CMT, neuropathic pain is an occasional symptom noticed by patients. The goal of our study was to determine neuropathic pain prevalence and clinical characteristics in different CMT subtypes.

Methods

For neuropathic pain assessment the Neuropathic Pain Diagnostic Questionnaire (DN4) was used. CMT neuropathy score (CMTNS) and 6 minutes walking test (6MWT) was used to evaluate clinical characteristics. Data from peripheral nerve conduction study (NCS) for electrophysiological characteristics was evaluated.

Results

In this study data from 53 patients were analysed. There were 32 patients with CMT1A (17p11.2 duplication) and 21 with others CMT subtypes. CMT1A patients tend to be more severely clinically affected (CMTNS 26.5 vs 20.5; 6MWT 290 m vs 365 m (p>0.05). Neuropathic pain was significant more common symptom in group of CMT1A (DN4 18/32 vs 5/21 (p>0.05)).

Conclusions

CMT1A patients have significant more common neuropathic pain than patients with other CMT subtypes. Higher functional disability is more common in patients with neuropathic pain. Further studies are needed to investigate possible pain mechanisms in patients with CMT1A.

References: None.

Keywords: Pain

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Neuropathy-causing mutations in TRPV4 disrupt TRPV4-RhoA interaction and cytoskeletal modulation

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Dominant mutations in the calcium-permeable cation channel TRPV4 (transient receptor potential vanilloid 4) cause two distinct diseases: Charcot-Marie-Tooth disease type 2C, a form of peripheral neuropathy that causes muscle weakness and sensory loss, and various forms of skeletal dysplasia that cause abnormalities of bone development. While prior work has demonstrated that both neuropathy and skeletal dysplasia mutations cause a gain of ion channel function, this finding alone cannot account for tissue-specific toxicity. Importantly, neuropathy-causing mutations cluster within a cytosolic protein-protein interaction domain, suggesting that such interactions are critical to neuropathy pathogenesis. Using proteomics, we identified that TRPV4 functionally interacts with the small GTPase RhoA, which plays a fundamental role in regulating the actin cytoskeleton and in modulating neurite outgrowth. Notably, both wild-type (WT) TRPV4 and skeletal dysplasia TRPV4 mutants are able to bind RhoA, but neuropathy mutations dramatically disrupt RhoA interaction. WT TRPV4 specifically interacts with the inactive, GDP-bound form and inhibits RhoA activation, whereas neuropathy mutant TRPV4 fails to inhibit RhoA. Furthermore, RhoA interaction with WT TRPV4 inhibits ion channel activity in response to environmental and chemical stimuli. Our data also demonstrate that both WT TRPV4 and skeletal dysplasia mutants of TRPV4 promote neurite outgrowth in cultured motor neuron-like cells. In contrast, neuropathy mutant TRPV4 leads to impaired neurite outgrowth, and neurite outgrowth can be restored by pharmacologic inhibition of RhoA activity. Together, our results demonstrate robust reciprocal functional interactions of TRPV4 and RhoA that serve to regulate cytoskeletal dynamics. Furthermore, we show that neuropathy-causing mutations specifically disrupt interactions with RhoA, leading to disinhibition of TRPV4 ion channel activity and dysregulation of RhoA. Thus, disrupted TRPV4-RhoA interaction may represent a specific and fundamental pathologic feature in TRPV4-related neuropathy.

References: None.

Keywords: Human Genetics, Axonal Biology

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Poster 126

Functional Characterization of Human iPSC-derived Motor Neurons with Loss of Neurofilament Light

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Neurofilament light (NEFL) is a gene encoding light chain of neurofilaments, and mutations in this gene cause Charcot-Marie-Tooth disease. We identified a novel homozygous nonsense mutation in NEFL, which is linked to early-onset axonal neuropathy in a Finnish family. To further characterize the mutation, we differentiated patient-derived induced-pluripotent stem cells (iPSC) to spinal motor neurons, and compare them to cells, differentiated from healthy donor iPSCs. We also generated NEFL knockout iPSCs from healthy donors by Crispr/Cas9-based gene editing.

The optimized differentiation protocol resulted in a nearly pure TUJ1+ neural population containing above 90% ISL1/2+ and 30-60% HB9+ motor neuron lineage cells. Neurons from control lines were functionally active, displaying spontaneous cytosolic calcium transients and action potentials with high frequency. All neurons recorded were able to produce repetitive action potentials upon membrane depolarization; and most of the cells exhibited spontaneous synaptic currents, which were blocked by AMPA-type glutamate receptor antagonist CNQX.

Neurons, differentiated from patient iPSCs and NEFL knockout neurons completely lacked NEFL protein, but did not show any structural disease-related phenotype. Loss of NEFL did not affect the initial differentiation into neurons or prevent elaborate neurite networks. The ongoing work is aimed at functional characterization of patient-derived and NEFL knockout motor neurons, using spontaneous calcium transients and action potential generation as readouts for functional maturity of the neurons; and synaptic currents as an indicator of the proper synaptic network formation. The results will hopefully elucidate the functional consequences of NEFL loss in motor neurons.


Keywords: CMTR, Human Genetics, Axonal Biology

Grant Support: This study is funded by the Academy of Finland Center of Excellence on Stem Cell Metabolism and Helsinki University Doctoral School of Biomedicine.
Serum neurofilament light chain is a sensitive biomarker for degeneration of immature SMA motor axons

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Spinal muscular atrophy (SMA) has an unusual clinical course characterized by initial decline and subsequent stabilization. To uncover the pathologies that may account for these observations, we collected and analyzed tissues collected from SMA patients and age-matched controls and SMAΔ7 mice. Ventral roots (VRs) in type I SMA autopsy cases are 2-3 fold smaller and contain 50-75% less myelinated axons compared to age-matched controls. The immature axon marker, GAP43, is robustly expressed in every SMA VR analyzed, but not in the controls. At the EM level, 80% of the total axons in the SMA VRs are retained in polyaxonal pockets, 1-2 microns or less in size and unmyelinated. Degenerating unmyelinated axons takes up 10-20% of the total axons, while less than 5% of the degenerating axons are myelinated ones. Reconstructed EM images of the lumbar level 1 (L1) VR in SMA mice demonstrates significant defects in radial growth (starting at E13.5) and sorting (starting at E17.5). At P1, about 20% of the small unmyelinated axons in SMA are either swollen or atrophied, indicating axonal degeneration. By P2, the total number of L1VR axons in SMA mice is reduced by half with no further loss seen at P14. Serum neurofilament light (NF-L) levels correlated with degeneration of the unmyelinated axons with maximal elevations observed at P1 and P2 in SMA. NF-L levels subsequently declined in both groups but remained modestly elevated in SMA mice. Here we demonstrated markedly impaired axon sorting and radial growth of SMA motor axons that begins embryonically. These immature axons rapidly degenerate in the neonatal period and this is associated with an early onset elevations of NF-L in SMA sera. Together our results show that blood NFL levels may be a sensitive biomarker of early degenerative events in severe SMA infants.

References: None.

Keywords: Axonal Biology, Other, Other, Other, Other

Grant Support: Cure SMA, SMA foundation, NINDS RO1
**Poster 128**

**Small Fibers impairment In Charcot-Marie-Tooth Disease: The Role Of Laser Evoked Potentials.**

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**Introduction** Pain is a common symptom in Charcot-Marie-Tooth (CMT) disease, either nociceptive or neuropathic (NP) in nature. Laser evoked potentials (LEPs) are the most reliable neurophysiological tool for Aδ fibers assessment.

**Purpose** We aim to investigate the small fiber involvement in different CMT through LEPs detection.

**Methods** Forty-six patients with different forms of CMT (19 CMT1A, 11 MPZ-CMT, 12 CMTX, 4 CMT2A) were enrolled. All subjects underwent a complete neurological examination; pain, whether present, was rated with the 11-point Numerical Rating Scale (NRS) and characterized by means of validated questionnaires (Neuropathic Pain Diagnostic Questionnaire -DN4- and Neuropathic Pain Symptoms Inventory -NPSI-). LEPs were recorded after right foot and hand stimulation, and patients' N2-P2 complex amplitude and latency were compared with 46 age-matched control subjects.

**Results** Overall pain prevalence was 34.8%. NP was present in 15.2% of patients with a length-dependent distribution in 85.7% of cases and was significantly more frequent in CMT1A (p<0.001); all descriptors of NP were involved as emerged from NPSI. Prolonged latency of N2-P2 complex from foot stimulation was noted in 11 CMT1A patients (57.9%), 6 of which (63.6%) were asymptomatic. MPZ-CMT patients showed different clinical and neurophysiological phenotypes, strictly dependent on the underlying motor conduction velocity pattern. LEPs results were normal in all but one CMTX patients, but amplitude after foot stimulation was significantly lower in males compared to females (p=0.043). CMT2A patients were NP free and LEPs recordings were all normal. We found a significant association between LEPs alteration and NP (p=0.017).

**Conclusions** NP is frequent in CMT disease and is highly related to Aδ fibers impairment, although different and concomitant mechanisms could be hypothesized. Aδ fibers involvement greatly varies between CMT subtypes and reflects differences in genetic mutations and pathophysiologic mechanisms.

**References:** None.

**Keywords:** Pain, Small Fibers, CMTR

**Grant Support:** None.
Using C. Elegans to model X-linked Charcot-Marie-Tooth (CMTX6) disease.

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Although mutations in more than 85 genes are known to cause Charcot-Marie-Tooth (CMT) neuropathy, the molecular and cellular mechanisms that underlie the pathogenesis of CMT still needs further elucidation. Animal models closely recapitulating pathogenic in vivo events in patients are crucial for investigating mechanisms of axonal degeneration and the development of drug therapies. C. elegans is a 1 mm long nematode with a simple nervous system that comprises of 302 neurons. The short life span along with a “toolbox” of various genetic and molecular assays available makes C. elegans a powerful system for modelling motor and sensory defects caused by CMT mutations. The p.R158H mutation in the pyruvate dehydrogenase kinase 3 (PDK3) gene has been reported by our group to cause an X linked form of CMT (CMTX6). Previously we generated a C. elegans model of CMTX6 overexpressing human wild type (PDK3WT) and mutant PDK3 (PDK3R158H) which demonstrates axonal degeneration. We have recently utilized the CRISP-cas9 system to engineer the p.R158H mutation into the worm ortholog of PDK3, pdkh-2R159H. Using behaviour studies in the PDK3 overexpression, knock-in and null mutants, we demonstrate that synaptic transmission is affected in our CMTX6 animal models. Defective synaptic transmission may lead to loss of signal at the neuromuscular junction resulting in muscle atrophy and neurodegeneration. In addition, we have characterised the effect of PDK3 mutations on the morphology of cholinergic excitatory and GABAergic inhibitory neurons. Further investigation of PDK3 associated synaptic transmission loss will help identify genes and pathways impacted by the mutation that can be targeted for drug development and therapy in CMTX6.

References: None.

Keywords: CMTR

Grant Support: None.
Assessment of neuropathic pain in patients with Charcot-Marie-Tooth disease type 1A

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Introduction: There have been a very few studies that have analyzed characteristics of neuropathic pain in CMT1A patients. Aim of this study was to determine frequency and features of neuropathic pain in CMT1A and to assess the association between neuropathic pain and clinical characteristics of patients.

Methods: Our research included 39 CMT1A patients with a genetically confirmed diagnosis. PainDETECT questionnaire (PD-Q) was used to assess neuropathic pain. The Medical Research Council (MRC) Sum Score, Overall Neuropathy Limitations Scale (ONLS) score, and Beck Depression Inventory were also applied.

Results: Neuropathic pain was present in 16 (41%) patients with CMT1A. The average severity of pain was 5.7±2.1 out of 10. The most sensitive neuropathic symptom was numbness which was present in all patients with neuropathic pain, while the most specific symptom was alldynia that was present in 50% of CMT1A subjects and virtually absent in patients without neuropathic pain. Patients with neuropathic pain were older (p=0.01) and they also had more pronounced disability of the upper extremities than patients without neuropathic pain (p<0.05). Depression was more frequent in patients with neuropathic pain compared to patients without it (56.2% vs. 13.6%, p<0.05).

Conclusions: Neuropathic pain was present in almost half of patients with CMT1A and it was moderate on average. Presence of neuropathic pain was associated with older age, worse functional disability and depression.

References: None.

Keywords: CMTR, Pain

Grant Support: This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (grant #175083 granted to Prof. Vidosava Rakocevic-Stojanovic).
Two families with Charcot-Marie-Tooth-4H due to mutations in FGD4: Broadening the phenotype

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Purpose: We report the clinical features of three patients from two families with CMT4H due to mutations in FGD4 encoding frabin. This will expand our knowledge of the phenotype of this rare disorder.

Patients: One family consists of two sisters of a consanguineous Kuwaiti family with relatively mild neuropathy and homozygous p.Y443X mutations. The 13 year old was found to have neuropathy discovered incidentally when she underwent a genetic evaluation for short stature, markedly reduced weight, pectus carinatum, scoliosis, partial webbing of her fingers and short 4th metatarsals. There were no foot abnormalities and CMT exam score was 4/28. Whole exome sequencing revealed only the p.Y443X mutations, and chromosomal microarray was normal. Her 16 year old sister had cavovarus foot deformities, the right side treated with surgical tendon transfers and osteotomies of the calcaneus and first metatarsal. Median motor velocity was 7 m/sec, ulnar motor velocity was 8 m/sec, with absent sensory responses. The third patient, compound heterozygous for a whole gene deletion and p.R577X, was seen at age 44 but had disease onset at age 11. She had pes cavus, scoliosis, and four previous foot surgeries. Her ulnar motor velocity was 8 m/sec with absent sensory responses. Her CMTNS was 17 indicating moderate dysfunction.

Discussion: Less than twenty families from around the world with CMT4H have been described. Early age of onset, distal weakness and scoliosis are common. Myelin outfoldings have been seen on nerve biopsy. Despite very severe conduction slowing below 10 m/sec the disease severity is mild to moderate in many instances. This striking difference may be unique to this disorder and provide a clue as to the pathophysiology of this disorder. We will review the phenotype of our patients in context of those reported in the literature.


Keywords: CMTR, Human Genetics

Grant Support: None.
Early-onset hereditary motor and sensory neuropathies are rare disorders causing variable degrees of impairment and disability, presenting with high clinical variability, frequent sporadic presentation and genotype-phenotype heterogeneity. Few reports focused on large cohorts of Charcot-Marie-Tooth (CMT) patients in paediatric age. Data from a series of 288 patients, aged 0-17 years, will be reported. On the basis of neurophysiological studies they were classified as affected with demyelinating, axonal, pure motor (HMN) and pure sensory (HSN) forms. Genetic analyses were performed with Sanger sequencing for single genes or through customized gene panels. 70% of cases were affected with demyelinating forms, 20% with axonal, 7% with HMN, 2% with HSN. A definite genetic diagnosis was achieved in 79% of cases. Causative mutations were detected in 88% of patients affected with demyelinating forms, in 57% of axonal, in 35% of HMN and in only 1/6 cases of HSN. Considering the whole series of patients, CMT1A represents the most frequent form (45% of total, 65% of demyelinating forms). The other genetic defects are largely more rare, with mutations in MPZ, MFN2, GDAP1 and GJB1 genes accounting for 6% each, while mutations in other genes were detected in few or single cases. In some children specific clinical features allowed us to address the genetic studies. The analysis of our case series confirms that also in childhood age CMT1A is the most frequent form; the identification of specific genetic defect is reached more frequently in patients affected with demyelinating forms while children with axonal or HMN forms more often still lack a definite genetic diagnosis. Both demyelinating and axonal CMT can be associate with congenital or very early onset. Sporadic, or apparently sporadic presentation is frequent (38%), and makes it difficult to address the molecular analyses towards a rapid diagnosis, crucial for the appropriate familiar counselling.

References: None.

Keywords: CMTR

Grant Support: None.
Objective: To identify the genetic distribution of hereditary motor neuropathies (HMNs) in a large cohort of Chinese patients with Charcot-Marie-Tooth disease (CMT) and evaluate the correlation of the HMNs with the clinical manifestations.

Methods: Next-generation panel testing or whole-exome sequencing was performed in 96 patients with clinically diagnosed HMNs out of 455 patients with CMT between January 2007 and October 2017. We recorded the clinical features, CMT neuropathy scores (CMTNS) and electrophysiological data at diagnosis.

Results: We identified 24 causative mutations in 70 index patients with HMNs (34.3%). If the patients with likely pathogenicity were included, the detection rate was 42.9% (30/70 families). HSPB1 mutations were the most common causative gene mutations in HMNs (10/32, 31.3%), followed by mutations in IGHMBP2 (3/32, 9.4%), GARS (2/32, 6.3%) and BSCL2 (2/32, 6.3%). Some CMT genes (MPZ, SH3TC2, GDAP1) were related to CMT disease (motor-CMT2) with minor sensory involvement. Patients with HMN-plus often had complicated phenotypes and included genes of hereditary spastic paraplegia (HSP), amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) (FUS, KIF5A, KIF1B, ZFYVE26, DNAJB2).

Conclusions: Pure motor neuropathies and motor neuropathies with minor sensory involvement share many genes with CMT. HMN-plus may have a complicated phenotype, and some of the disease-causing genes were shared with ALS. Axonal transport defects and autophagic dysfunction may play a crucial role in the downstream pathogenesis of HMNs.

References: None.

Keywords: CMTR

Grant Support: None.
Charcot-Marie-Tooth disease is an incurable hereditary neurodegenerative disorder characterized by demyelination and/or axonal degeneration of the peripheral motor and sensory neurons. Aminoacyl-tRNA synthetases (ARS) represent the largest cluster of proteins implicated in CMT etiology. These are ubiquitously expressed enzymes involved in the initial step of protein biosynthesis and therefore they are indispensable for cell viability. So far, it remains mysterious how molecular defects in these essential enzymes cause specifically neurodegeneration and lead to dominant forms of neuropathies sharing common symptoms. We aim to investigate whether there is a common toxic pathway triggered by the CMT mutations in ARS. To streamline our studies, we developed new cellular and fly models of CMT induced by four different ARS. To ensure maximal comparability between the vertebrate and invertebrate models, we expressed the same transgenic constructs using a modified GeneSwitch™ technology. This inducible system allows for temporal and spatial modulation of ARS expression levels. After functional and morphological characterization of these new models, we aim to perform proteomics studies deciphering the ARS protein network and its molecular perturbations after induction of the mutant proteins in cellulo and in vivo. The knowledge gained will provide a comprehension towards the pathomechanism underlying ARS CMT causing mutation and might contribute to the development of common treatment strategies for all ARS-linked CMT neuropathies.

References: None.

Keywords: CMTR

Grant Support: None.
Acupuncture Management for Diabetic Neuropathy: A case report

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Introduction: Neuropathies are among the most common of all the long-term complications of diabetes, and it is the most common form of neuropathy in the developed countries of the world, accounts for more hospitalizations than all the other diabetic complications combined[1], and is responsible up to 50% of patients of non-traumatic amputations[2]. It is defined as damage to peripheral nervous system and caused by a primary lesion or dysfunction[3]. Recently acupuncture is beneficial for management of neuropathic pain. Here, we reported a case report of acupuncture management for diabetic neuropathy.

Methods: Thirty patients diagnosed with diabetic neuropathy patients were observed. Used acu points were LR4, LU5, LI11, KI27, ST 36, GB34, SP6, Sp9, and LI4. The acupuncture needles (sterilised single-use stainless steel needle, size: 0.3X40mm; Hansol Medical Co. Reg. No.:141024) were punctured into the muscle layer, the acupuncture needles were kept in place for 20 minutes. Patients received acupuncture management three times per week, during four months. Clinical outcomes were measured by visual analogue scale, clinical signs and symptoms, and Hamilton anxiety rating scale (HAM-A).

Results: Thirty patients indicated improvement on the visual analogue scale, and its clinical signs and symptoms, also Hamilton anxiety rating scale (HAM-A). Conclusion: This case report describes the patients on acupuncture management of diabetic neuropathy experienced positive clinical outcomes during four months acupuncture treatments. Further studies need to be carried out on a larger sample size, with better designs for validation, and evidence-based scientific mechanisms.


Keywords: Diabetes, Pain

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Multimodal Assessment Of Intensive Care Unit-Acquired Weakness (ICU-AW) In Severe Acute Stroke Patients

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Purpose: Intensive care unit-acquired weakness (ICU-AW) is an acute neuromuscular impairment that occurs in approximately 40% of critically ill patients (1,2), and associated with delayed weaning, longer ICU and hospital stays, higher mortality (3,4,5). In this study, we aim to investigate the frequency of ICU-AW in severe stroke patients in neurological ICU, and diagnostic correlations between electrophysiological studies and muscle biopsy. Methods: All stroke patients followed in our intensive care unit, with NIHSS ≥16 and a life expectancy longer than three weeks, without any known neuromuscular disease were included. The baseline unilateral electrophysiological (EP) studies and bioimpedance analysis (BIA) were evaluated within the first 72 hours of admission, and afterward with an interval of 3-5 days. Muscle biopsy was performed in patients whose EP studies revealed critical illness myopathy. Results: Fourteen patients met the inclusion criteria. Three patients refused to participate in the study, and 3 were excluded due to the presence of neuropathy in basal electrophysiological studies. Thus, eight patients were included. The mean age was 81.87 and seven patients were female. Myopathy developed in two and neuromyopathy developed in one patient almost within one month (31st-33rd days). Peroneal and ulnar nerve CMAP and sural nerve SNAP amplitudes were the most affected parameters. The baseline phase angle values were below 4.5⁰ in all and continued to decrease during follow-up BIA tests. Muscle biopsy was performed in 2 patients. Type 2 muscle fiber atrophy was seen in accordance with critical illness myopathy. Inflammatory infiltrate or mitochondrial damage was not observed. Conclusions: Intensive care unit-acquired weakness developed in three of 8 patients within one month. Our preliminary findings suggest that the percent of the decrease in CMAP and SNAP amplitudes were associated with the degree of type 2 fiber atrophy and the decrease in phase angle values.


Keywords: Other

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Dose-dependent Chemotherapy-induced peripheral autonomic neuropathy: acute injury and slow recovery

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Most chemotherapy-induced peripheral neuropathy (CIPN) studies preferentially focus on sensory fiber loss and dysfunction. Here, we compared the structural and functional recovery of autonomic fibers in sweat glands (SGNFD) and sensory fibers (IENFD) in mouse footpads after exposure to a maximum tolerated dose (MTD) of several common chemotherapy agents. Additionally, we assessed footpad sweat production as a functional correlate to SGNFD reductions. Female Balb-c mice were treated with a MTD of four anti-tubulin agents: paclitaxel (PCA), ixabepilone, eribuline, vinorelbine, or corresponding placebo given intravenously over a two weeks (MWF dosing) period. Recovery was assessed at 7 post-treatment time points: 24hr, 1, 2, 4, 8, 12 and 24 weeks post chemotherapy exposure. Footpads were processed to visualize epidermal and sweat gland nerve fibers using PGP9.5 and TH. All four agents resulted in comparable or more severe loss of SGNFD compared to IENFD, and SGNFD was slower to recover than IENFD with PCA-treated animals showing the most severe and persistent changes. The dose-dependent and functional study on autonomic nerves was performed on Male Bl6 mice, treated (i.p) with PCA at doses of 10, 20, 25, 30 and 50 mg/kg. Sweat droplet formation (autonomic) and hot plate paw withdrawal (sensory) function was assessed at 24hr, 1 and 2 weeks following the last dose. Footpad sweat droplet number remained significantly reduced from baseline at 2 weeks while paw withdrawal normalized at 2-weeks. Together, these data indicate that in mouse models of CIPN, autonomic nerve fiber structure and function are affected to a greater degree than sensory nerve fibers, and recover more slowly. Autonomic dysfunction may be an important and under-appreciated consequence of chemotherapy exposure.

References: None.

Keywords: Axonal Regeneration, Small Fibers

Grant Support: None.
Quantitative gait analysis in patients with diabetic polyneuropathy

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Neuropathic pain, sensory loss, and distal motor weakness are the main symptoms of diabetic polyneuropathy. Gait disturbance is also commonly observed in patients with diabetic polyneuropathy, especially as a form of sensory ataxia. However, the studies to quantitatively analyze gait in patients with diabetic polyneuropathy using several infrared cameras were few. The object of this study is to quantify the gait in patients with diabetic polyneuropathy and to determine the association between clinical and electrophysiological parameters and gait parameters.

Forty-seven patients with diabetic polyneuropathy were enrolled in this study. Diabetic polyneuropathy was clinically assessed by with Toronto clinical scoring system (TCSS). All enrolled patients underwent nerve conduction study and quantitative gait analysis using 3-dimensional motion analysis system. The correlation of various gait parameters according to TCSS, compound muscle action potential of the peroneal nerve (A-CMAP), and sensory nerve action potential of the sural nerve (A-SNAP) were analyzed.

Decreased step length and stride length were associated with increased TCSS. Increased stance phase and decreased step length, stride length and walking speed were associated with decreased A-CMAP. Increased anterio-posterior range of motion was also associated with decreased A-SNAP.

Gait parameters associated with decreased motor electrophysiological parameter were stance phase, step and stride lengths and walking speed, on the other hand, gait parameter associated with decreased sensory electrophysiological parameter was anterior-posterior range of motion which is associated with postural stability. Various quantitative gait parameters can be used in assessing neurological status in patients with diabetic polyneuropathy.

References: None.

Keywords: Diabetes

Grant Support: None.
Regeneration can occur in the peripheral nervous system after injury, but the mechanisms that underlie this process have not been fully determined. We have previously demonstrated the involvement of macrophages acting in peripheral ganglia in the enhanced regeneration that occurs in sensory and sympathetic neurons after a conditioning lesion (CL). Oncomodulin (Ocm) has been proposed as a macrophage and neutrophil secreted pro-regenerative molecule that stimulates optic nerve regeneration following inflammation in the eye. We have utilized an Ocm knockout (KO) mouse strain to investigate whether Ocm plays a role in the CL response in sensory neurons after sciatic nerve injury. First, we measured neurite outgrowth in cells maintained in dissociated culture after a CL. A robust increase in neurite outgrowth was seen in neurons from both wild type (WT) and Ocm KO mice after a CL. Next, we examined the CL response in explanted ganglia. Increased neurite outgrowth following a CL was seen in explants from both WT and KO mice; however, the magnitude of the effect was significantly smaller in the explants from KO animals. Finally, we examined the CL effect in vivo measured in response to a sciatic nerve crush. A CL response was seen in WT animals but not in KO animals. Flow cytometry studies measuring macrophage number in dissociated culture, explant culture, and DRG in vivo, demonstrated that the Ocm-dependent deficit in regeneration is seen only under experimental conditions in which a significant number of macrophages are present. To begin to determine how Ocm influences regeneration, Il-6 mRNA was measured in axotomized DRG from WT and Ocm KO animals where increased levels were significantly higher in ganglia from WT animals. Thus, our data shows that Ocm is necessary for the conditioning lesion response in vivo and may act to support regeneration through IL-6.

References: None.

Keywords: Axonal Regeneration, Inflammatory

Grant Support: None.
Aberrant DEGS1 activity alters sphingolipid metabolism and causes leukodystrophy and axonal degeneration

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BACKGROUND:

Sphingolipids are important components of cellular membranes and functionally associated with fundamental processes such as cell differentiation, neuronal signaling and myelin sheath formation. Defects in the synthesis or degradation of sphingolipids lead to various neurological pathologies, however, the entire spectrum of sphingolipid metabolism disorders is still elusive.

RESULTS:

By whole-exome sequencing in a patient with a multisystem neurological disorder of both the central and peripheral nervous system, we identified a homozygous p.(Ala280Val) variant in DEGS1, which catalyzes the last step in the ceramide synthesis pathway. The blood sphingolipid profile in the patient showed a significant increase in dihydro sphingolipid species which was further recapitulated in patient-derived fibroblasts, in CRISPR/Cas9-derived DEGS1 knockout cells, and by pharmacological inhibition of DEGS1. The enzymatic activity in patient fibroblasts was reduced by 80% compared to wild type cells which was in line with a reduced expression of mutant DEGS1 protein. Moreover, an atypical and potentially neurotoxic sphingosine isomer was identified in patient plasma and in cells expressing mutant DEGS1.

CONCLUSION:

We report DEGS1 dysfunction as a novel sphingolipid disorder with hypomyelination and degeneration of both the central and peripheral nervous system.


Keywords: Metabolic, Human Genetics, Schwann Cell, Axonal Biology, Small Fibers

Grant Support: None.
Poster 141

Sensory nerve conduction studies in ALS patients: a retrospective study

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Introduction: This retrospective research study aimed to evaluate abnormalities in the sensory nerve conduction studies in patients with ALS.

Methods: The results of the routine sensory nerve conduction studies (median, ulnar, superficial peroneal and sural nerve) of 104 patients with clinically definitive or probable ALS according to the El Escorial classification criteria (61.5±10.7 years) were compared to the results of 120 age-matched controls (58.6±11.7 years) suffering from radiculopathy (control subgroup A, n=63), myopathy or myasthenia gravis (control subgroup B, n=57). Patients with concomitant reasons for sensory polyneuropathy or with severe malnutrition were excluded from the study. According to results all patients were classified in three subgroups: one with normal values, one with abnormal findings in only one nerve and a one with abnormal findings in two or more nerves.

Results: 17.3% (median age 58.5, range 34-76 years) of the ALS patients had abnormal sensory nerve conduction studies in two or more nerves, compared to 24.2% (median age 67, range 45-80 years) of patients in the control group. Abnormal findings in one nerve was detected in 16.3% of ALS patients compared to 22.5 % of patients in the control group.

There was no statistically significant difference in the percentage of pathological findings in the ALS patients versus controls (Chi square= 3.9, p=0.14, K: 0.13). The statistical comparison between the ALS patients and the two control subgroups provided same result (Chi square= 6.9, p=0.92).

Conclusion: A significant higher percentage of abnormal sensory nerve conduction studies in ALS patients could not be proved in this study.

References: None.

Keywords: Other

Grant Support: None.
Electrophysiological Findings in Critical Illness Neuropathy

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About 80% of patients admitted to intensive care unit (ICU) develop ICU acquired weakness (ICUAW). Critical illness neuropathy (CIN) is part of the ICUAW, a source of disability associated with debilitating outcomes. Significant knowledge gaps exist concerning CIN incidence, neurophysiological patterns and the impact in the neurorehabilitation setting. The aims of this study are to assess the occurrence of CIN, its electrophysiological patterns and rehabilitative outcomes in a series of severe brain-injured patients.

We enrolled 52 consecutive critically ill patients (male/female: 44/8; mean age: 51.6±19.0 years) treated for at least seven days in ICU without any previous known cause of neuropathy. Extensive electrophysiological investigation was performed. Rehabilitative outcome was assessed through 2 measures: the gain of the Functional Independence Measure (FIM) score at end of the treatment (ΔFIM = FIM at discharge – FIM at admission) and the rehabilitation length of stay (RLoS).

In 63.5% of patients, a diagnosis of CIN was achieved, while in the remaining 36.5% (no-CIN group) a diagnosis of single/multiple mononeuropathies (16.9%) or normal neurophysiological findings (19.6%) were found. Among the CIN patients, we identified three electrophysiological patterns: A) generalized sensory-motor neuropathy (75.7%); B) lower limb sensory-motor neuropathy (14.8%) and C) generalized motor neuropathy (9.5%). Most of the mononeuropathies were due to nerve entrapment (ulnar and peroneal nerves most involved). The ΔFIM was 20.4±20.6 for CIN patients and 50.1±31.3 for no-CIN patients (p=0.0007), RLoS was 191.5±97.0 days for CIN patients and 100.0±58.3 days for no-CIN patients (p=0.0002).

Peripheral nervous system damage is very common in patients with history of ICU hospitalisation admitted in rehabilitative setting. CIN is a spectrum of different electrophysiological patterns with axonal, sensori-motor, length-dependent polyneuropathy as the most common one. Entrapment neuropathies represent a frequent finding. The presence of CIN is associated with a worst functional outcome and a delayed discharge of patients.


Keywords: Metabolic, Axonal Biology, Inflammatory

Grant Support: None
Ischiofemoral impingement syndrome provoked by childbirth: an unusual case of a severe sciatic mononeuropathy

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Post-partum neuropathy is a recognized complication of childbirth occurring in up to 1% of deliveries. Risk factors include nulliparity and prolonged second stage of labor. While the femoral nerve is the most commonly involved, post-partum sciatic mononeuropathy has been rarely described without clear description of underlying mechanisms.

A 29 year-old Caucasian multiparous woman (gravida 4 para 2) presented with acute onset left lower limb weakness following the spontaneous vaginal delivery of twins. The second stage of her labor was 39 minutes. She had a routine uncomplicated epidural anaesthesia. When the anesthesia started to wear off, she noted she had no movement in her left foot associated with tingling and numbness. Examination revealed 0/5 strength in sciatic-innervated muscles and decreased pinprick sensation in the foot most severe in the superficial peroneal distribution. Day 13 following her presentation, nerve conduction studies/EMG demonstrated a severe acute left sciatic neuropathy with increased insertional activity, no fibrillation potentials and no activated motor unit potentials in all the left sciatic-innervated muscles. An MRI of the lumbar spine was normal. A lumbosacral plexus MRI showed flattening of the sciatic nerve as it passed through the ischiofemoral space, with mild edema of the quadratis femoris and T2 hyperintensity immediately distal to the sciatic notch. The space itself was noted to be tight (measuring at 8mm).

Ischiofemoral impingement syndrome is defined as a decreased ischiofemoral and quadratis femoris space affecting the contents within. As seen with our case, quadratis femoris muscle edema is prototypical. While patients usually present with chronic non-specific pain in the deep gluteal region, our patient had acute sciatic nerve compression in the ischiofemoral space during childbirth. Women with baseline tight ischiofemoral space may be at risk of postpartum sciatic nerve injury. Twin pregnancy and positioning during labor likely represent additional risk factors.

References: None.

Keywords: Axonal Regeneration

Grant Support: None.
Autophagy inhibition affects from the spinal cord level which induces symptom change in PIPN mouse

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Background: Paclitaxel is a widely applied chemotherapeutic drug but neuropathic pain is a troublesome complication during treatment. Autophagic regulation has been proposed to alleviate neuropathic pain in chronic constriction injury model but the alteration of autophagy has not been studied in the paclitaxel-induced peripheral neuropathy (PIPN) mouse model.

Method: LC3 GFP-RFP mouse were administered with paclitaxel 16mg/kg 3 times/weekly for 4 weeks. Autophagy inhibition with 3-methyladenine (3MA) was done at 30 mg/kg, 30 minutes before the paclitaxel injection.

Result: Four groups in this study were injected with vehicle (group 1), 3MA (group 2) paclitaxel only (group 3), 3MA with paclitaxel (group 4). A marked reduction of the mean mechanical withdrawal threshold was observed by manual von Frey test after 4 weeks of paclitaxel injection (group 1 vs. group 2; group 1 vs. group 3; group 1 vs. group 4; group 2 vs. group 3; and group 2 vs. group 4, all P < 0.0001, respectively) but there was no statistical difference between group 3 and 4. By catwalk gait analysis, showed distinctive change in group 1 vs. group 3 and group 3 vs. group 4, especially in terms of single stands and step cycles in front and hind paws; initial dual stance in front paws; and body speed in hind paws. All these parameters which changed after paclitaxel injection showed reversal of changes when paclitaxel was injected in 3MA injected animals. Western blot of p62 showed a markedly increased level in spinal cord and sciatic nerve but not DRG in group 2, 3 and 4.

Conclusion: Suppression of autophagic activity alleviated symptom in PIPN mouse model which was observed to be the consequence affecting the spinal cord and sciatic nerve level but not DRG. Regulation of autophagy could be a therapeutic target for paclitaxel-induced peripheral neuropathy.

References: None.

Keywords: Pre-clinical Studies, Metabolic

Grant Support: This work was supported by the Korean National Research Fund (NRF-2017R1C1B5014853).
Objective: Peripheral neuropathy (PN) is one of the major microvascular complications of diabetes, affecting >50% of diabetic patients. While the pathophysiology remains unclear, recent evidence has linked obesity and pre-diabetes to PN risk prior to development of overt hyperglycemia. We utilised a translationally relevant rodent model of obesity to examine early changes in peripheral nerve electrophysiology.

Methods: Thirty adult male Sprague-Dawley rats were randomised to control (n=15) or cafeteria style (n=15) diet (pre-diabetes). After 12 weeks of diet, nerve conduction studies were undertaken in caudal (sensory) and tibial (motor) nerves. Nerve excitability, an indirect measure of ion channel function and membrane potential, was undertaken in the tibial nerve. Body composition, fasting blood glucose (FBG), triglycerides and HDL cholesterol were measured 1 week later prior to intra-peritoneal glucose tolerance test (ip-GTT). Fasting plasma insulin, IL-1β and IL-6 were measured by ELISA at cull (15 weeks of diet).

Results: The pre-diabetes group had significantly higher body weight, FBG, fasting insulin and adiposity. Pre-diabetic rats also showed dyslipidemia (higher triglycerides and lower HDL cholesterol), impaired glucose tolerance, insulin resistance (HOMA-IR) and increased IL-1β (all \(p<0.05\) although IL-6 remain unchanged. Standard nerve conduction parameters including amplitude and latency of motor or sensory nerves were not different between groups. However, nerve excitability measures demonstrated a significant difference in superexcitability (control: 2.18±0.77 [SEM], pre-diabetic: -0.54±0.64; \(p<0.05\)), which was significantly positively correlated with fasting HDL and body composition (\(rs>0.4; p<0.05\)). This suggests abnormal fast potassium conductances at the node of Ranvier. While sensory nerve amplitudes did not differ between groups, there was a significant negative correlation between FBG and sensory amplitudes (\(r=-0.48; p=0.008\)).

Conclusion: This dietary pre-diabetes model demonstrates dyslipidemia, metabolic impairment, elevated IL-1β and changes in peripheral nerve function, thus providing a platform to investigate pathophysiological mechanisms and relationships between metabolic parameters and peripheral nerve damage.

References: None

Keywords: Diabetes, Metabolic, Inflammatory, Pre-clinical Studies, Axonal Biology

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Poster 146

Caloric Restriction Improves Peripheral Nerve Function and Glucose Tolerance in Diet-Induced Obese Mice

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Common diabetic complications like diabetic peripheral neuropathy (DPN) are becoming more prevalent with rising rates of obesity and diabetes. Tight glucose control is the only available treatment for DPN, but it does little to alleviate symptoms in patients with Type 2 diabetes. Lifestyle interventions such as diet and exercise are potential alternative therapeutics.

In diet-induced obese mice, changing the diet from 60% lard-based high fat chow to 12% corn oil-based chow (dietary reversal) completely reverses DPN and ameliorates the diabetic phenotype. However, it is unclear if these positive effects result from changes in diet composition or from decreased caloric intake. Therefore, this study aims to determine if caloric restriction alone improves DPN.

We fed male C57BL/6 mice a 60% lard-based high fat diet (HFD; n=16) or a standard 12% corn oil-based control diet (n=8) ad libitum until 18 weeks of age (wks). At this point, 8 HFD mice were placed on caloric restriction (CR), limited to 40% of food consumed by paired HFD controls. Neuropathy phenotyping was measured by sural and sciatic motor nerve conduction velocities (NCVs) at baseline (15 wks) and terminal (26 wks) time points. Baseline and terminal metabolic phenotyping was assessed by insulin and glucose responses to intraperitoneal glucose tolerance testing.

Following 8 weeks of caloric restriction, mice demonstrated improvement in their metabolic phenotype and partial restoration of their neuropathy phenotype. Terminal insulin and glucose area under the curve were significantly higher for HFD compared to CR and control mice. NCVs significantly improved from baseline to terminal for CR mice but remained significantly lower than controls. These data indicate that caloric restriction alone appears to partially restore peripheral nerve function and improve metabolic phenotype in diet-induced obese mice, but further studies are needed to fully differentiate the effects of caloric restriction versus dietary reversal on DPN.

References: None.

Keywords: Diabetes

Grant Support: None.
Poster 147

Bilateral abducens palsy associated with anti-GQ1b antibody: A single center experience

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Introduction

Anti-GQ1b antibody is known to be associated with acute ophthalmoplegia without ataxia which is an atypical form of Miller Fisher syndrome. We evaluated clinical features and antiganglioside antibody profile of bilateral abducens palsy.

Methods

We retrospectively reviewed bilateral abducens palsy patients from 2016 to 2018. Those caused by structural lesions or increased intracranial pressure were excluded. Four patients were identified and their medical records were reviewed. Antiganglioside antibodies tests were done by enzyme-linked immunosorbent assay.

Results

Patient 1 and 2 were positive to antiganglioside antibodies (Pt 1: IgM GT1a (1+), IgM GQ1b (1+), IgG GQ1b (1+); Pt2: IgG GQ1b (2+)). Each age was 25 and 18 years old. Both were male and had a history of antecedent infection. Only patient 2 had areflexia and both did not show ataxia. Albuminocytologic dissociation was not observed. Ophthalmoplegia of patient 1 was fully recovered in 1 month after intravenous immunoglobulin infusion. Patient 3 and 4 were negative to antiganglioside antibodies. Clinical features, such as young age (24 and 17 years old), absence of albuminocytologic dissociation, ataxia, and favorable outcome, were similar to those of antibody-positive patients. Patient 4 had generalized ataxia and both did not have antecedent infection.

Conclusions

Patients of bilateral abducens palsy type acute ophthalmoplegia showed young age of onset and favorable outcome. Clinical features were not significantly different according to the presence of antibody except antecedent infection.

References: None.

Keywords: Inflammatory

Grant Support: None.
Reliability of Resynthesis technique to identify proximal conduction block: A series of 20 cases.

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Background: Detection of conduction block (CB) in generalized neuropathies is mainly associated to conditions susceptible to a variety of immunological treatments. However, routine nerve conduction studies (NCS) are not effective to identify a proximally located CB, frequently resulting in wrong diagnosis and unappropriated treatments. Furthermore, many patients are treated based on the presumption of a hidden CB that may not exist. Both situations should be avoided. Several techniques may be used to identify these proximal CB, including spinal root stimulation, triple stimulation and magnetic stimulation. Resynthesis is a technique that compares the summation of volitional evoked MUAP to the distal electrical evoked CMAP, aiming to identify a CB proximal to the stimulus. Additionally, in patients with few motor units we may try to evoke electrically MUAPs that are not evoked voluntarily. Purpose: To analyze the effectivity of Resynthesis to detect CB. Methods: We describe a series of 20 patients in whom Resynthesis was applied. Initially we applied the technique to check if it was effective to identify a CB that had already been demonstrated by routine techniques. Subsequently, we evaluated the response to therapy of patients that were treated based on the existence of a CB detected only by Resynthesis. Results: Resynthesis technique was effective to demonstrate the existence of CB in 13 patients already known to have CB by routine NCS. In 7 patients CB was identified only by Resynthesis at first. Six received the diagnosis of Multifocal Motor Neuropathy and one of CIDP. Six (85%) of them had clinical improvement after treatment and five (71%) had neurophysiologic improvement. In addition, two (25%) posteriorly developed CB on routine NCS. Conclusion: Resynthesis seems to be a useful technique to apply on clinical practice. It may be helpful in order to select candidates for immunotherapy based on detection of proximal CB.


Keywords: Inflammatory, Node, Other, Other

Grant Support: FAEPA, INCT Translational Medicine
Clinical Subtypes And Anti-Glycolipid Antibodies In Chronic Inflammatory Demyelinating Polyneuropathy

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is classified into either typical or atypical CIDP. Characteristics of electrophysiological findings and treatment responses are different between typical and atypical CIDP, indicating varied pathogenetic mechanisms. Herein, we focused on the association between clinical subtypes and anti-glycolipid antibodies in CIDP. We retrospectively collected clinical features of CIDP patients for whom IgM and IgG antibodies to 10 glycolipids (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b, Gal-C, and LM1) were examined in 2015 and investigated the association between clinical subtypes and those antibodies. Clinical information including subtypes could be obtained in 146 patients with CIDP. Of the 146 patients, 103 (71%) were classified as typical CIDP, 14 (10%) as distal acquired demyelinating symmetric (DADS) neuropathy, 14 (10%) as multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy, 6 (4%) as pure motor neuropathy, 5 (3%) as pure sensory neuropathy, and 3 (2%) as focal neuropathy. Among IgM antibodies, anti-GM1 antibody was most common (27/146, 18%), whereas anti-LM1 antibody was the most frequently observed IgG antibody (8/146, 5%). While anti-GM1 IgM antibody was detected in various clinical subtypes, anti-LM1 IgG antibody was detected in 7 patients with typical CIDP and one with DADS. Additionally, IgG anti-LM1 antibodies belonged to IgG3. The frequency of each subtype of CIDP in the present series is almost the same as described in the previous reports. IgG antibodies to LM1, which is localized in the human peripheral nerve myelin, were detected in predominantly typical CIDP. Because IgG3 antibodies can cause complement activation, anti-LM1 IgG antibodies may be involved in the complement-mediated demyelinating mechanisms in typical CIDP.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 150

Usefulness of subperineurial edema and C5b9 deposition in sural nerves for predicting treatment response

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Introduction

Subperineurial edema (SPE) is easily identified on sural nerve biopsies, and has been described to be associated with various etiologies, including inflammatory neuropathies. We investigated the clinico-pathologic features associated with SPE, and other histopathologic markers of treatment response.

Methods

We compared the patient and pathologic data of 68 sural nerve biopsies showing SPE with 33 biopsies showing axonal loss alone.

Results

More patients with SPE on their biopsies responded to treatment compared to patients with axonal loss alone (p<0.01), even when they had symmetric axonal neuropathies (p<0.05). More patients with SPE had symptom duration of ≤ 12 months prior to biopsy (p<0.01). SPE was more commonly associated with other histopathological markers of immune-mediated neuropathies (differential fascicular loss, p<0.05, alkaline phosphatase staining, p<0.05) and evidence of Wallerian degeneration (p<0.01). Other than inflammatory neuropathies, final diagnoses of patients with SPE on their biopsies included motor neuronopathy/motor neuron disease (n=4), Friedrich’s ataxia (n=1), and cerebellar syndrome associated with autoimmune encephalitis (n=1).

Treatment response was more likely if the nerve biopsy showed CD4 cells (p<0.05), and abnormal endoneurial or perineurial vessels (p<0.01). Patients with both SPE and microvascular C5b-9 deposition on biopsy were more likely to respond to treatment than those with SPE alone. More biopsies with C5b-9 deposition were also associated with other markers of immune-mediated neuropathies (abnormal alkaline phosphatase staining and CD4 cell foci, p<0.01). In patients with biopsies without SPE, more responded to treatment if their biopsies showed C5b-9 deposition and abnormal blood vessels (p<0.05).

There was no significant correlation of symptom duration prior to biopsy with treatment-response. Patients with microvascular C5b-9 deposition were more likely to be diabetic (p<0.05).

Conclusion

SPE and microvascular C5b-9 deposition, a probable marker of humoral immunity, may predict treatment response, even in symmetric axonal neuropathies.


Keywords: Inflammatory, Diabetes

Grant Support: Washington University Neuromuscular Research Fund
The aim of our study was to determine the usefulness of MR neurography (MRN) in the differential diagnosis of demyelinating neuropathies. Eight patients with chronic inflammatory demyelinating polyneuropathy (CIDP), five with multifocal motor neuropathy (MMN), and three with Charcot–Marie–Tooth disease (CMT) were included in this study. Mean patient age was 56.5 years (range, 41-81 years) in the CIDP group, 57.0 years (range, 45-72 years) in the MMN group, and 46.3 years (range, 33-67 years) in the CMT group. Brachial plexus MRN by using three-dimensional nerve-SHeath signal increased with INKed rest-tissue RARE Imaging (3D-SHINKEI), which was performed to measure nerve root diameter (NRD) at 15-mm distal from the dorsal root ganglion. Mean NRD was enlarged in all groups which the normal range has been reported as 3.39±0.80 mm according to a previous study using short inversion tau recovery imaging on MRI. CIDP group tended to have larger NRD value (5.4±1.7 mm) than in the MMN group (3.9±0.77 mm), but the difference was not significant. Mean NRD was 4.6±0.61 mm in the CMT group. With regard to CIDP subtype, NRD enlargement was prominent in NF-155-positive cases, moderate in multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy cases, and mild in typical CIDP cases. NRD was not related to disease duration; moreover, NRD showed negative association with age in the CIDP group probably due to the higher frequency of NF-155-positive cases in the younger population. In conclusion, enlarged NRD in CIDP, especially in NF-155-positive cases, was an important factor but did not influence definitive differential diagnosis from CMT. Moderate enlargement of NRD in MADSAM neuropathy cases could be a contributing factor to differentiate cases of dominant motor presentation from those of MMN.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
A case of Lewis-Sumner syndrome mimicking vasculitic neuropathy

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Lewis-Sumner syndrome (LSS), which is also called multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), is a rare disease characterized by asymmetrical and multifocal mononeuropathy commonly located in the upper limbs [1]. LSS is considered as one of the phenotypic variants of chronic inflammatory demyelinating polyradiculoneuropathy [2]. In this paper, we report a case of LSS which initially presented like vasculitic neuropathy. A 57-year-old woman visited our emergency room with weakness and tingling sense of left arm which had rapidly progressed from distal to proximal part within a few hours. She also presented with a two-week period of both calf pain with rash. Neurological examination revealed left upper extremity weakness which was more severe in distal part. All modalities of sensation were decreased on the left arm. Nerve conduction studies (NCS) demonstrated demyelinating sensorimotor neuropathy with conduction block between the elbow-axilla segment of the left median nerve and sensory nerve action potential showed reduced amplitude in the left median nerve. Her left posterior tibial nerve showed no potential and both peroneal nerves showed reduced compound muscle action potential amplitude. Cerebrospinal fluid examination showed normal findings. Antiganglioside antibodies were all negative including anti-GM1 antibodies. Other systemic vasculitis studies were all negative and the computed tomography angiography of four extremities showed no evidence of vasculitis. On the diagnosis of MADSAM, she was treated with intravenous immunoglobulin (IVIG) for 5 days and showed improvement of her weakness and sensory symptoms. At initial presentation, vasculitic neuropathy was considered. The upper arm weakness with both legs’ pain and rash were compatible with vasculitis. However, NCS revealed definite conduction block and sensory involvement, which led to the diagnosis of MADSAM. So we suggest that IVIG can be treatment of choice when NCS findings are compatible with MADSAM, even though the patients show clinically vasculitic manifestation.


Keywords: Inflammatory, Pain, Other

Grant Support: None.
Poster 153

GBS- Getting Better Slowly and Growing Back Slowly; Do Not Give Up too Early!

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A 59-year-old gentleman, with preceding diarrhoea, presented with rapidly progressive quadriplegia over 2 days. Serum anti-GM1 IgG was raised. Acute Motor Axonal Neuropathy (AMAN) subtype of Guillain-Barré syndrome (GBS) was diagnosed. He received 2 gm/kg of intravenous immunoglobulins. At day 3 of admission, Modified Erasmus GBS outcome score (MEGOS) was 11, Erasmus Guillain-Barré syndrome Respiratory Insufficiency Score (EGRIS) 7; GBS Disability score (GDS) 5. At Day 5, which was the nadir of weakness, MRC sum score was 0. He was intubated and stayed in the intensive care ward for 9 days. Nerve conduction study at 3 and 10 weeks showed inexcitable motor nerves. Sensory studies were normal. Microbiologic evaluation suggested recent exposure to Zika virus. Besides respiratory failure his clinical course was complicated by pneumonia and deep venous thrombosis. He stayed in acute hospital for 30 days and thereafter underwent in-patient rehabilitation for 9 months. At 3 months and 6 months GDS remained 4 while MRC sum scores were 6 and 14 respectively. GDS improved to 3 at 10 months and 2 at 13 months. He now walks with use of ankle-foot orthoses. Poor prognostic scores and marked impairment should not deter patients and physicians from persevering with prolonged intensive physical therapy. The expertise and finances needed to “Get Better Slowly” are unfortunately not available uniformly throughout the world. This and the morbidity associated with severe sustained disability underline the importance of finding better treatment to augment the effects of IVIg and plasma exchange for patients with severe GBS.

References: None.

Keywords: Inflammatory, Axonal Regeneration, Schwann Cell, Node, Node Biology

Grant Support: None.
Fatigue accounts for an important residual symptoms experienced by patients with Guillain-Barré syndrome (GBS). This can surprisingly persist for many years of disease onset and lead to tremendous impairment of daily life and social activities. We investigated overall burden and factors associated with fatigue after one year of disease using one of the largest GBS cohorts from developing countries. We have included 147 GBS patients from Dhaka, Bangladesh based on the availability of data after one year of disease onset. Fatigue was assessed using Fatigue Severity Scale (FSS). An average score ≥4 was used to indicate fatigue, and ≥5 for severe fatigue. Associations of different factors with fatigue were tested using Fisher’s exact test or χ² test. Among 147 patients, 65% were male; median age 28 years. After one year, fatigue and severe fatigue was reported by 8% and 14% patients respectively. Fatigue interfered with physical functioning in 23% patients; 15% reported fatigue as one of the three most disabling symptoms. Fatigue was found significantly higher among females (35% vs. 15%; p=0.004). No significant associations were found between fatigue and age, disease severity, antecedent infections and serology, GBS subgroups or treatment. Fatigue was found significantly higher among patients with incomplete physical recovery measured by GBS Disability Score (36% among GBS-DS=2 and 64% among GBS-DS=3; p<0.001) and MRC score (75% and 17% patients with MRC 21-40 and 41-60 respectively; p<0.001). Fatigue was found significantly higher (78%) among patients having moderate anxiety/depression (self reported EQ-5D) compared to mild or no anxiety/depression (34% and 2% respectively; p<0.001). Fatigue as a residual complication of GBS was reported much lower among Bangladeshi GBS patients compared to developed countries (40-60%). However, more rigorous studies are needed to reconfirm the findings and develop integrative management of fatigue for GBS patients in developing counties.

References: None.

Keywords: Inflammatory, Other

Grant Support: None.
Guillain-Barré syndrome (GBS) is the commonest cause of acute flaccid paralysis in Vietnam. Neurological deficits reach a nadir generally within 3 weeks and do not progress beyond 4 weeks. However, marked deterioration following a period of stabilization, usually after immune therapy, can occur. A forty-six-year-old man presented to a tertiary hospital at Ho Chi Minh City with a one-week history of progressive weakness and numbness of all four limbs. He had no antecedent infection symptoms. Clinical and electrodiagnostic features suggested acute inflammatory demyelinating polyneuropathy. At day 5, which was the nadir of weakness, Medical Research Council (MRC) sum score was 42 and GBS Disability score (GDS) was 3. His weakness and numbness improved after seven cycles of plasma exchange; MRC sum score 48 and GBS GDS 2. Three days later his condition worsened; MRC sum score 18 and GDS 5. He required mechanical ventilation. Intravenous immune globulin was administered; and the managing physician added methylprednisolone. He recovered almost fully three weeks later. Treatment-related fluctuations (TRF) is defined as an improvement in disability score of at least one grade or in MRC sum score of more than five points within 4 weeks, followed by a reduction in the MRC sum score of more than five points or a worsening in functional disability score of at least one grade. His subsequent, uneventful recovery ruled out acute-onset chronic inflammatory demyelinating polyradiculoneuropathy. Physicians should be aware of TRF in view of its potential to cause harm if unanticipated. The management of TRF is unclear; although most experts believe it warrants a second course of immunotherapy. Our patient was switched to IVIG. The role of methylprednisolone is controversial. However, many physicians in Vietnam use corticosteroids to treat GBS although there is no evidence to support its use.


Keywords: Inflammatory

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Multicentre Study Investigating the Association of Guillain-Barre Syndrome with Flaviviruses and other Arboviruses in Singapore.

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The aim of this study is to understand the relationship between Guillain-Barre Syndrome (GBS) and antecedent Flaviviruses and other arbovirus infections in South and South-East Asia. The study involves hospitals in Singapore, Myanmar, Laos, Vietnam, Thailand, Pakistan, Sri Lanka and India. GBS patients, hospital controls and community controls were examined for evidence of recent Dengue (DENV), Zika (ZIKV) and Chikungunya (CHIKV) infections. Multiplex real-time RT-PCR, ZCD multiplex PCR followed by single-plex PCR reconfirmation, and virion-based ELISA were performed on the patients’ sera and urine for ZIKV, DENV serotypes 1-4, and CHIKV. Neutralisation assays were performed to exclude cross-reactivity between ZIKV, DENV and CHIKV. We present the preliminary data of 16 patients and 2 hospital controls from Singapore, recruited from Dec 2017 to Jan 2019. Of 16 patients only 1 patient had evidence of recent ZIKV infection: positive serum ZIKV PCR obtained at days 43 and 89 from onset of GBS symptoms. Serum and urine had been negative for ZIKV on initial sampling on day 28. The patient had no significant IgM response against ZIKV, DENV and CHIKV. The positive ZIKV PCR in the convalescent rather than acute sera makes ZIKV unlikely to be the responsible antecedent infection. This patient reported diarrheal illness rather than symptoms suggestive of acute ZIKV infection prior to onset of GBS. There was no evidence of recent ZIKV, DENV or CHIKV infections in any of the other cases. As expected in an endemic region, the majority of cases and controls had evidence of previous exposure to various combinations of ZIKV, DENV and CHIKV. Our preliminary data suggests that Flaviviruses and other arboviruses might not be significant antecedent infections of GBS in Singapore. More prospective data from on-going recruitment as well as from our international collaborators will be presented at the PNS meeting.

References: None.

Keywords: Inflammatory, Other

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Serial Studies Reveal “Covert” Sural-sparing Pattern in Guillain-Barre Syndrome

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Our previous studies established: i) Relative sural-sparing, defined as a greater reduction of median or ulnar sensory nerve action potential (SNAP) compared to sural SNAP, is seen in the initial nerve conduction studies (NCS) of more than one-third of Guillain-Barre syndrome (GBS) patients, ii) Sural-sparing pattern is seen in both demyelinating and axonal subtypes, including Miller-Fisher syndrome (MFS) and iii) Disruption of blood-nerve barrier at entrapment sites rather than terminal nerve endings is the likely cause of the sural-sparing pattern. We also encountered cases that initially did not demonstrate sural-sparing but serial NCS showed greater involvement of median or ulnar SNAPs compared to sural SNAP. We aim to understand the frequency of this “covert” sural-sparing pattern in GBS patients. We reviewed the serial NCS of consecutive patients enrolled into our prospective GBS database. Patients with relative sural-sparing pattern on initial NCS were delineated as shown, using age and height matched normal values derived from 245 controls: (Normal Median or Ulnar SNAP - patient's Median or Ulnar SNAP)/(Normal Median or Ulnar SNAP) > (Normal Sural SNAP - patient's Sural SNAP)/(Normal Sural SNAP). Serial NCS of those without initial sural-sparing were examined for significant change in SNAP, as validated by Capasso et al, i.e. at least 44%,47% and 58% for median, ulnar and sural SNAP amplitudes respectively. "Covert" sural-sparing was defined as a greater change in median or ulnar SNAPs compared to sural SNAP. 55/86 (64%) patients had relative sural-sparing at initial study. 8 were AIDP,11 AMAN/AMSAN,28 MFS/MFS-GBS and 8 unclassified. Of the remaining 31 patients without initial sural-sparing pattern, 5 had “covert” sural-sparing. These were 2 AIDP,2 AMAN/AMSAN and 1 MFS. We believe sural-sparing is a fundamental electrodiagnostic footprint of all GBS subtypes and, depending on the sensitivity of the methods used, is present in at least 2/3 of GBS patients.

References: None.

Keywords: Inflammatory

Grant Support: None.
Pharmacokinetic Modelling and Simulation of Flexible Dosing Regimens of Subcutaneous Immunoglobulin (IgPro20) in CIDP Patients

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Introduction: A population pharmacokinetics (PopPK) model was developed to characterise the pharmacokinetics of immunoglobulin G (IgG) following intravenous (IV) or subcutaneous (SC) administration of IgPro10 (Privigen®, CSL Behring, King of Prussia, PA, USA) or IgPro20 (Hizentra®, CSL Behring) in CIDP patients. This model was used to simulate concentration-time profiles and PK parameters at steady state following various SC dosing regimens to enhance flexible dosing for patients’ convenience.

Methods: The PopPK analysis was conducted using the data from PRIMA (NCT01184846) and PATH (NCT01545076) studies, including 1558 observed IgG concentrations from 235 adult patients. Data exploration and PopPK modelling were conducted using R and nonlinear mixed-effects modelling software (NONMEM), respectively. Using the final PopPK model, IgG concentration–time profiles were simulated (300 simulated trials of 25 CIDP patients) and corresponding exposure metrics were calculated from different dose regimens (daily to bi-weekly dosing) and compared with the weekly dosing regimen.

Results: A two-compartment model with first-order absorption (for SC administration) and elimination described the observed IgG serum concentration data well. IgG disposition in patients was characterised by low clearance (CL, 0.45 L/day) and a small volume of distribution and (V2, 4.7 L). Relative bioavailability of the SC formulation was approximately 85% compared with the IV formulation. Additionally, body weight was a significant covariate on both CL and V2. The results of the simulations suggested that exposure (AUC, Cmax and Cmin) from flexible dosing (daily to bi-weekly) was comparable with that of a weekly dosing regimen within the equivalence boundaries of 0.8–1.25.

Conclusions: The PK of IgG following IV and SC administration to CIDP patients was well characterised by a two-compartment model with the first order absorption (for SC) and elimination. Based on the simulation results, flexible dosing from daily to bi-weekly is feasible resulting in equivalent exposure across dose regimens.

References: None.

Keywords: Inflammatory

Grant Support: This study was supported by CSL Behring.
CSF neurofilmament heavy chain: A possible biomarker of Guillain-Barré syndrome

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Introduction: Guillain-Barré syndrome (GBS) have diverse variants and mimics that might delay the diagnosis. About 20% of GBS develops permanent severe disability at long term follow up. From this reasons, early accurate diagnosis and predicting prognosis are important in treating GBS and improving outcome. We investigated the diagnostic and prognostic role of 4 cerebrospinal fluid (CSF) proteins which are axonal or glial markers – neurofilmament heavy chain(NfH), tau, S100B and glial fibrillary acidic protein (GFAP)– in GBS.Method: We prospectively recruited acute stage of GBS patients diagnosed by Asbury criteria (1990) from multicenter. Serial nerve conduction studies (NCS) were performed to classify subtypes of GBS.CSF levels of axonal (NfH and tau) and glial (S100B and GFAP) proteins were measure by ELISA. Outcome was assessed for 6 months and assessed with Hughes functional score (F-score). F-score≥3, which indicates inability to walk independently, was determined as poor outcome. Thirteen healthy volunteers were used as control. Results: Total 40 GBS patients were recruited and 4 patients were excluded due to inappropriate CSF specimen. Analyzed 36 patients (Female to male ratio = 1:1) are classified as 17 AMAN, 11 AIDP, 8 Miller-Fisher syndrome or other anti-GQ1b antibody syndrome. Among 4 protein biomarkers, only NfH was significantly elevated in GBS compared to normal control. There is no significant difference in NfH, S100B, GFAP, tau CSF levels between subtypes of GBS. NfH level in CSF is distinctively dichotomized in GBS and NfH and S100B were associated with residual neurological deficit after 6 months. Conclusions: CSF NfH and S100B are possible diagnostic and prognostic biomarkers that can predict prognosis after 6 months in GBS. NfH, tau, S100B and GFAP might not be useful for differentiate GBS subtype, but rather it might be a marker for the severity of degree of inflammation.

References: None.

Keywords: Inflammatory

Grant Support: None.
The etiology of Guillain-Barré syndrome (GBS) is still an enigma although genetic and environmental factors are highly speculated for this autoimmunity. Among the genetic factors, the human leukocyte antigen (HLA)-DQB1 gene displays an impressive degree of polymorphism and haplotype structures may provoke autoimmune responses to infection and thereby influence GBS development. We determined HLA-DQB1 polymorphic alleles (*0201,*030x,*0401, *050x, *060x) among 151 patients with GBS and 151 ethnically matched healthy controls in Bangladesh using sequence-specific PCR. Pairwise linkage disequilibrium and haplotype patterns were analyzed based on D’ statistics. Fisher’s exact test and logistic regression analysis were used for association studies. No association was observed between HLA-DQB1 alleles and susceptibility to GBS. In haplotype analysis, haplotype 9 (DQB1*0303-*0601) was significantly decreased in GBS patients compared to controls (P=0.006, OR=0.49, 95% CI=0.30-0.82). Frequencies of DQB1*0303 alleles were prevalent in patients with severe form (P=0.025, OR=2.49, 95% CI=1.13-5.48). Clinical and serological subgroup analysis revealed a higher frequency of DQB1*0201 allele in demyelinating subtype (P=0.027, OR=2.68, 95% CI= 1.17-6.17). Patients with haplotype 5 (DQB1*0501-*0602) were associated with C. jejuni-triggered axonal subtype of GBS (P=0.02, OR=4.06, 95% CI=1.25-13.18). Individuals with haplotype 9 (DQB1*0303-*0601) possess 53% less frequency of anti-GM1 antibody sero-positivity compared to healthy controls (P=0.029, OR=0.47, 95% CI=0.24-0.93). Finally, HLA-DQB1 polymorphism is not associated with disease susceptibility though haplotype 9 (DQB1*0303-*0601) is less likely to be found in patients with GBS and expression of GM1 is lower in the presence of haplotype 9. Nevertheless frequencies of DQB1*0303 alleles are significantly evident in severely affected patients with GBS.

References: N/A

Keywords: Human Genetics, Inflammatory, Other

Grant Support: N/A
Temporal Profile of Anti-Ganglioside Antibodies in Recurrent Guillain-Barre Syndrome

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Introduction: In the serum of patients with Guillain-Barre syndrome (GBS), the level of anti-ganglioside antibodies decreased after reaching its peak in several months after the onset. However, the temporal profile of serum anti-ganglioside antibodies in patients with recurrent Guillain-Barre syndrome (RGBS) is unclear. We demonstrate a longitudinal change of anti-ganglioside antibodies for 2 years in an RGBS case.

Case: A 36-year-old woman was admitted with a 3-day history of distal paresthesia and weakness in her extremities. She had two episodes of GBS at 13 and at 19-year-old. 10 days prior to admission, she developed diarrhea. Her Hughes grade scale was 3 and deep tendon reflexes were decreased on the day of admission. Nerve conduction study (NCS) demonstrated demyelinating changes including conduction block and reduced amplitude of sensory nerve action potentials in the median and ulnar nerves. 2 courses of intravenous immunoglobulin were administered after admission. The symptom reached nadir on the third day (Hughes grade scale: 4) and improved gradually thereafter. 4 months after admission, she recovered (Hughes grade scale: 1) with leaving mild paresthesia in her hands. The parameters of NCS were completely improved 1 year after admission. Anti-GD1b IgG antibody was strongly positive in both of sera obtained at the time of the second and last episodes, although symptoms of preceding infections were different between in these two episodes. She had respiratory symptoms at the first and second GBS episodes, whereas she had diarrhea at last GBS episode. In addition, we examined the levels of anti-ganglioside antibody in serum at 4 months, 1 year and 2 years after admission. Strongly positive level of anti-GD1 IgG antibody was kept at the respective points of time.

Conclusions: Continual strongly positive anti-ganglioside antibodies may be the recurrent risk of GBS.

References: None.

Keywords: Inflammatory

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Experimental autoimmune neuritis (EAN): Morphological evidence for mitochondrial damage

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Experimental autoimmune neuritis (EAN) is used as an animal model for Guillain-Barré syndrome (GBS). In this study we examine mitochondrial morphology in different cellular compartments by longitudinal histological examination including electron microscopy, qPCR and immunohistochemistry in EAN.

Lewis rats were injected with P0 Protein and adjuvants. 7 days after injection animals developed pathogenic signs, after 14 days the disease peaked, after 21 days severity decreased. Animals were sacrificed after 14 and 28 days. Sural, tibial and sciatic nerves were dissected. Semithin sections were used to study axon count and g-ratio. Electron microscopy was performed to examine mitochondrial diameter in myelinated and unmyelinated axon as well as in Schwann cells. Immunohistochemistry stainings and qPCR were performed to investigate spatial relationship between mitochondrial pathophysiology and immune reaction against myelin.

Histological examination revealed no changes in axon count, but significant changes in the g-ratio in all nerves after 14 and 28 days. There was a significant increase in mitochondrial diameter at the peak of the disease (14days) in myelinated and unmyelinated axon as well as in Schwann cells. Furthermore, after 14 days changes were seen in mitochondrial physiology investigated by qPCR and immunohistochemical stainings. Pathological changes can be linked to changes in myelination and immune reaction.

Segmental demyelination in EAN is associated with profound changes in mitochondrial morphology. During the disease peak mitochondria tend to be swollen in axons and Schwann cells, slight differences are to be seen between the different nerves. These morphological changes in the mitochondria were correlated with formation of onion bulbs and axonal sprouts. Whereas in the recovery phase of the disease mitochondria show almost no significant differences compared to disease onset. In summary alteration in mitochondrial morphology correlated with the disease course in EAN, which could point to a role of mitochondrial dysfunction for disease severity and recovery potential.

References: None.

Keywords: Inflammatory, Schwann Cell, Axonal Regeneration, Axonal Biology, Other

Grant Support: None.
Predominantly Abnormal Sensory Responses at Disease Onset and Electrophysiological Characteristics of Anti-Neurofascin 155 Neuropathy

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Introduction

Sensory ataxia is one of the prominent clinical features of patients with anti-neurofascin 155 (NF-155) neuropathy

Methods

We report the early electrophysiology characteristics of 2 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) patients with NF-155 antibody, their clinical phenotype and treatment response

Results

Both patients had symptoms onset at 21-years-old. One had preceding febrile illness and the other had yellow fever vaccination, but no specific identifiable infections detected. Both patients presented with progressive distal upper and lower limbs paraesthesia and weakness with areflexia, sparing all cranial nerves. Clinical phenotype was consistent with atypical CIDP subtype of distal acquired demyelinating symmetric (DADS). Both patients showed prominent sensory ataxia and hand tremor. The first patient was more severely affected. Nodo/paranodal antibody testing was performed, and both patients were positive for anti-NF155 with the cell-based assay and anti-NF155 titers by ELISA of 1:24300 and 1:8100 respectively. Initial electrophysiology of both patients was performed within 2 months from symptoms onset. In the first, sensory nerve action potentials (SNAPs) were absent in all upper and lower limbs with typical compound motor action potentials (CMAPs) demonstrating demyelinating changes. For the second patient, SNAPs responses were predominantly reduced in amplitudes with mild conduction slowing, involving only the upper limbs, sparing the sural nerves. Motor neurography showed prolonged DML and F-wave latency. Follow-up electrophysiology studies demonstrated rapid deterioration of SNAPs responses to inexcitability. Treatment responses were variable. The first patient responded partially to IV immunoglobulin (IVlg), but not to corticosteroid and Azathioprine. The second patient responded partially to corticosteroids but stopped due to intolerance and did not respond to IVlg, Azathioprine and Mycophenolate mofetil. IV rituximab administered over the last 2 years stopped clinical progression, although anti-NF155 titers remained high

Conclusion

These cases demonstrated the predominant and rapid sensory nerve disturbance progression in patients with NF-155 neuropathy

References: None.

Keywords: Other

Grant Support: None.
Detection of IgG and IgM antibodies against nodo-paranodal proteins in CMT and CIDP

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INTRODUCTION AND PURPOSE: A small percentage of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have IgG4 antibodies against Neurofascin and Contactin. Recently IgG and IgM antibodies against the same antigens have been described in patients with Charcot-Marie-Tooth (CMT)¹ and IgM antibodies against NF155 have been detected in CIDP and GBS patients by ELISA². Our objective is to study the presence of nodal and paranodal IgM and IgG antibodies in patients with CMT and CIDP.

METHODS: 70 patients fulfilling the EFNS/PNS diagnostic criteria for CIDP and 100 patients fulfilling diagnostic criteria for CMT from three different centers were included. The presence of IgG and IgM antibodies against Neurofascin 155 (NF155), nodal neurofascin (NF186 and NF140) and Contactin-1 (CNTN1) have been investigated by immunocytochemistry in transfected HEK293 cells. The presence for NF155 IgM was also tested by ELISA. Sera with positive or with uncertain results were further tested by ELISA and immunohistochemistry (IH) in pig teased-nerve fibers.

RESULTS: Seventy patients with CIDP and 52 patients with CMT have been analyzed until now. Five patients with CMT have a doubtful pattern staining for IgM against nodal neurofascin, which were not confirmed by ELISA. Two patients with CMT have a doubtful pattern staining for IgG against nodal neurofascin, not confirmed by ELISA or IH.

CONCLUSIONS: Our pilot study suggests that patients with CIDP have not IgM antibodies against nodal and paranodal antigens. Until now, we did not detect nodal or paranodal antibodies in patients with Charcot-Marie-Tooth and have not confirmed the presence of IgM antibodies against paranodal proteins in CIDP. Final results will be presented at the congress.


Keywords: Inflammatory, CMTR, Node, Node Biology

Grant Support: None.
Disability, Fatigue and Treatment Safety During Long-Term Intravenous Immunoglobulin (Gamunex® 10%) Therapy in CIDP Patients

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Purpose: Chronic inflammatory demyelinating polyneuropathy (CIDP) is marked by disability progression and fatigue. Here, long-term assessment of these features in CIDP patients receiving intravenous immunoglobulin (IVIG) therapy in daily routine practice is described.

Methods: GAMEDIS was a multi-centre, prospective, non-interventional study performed on CIDP patients aged ≥18 years treated with IVIG (Gamunex® 10%), who were followed-up for 2 years. Inflammatory Neuropathy Cause and Treatment (INCAT) disability score, Hughes scale and Fatigue Severity Scale (FSS) were assessed at baseline and each quarterly visit. Dosing and treatment intervals, the change of clinical outcome parameters, and adverse events (AEs) were analysed.

Results: 158 patients were enrolled, of which 148 (93.7%) were evaluable and 81 (54.7%) had full dosing records available. 86.5 % of patients had a previous IVIG-treatment history and received a median maintenance IVIG dose of 0.9 g/kg per treatment cycle (median: 28 days) during a mean observational period of 83.3 weeks. Disability and fatigue remained stable throughout the study. Mean INCAT score was 2.4±1.8 at baseline and 2.5±1.9 at last observation. Patients regarded as healthy or with minor symptoms by Hughes score were 74.3% at baseline and 71.6% at the end of study. Mean FSS was 4.2 ± 1.6 and 4.1±1.7 at baseline and end of the study, respectively. Fifteen patients (9.5%) experienced 34 potentially treatment-related AEs. There were no AEs in 993% of all documented infusions.

Conclusion: Long-term treatment of CIDP patients with Gamunex® 10% in every day practice had a very good tolerability and safety records. Disability and fatigue remained stable through the 2 years observational period.

References: None.

Keywords: Inflammatory

Grant Support: None.
Introduction: PATH was a randomised study of subcutaneous immunoglobulin (SCIG) for chronic inflammatory demyelinating polyneuropathy (CIDP) that included a preceding immunoglobulin (IgG) dependency test period. The time to relapse in the IgG dependency period as a predictor of subsequent relapse in subjects randomised to placebo was measured to evaluate the utility of the IgG dependency test as an enrichment strategy.

Methods: Subjects were withdrawn from their previous intravenous immunoglobulin (IVIG) regimen for up to 12 weeks unblinded. Those who relapsed were restabilised and randomised to receive SCIG or placebo for 24 weeks. Relapse was defined as a ≥1 point increase in adjusted INCAT score. In a post-hoc analysis, time to relapse in the IgG dependency period was analysed in relation to likelihood of relapse for subjects treated with placebo in the subsequent randomised treatment period.

Results: Of 57 patients treated with placebo in the randomised SCIG treatment period, 40 relapsed by INCAT relapse criteria in the preceding dependency period and 24 relapsed by the same criteria in the SCIG treatment period. Those who relapsed in the SCIG treatment period tended to have a shorter time to relapse in the IgG dependency period (median 4.5 weeks, interquartile range 3.0 to 6.0 weeks, versus 7.8 [6.1 to 10.8] weeks) than those who did not relapse in the IgG dependency period; 75% of relapers demonstrated IgG dependency within 6 weeks, whereas 75% of non-relapers (n=16) demonstrated IgG dependency only after 6 or more weeks.

Conclusion: Subjects who deteriorated within 6 weeks when withdrawn from IVIG in a non-blinded manner were more likely to relapse when treated with placebo in the randomised treatment period than those who remained stable for 6 weeks off therapy before relapsing. These facts should be taken into account in future clinical trials to minimise subject numbers and subject burden.

References: None.

Keywords: Inflammatory

Grant Support: This study was supported by CSL Behring.
Medical Research Council Grading System Revisited in CIDP Through Rasch Analyses: The PATH Study

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Introduction: The Medical Research Council (MRC) grading system (ranging from 0–5) has been used for decades in clinical practice for muscle strength assessment, but its applicability has been debated particularly as sum scores are being generated from what is an ordinal scale. In a recent analysis of the peripheral neuropathy outcome measures standardisation study (PeriNomS) group, the applicability of the MRC grades showed inconsistency when investigated through Rasch analyses using published data on 72 muscles in various neuromuscular illnesses. Fewer inconsistencies were seen in proximal versus distal muscles/muscle groups, mainly in inflammatory neuropathies like chronic inflammatory demyelinating polyneuropathy (CIDP); however, the CIDP series was relatively small.

Methods: The PATH study, the largest worldwide randomised controlled trial currently performed in CIDP, provides a unique opportunity to examine whether the MRC grading system could meet Rasch-model expectations. Available initial data on all randomised patients (n=172) with CIDP will be subjected to a Rasch model to examine whether 1) physicians could differentiate between the MRC grades in the 8 muscle pairs examined (shoulder abductors, elbow flexors, wrist extensors, first dorsal interosseous, hip flexors, knee extensors, ankle dorsiflexors and extensor hallucis longus), and 2) whether each muscle contributes to the same degree to the sum score used in CIDP.

Results: The findings of this analysis will be presented at the PNS congress. The PATH study data provides a unique opportunity to contribute to the methodological questions in the field of inflammatory neuropathies.

Conclusion: This analysis will provide further information on the use of Rasch-transformed MRC scores in neuropathies.

References: None.

Keywords: Inflammatory

Grant Support: This study was supported by CSL Behring.
Impact of Diagnosis Delay in Chronic Inflammatory Demyelinating Polyneuropathy: Results from a Global Patient Survey

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Background: Chronic inflammatory demyelinating polyneuropathy (CIDP), a rare peripheral neuropathy, is often misdiagnosed. Diagnosis delay can adversely impact treatment decisions and disease progression.

Methods: Online global GBS CIDP Foundation survey data from 595 adult CIDP patients, with self-reported CIDP, was used to assess impact of diagnosis delay (after incident symptoms) on physical function (PF) based on PROMIS PF T-scores using Short Form-4 and Inflammatory Rasch-Built Overall Disability Scale (I-RODS) scores. Logistic models predicted the worst two tertiles per outcome, associated with work disability and residential changes. Diagnostic delay thresholds were evaluated using receiver operating characteristic curves.

Results: Patients were stratified into “Likely/somewhat likely CIDP” (n=426) and “Unlikely CIDP” (n=169, excluded from analysis) based on symptom patterns and EFNS/PNS guidelines. Median time to CIDP diagnosis after symptom recognition: 8 months (≥12 months: 43%; ≥30 months: 24%). Overall, mean [SD] PROMIS PF T-score was 36.5 [7.9] (internationally accepted population norm: 50 [range 23-57]), mean I-RODS centile score was 56.2 [16.9] (range 6-100); these were significantly lower (worse) (p=0.009, p=0.05 respectively) following ≥12 month diagnosis delay versus <12 month delay. A ≥12-month delay increased risk of being in lower two tertiles of PROMIS PF or I-RODS centile scores (1.7 times higher odds [p=0.015]) or I-RODS centile scores (1.6 times [p=0.04]). Assessing sensitivity versus false positive rate (FPR) of alternative diagnostic delay thresholds for being in lower two PROMIS PF or I-RODS tertiles, a 6-month delay had higher sensitivity and FPR, a ≥30-month threshold had lower sensitivity and FPR. Being female or a shorter time post-diagnosis to survey were associated with higher risk of being in lower two PF tertiles.

Conclusions: CIDP diagnosis delay beyond 12 months of symptom onset is associated with significant PF impairment. Limiting diagnosis delay to 6-months from symptom onset may be desirable, however this could increase FPR in identifying those at risk.

References: None.

Keywords: Inflammatory

Grant Support: This study was supported by CSL Behring.
Epitope Mapping for Anti-FGFR3 Autoantibodies in Sensory Neuropathy

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Sensory neuropathies (SNs) are rare diseases of the peripheral nerve system. Although being often classified as idiopathic, many cases are associated with immune-mediated diseases, suggesting an active involvement of the immune system. Indeed, autoantibodies against Fibroblast Growth Factor Receptor 3 (FGFR3) were recently identified in a subgroup of patients with sensory neuropathies.[1] To assess these autoantibodies’ pathobiological role, we aimed for detecting their epitope(s). In a first pre-screening approach, we synthesized and spotted 158 peptides covering the FGFR3 full-length sequence (806 amino acids (aa)) onto a cellulose membrane. Each peptide was 25 aa long, 20 aa overlapped between adjacent peptides. In a second step, we focused on the intracellular domain applying a higher resolution of peptide coverage (22 aa overlap) and on phosphorylated aa at their natural sites besides the unphosphorylated peptide. Upon these pre-screenings via immunostaining with four anti-FGFR3-positive patient sera, nine interesting cytosolic epitopes were selected and tested in a systematic screening array with 66 anti-FGFR3-positive SN patients and 34 healthy controls. The first pre-screening localized the major epitopes in the intracellular domain. The second, more detailed pre-screening showed that (1) reactivity of several epitopes is highly depended on the phosphorylation state and (2) there are clear interindividual differences among the patients. In the systematic screening based on nine selected epitopes, 16 of 66 anti-FGFR3-positive SN patients and 2 of 34 healthy controls bound at least one epitope. The epitopes reacting with healthy control sera were rejected. Five epitopes remained, each significantly targeted by at least two patients: aa positions 415-436, 457-478, 634-652 with phosphorylated tyrosines 647/48, 634-652 with unphosphorylated tyrosines 647/48, and 742-760. These epitopes cover 7/14 functionally relevant sites, such as pathogenic mutation or phosphorylation sites. To our knowledge, our results represent the first description of phosphorylation state-dependent autoantibodies in a neurological disease.


Keywords: Inflammatory

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Multicentre Study Investigating the Association of Guillain-Barre Syndrome with Flaviviruses and other Arboviruses in Myanmar

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The aim of this study is to understand the relationship between Guillain-Barre Syndrome (GBS) and antecedent Flavi and other arboviruses infections in South and South-East Asia. The study involves hospitals in Singapore, Myanmar, Laos, Vietnam, Thailand, Pakistan, Sri Lanka and India. The methodology involves examining GBS patients, hospital and community controls for evidence of recent Dengue (DENV), Zika (ZIKV) and Chikukunya (CHIKV) infections, using various microbiologic assays that account for confounding cross and co-infections. To date we have recruited a total of 16 patients, 11 hospital controls and 13 community controls from Yangon, Myanmar. Only 1 patient, MR 15, had a clinical diagnosis of DENV in Yangon. He presented with fever, epistaxis, positive Hess test and leucopaenia. On days 3 of fever he developed acute flaccid paralysis and a diagnosis of GBS was made. On day 4, NS1 antigen (for DENV) was positive, but DENV Ig M and Ig G were negative. On day 10 he developed a typical DENV rash. Sera and urine specimens of all cases and controls have been transported to Singapore for the following tests: multiplex real-time RT-PCR, ZCD multiplex and single-plex PCR reconfirmation as well as virion-based ELISA, for ZIKV, DENV serotypes 1-4, and CHIKV. Neutralisation assays will then be performed to exclude cross-reactivity between ZIKV, DENV and CHIKV. Preliminary ELISA serology suggests that 10 out of the 16 GBS patients had one of these infections recently. As expected in an endemic region, there is evidence of previous exposure to various combination of ZIKV, DENV and CHIKV in the remaining cases. The pending PCR tests and neutralization assays will help delineate infections that could antedate, and therefore possibly trigger, GBS.

References: None.

Keywords: Inflammatory

Grant Support: International GBS-CIDP foundation
Objective: To present the clinical features of 92 CIDP patients based on a retrospective analysis of a large cohort diagnosed at a reference center.

Methods: Among the 146 patients with immune mediated demyelinating neuropathy treated between March 1993 and January 2019, 92 patients (57 males) who fulfilled the EFNS/PNS diagnostic criteria for definite (n=90) or probable (n=2) CIDP were recruited. Patients were clinically classified into typical and atypical CIDP.

Results: Atypical CIDP group (52%) consisted of MADSAM (30%), DADS (16%), pure sensory (4%), and focal CIDP (1%). Gender, age at presentation, duration of follow-up, disease duration and course, CSF protein level were similar between groups. Childhood-onset disease was more frequent in typical CIDP (34%, p=0.018), and were more likely to have progressive disease course and less favorable disability scores in lower extremities (p=0.027). The overall response rate to the initial treatment was 64%. The response rates among CIDP subgroups were similar (p=0.565). In patients who deteriorated within 2 months, switching to a second immunotherapy increased the overall response rate to 75%. Compared with typical CIDP, the overall response to conventional therapies was similar in patients with MADSAM (p=0.203) but significantly lower in patients with DADS (p=0.023). Furthermore, patients with DADS and MADSAM responded less to steroids compared to typical CIDP (p=0.046, p=0.044 respectively). Although MADSAM patients had higher disability scores and were more likely to have unstable active disease according to CDAS, there was no significant difference in disability scores or disease outcome among subgroups.

Discussion: The frequency of atypical CIDP patients (52%) is high in our cohort compared to previous studies. Atypical cases are usually referred to our clinic which is one of the main centers in country. This probably explains the high number of atypical cases. Atypical CIDP patients tended to have less favorable response to therapy with a higher disability score. Early onset patients and atypical CIDP cases should be more closely followed and early initiation of third line treatment should be considered especially in atypical cases.

References: None.

Keywords: Inflammatory, Clinical Trials

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**Poster 172**

**IVlg treatment in chronic inflammatory neuropathies – experience of single neuromuscular centre.**

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**The aim of the study is** characteristic of management protocols of IVlg- treated patients with chronic inflammatory neuropathies in experience of single neuromuscular centre. Since Jun 2015 reimbursement procedures allowed to treat with IVlg MMN as first line and CIDP as a second line regimen (contradiction to GCS or lack of effectiveness of GCS).

**Material and methods:** retrospective analysis of clinical response and dose regimen of patients diagnosed with MMN or CIDP who received at least one full course of IVlg between Jun 2015 and Feb 2019.

**Results:** 39 patients with CIDP and 11 with MMN were identified: In CIDP cohort 25 M and 14 F, aged 21-89, mean 53 years; in MMN 7M and 4F, aged 34-61, mean 47 years. In CIDP group 17 patients are currently treated with IVlg: 14 at regular intervals (3-12 weeks, mean 5.4; dose 0.6-2g/kg, mean 1.2), and 3 in case of exacerbation of symptoms. 5 patients receive additional immunosuppressive treatment. In 22 subjects IVlg treatment was discontinued: 7 are in remission, one died (death not related to CIDP), one was lost to follow up, one due to side effects of IVlg- aseptic meningitis, 12 (30%) did not respond. In 3 of 7 patients remission was achieved by adding low doses of steroids to IVlg. 8 subjects with lack of response were re-diagnosed, two patients were treated with plasma exchange or GCS, two patients with poor response to IVlg had coexisting diabetic neuropathy.

In MMN cohort one patient was discontinued due to mild symptoms. In 10 patients long term IVlg treatment have been administrated (interval 3-7 weeks, mean 4.3; dose 1-2g/kg, mean 1.2). 3 patients receive additional immunosuppressive treatment.

**Conclusion:** In CIDP and MMN individualised IVlg regimens are used. 18% of CIDP patients achieved remission, while MMN need chronic treatment.

**References:** None.

**Keywords:** Inflammatory

**Grant Support:** no support
Poster 173

MUNIX: A Potential New Monitoring Tool of Treatment Response in Chronic Inflammatory Demyelinating Polyneuropathy

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Background

Traditional outcome measures used to assess treatment response in chronic inflammatory demyelinating polyneuropathy (CIDP) include a mixture of clinical assessments and disability scores\textsuperscript{1}. Reports vary regarding usefulness of conventional electrophysiological parameters\textsuperscript{2}. A relatively new electrophysiological technique for assessing number of functioning motor units (motor unit number index; MUNIX) has been shown to correlate with muscle strength and disability scores in CIDP\textsuperscript{3} and improvements in MUNIX values have been reported in a single study following immunoglobulin therapy\textsuperscript{4}. We investigated short-term changes in MUNIX values in patients with CIDP on regular intravenous immunoglobulin (IVIg) therapy.

Methods

26 patients with pre-existing diagnosis of CIDP (15 on regular IVIg therapy) were recruited prospectively as part of an ongoing observational study. All patients had clinical assessment of strength and sensory function, disability scores and electrophysiological studies. MUNIX sumscores were calculated from 3 muscles unilaterally (APB, ADM and TA). 20 healthy controls had MUNIX studies for comparison. Patients receiving IVIg therapy had a baseline study immediately prior to a planned treatment and repeat study 15 days later. 5 patients not on treatment also underwent repeat studies.

Results

MUNIX sumscores were significantly lower in patients than healthy controls at baseline (mean 214.0 (SD 124.4) vs mean 516.9 (SD 91.4), respectively; \(p<0.001\)). MUNIX sumscores at baseline significantly correlated with MRC scores, grip dynamometry, INCAT sensory sumscores, R-ODS and ONLS scores. A significant increase from baseline in MUNIX values was seen in IVIg treated patients (mean 188.3 (SD 110.5) baseline vs 226.4 (SD 132.0) post-treatment; \(p<0.001\)). No significant change in MUNIX sumscores compared to baseline values was seen in untreated patients or controls.

Conclusion

MUNIX sumscores correlate with assessments of motor and sensory function and disability scores in CIDP. These findings highlight a potential role for MUNIX sumscores in monitoring response to IVIg therapy.


Keywords: Inflammatory

Grant Support: None.
Guillain-Barré syndrome (GBS) is the most common cause of acute paralysis globally. It is estimated to affect 1.3/100000 people/year. GBS is self-limiting, but can be lethal during the acute stage of the disease due to paresis of the respiratory muscles or catastrophic cardiac events from autonomic failure. Mortality of GBS is 3% in the developed world; however in the developing world it often exceeds 10%. This is largely because of inadequate intensive care facilities, the unaffordability of standard immunotherapy, namely plasma exchange (PE) and intravenous immunoglobulin, as well as the lack of specialised equipment and expertise. To circumvent these difficulties colleagues in Sri Lanka, Bangladesh and Myanmar have devised an innovative alternative solution, small volume plasma exchange (SVPE). SVPE is the repeated removal of small volumes of supernatant plasma over several days via sedimentation of the patient’s whole blood that eventually removes a therapeutic amount of plasma. SVPE generally achieves up to 50% of the volume exchanged in standard PE. SVPE is simple and in principle can be applied at basic medical facilities. This technique has been tested in a pilot-study in Bangladesh. Video link: [bmjopen-2018-022862-SP1.mp4]. The Bangladeshi protocol employs a very basic circuit without the need of a centrifuge. Preliminary studies indicate its safety. The SVPE set-up involves manually connecting several bags (containing blood, anti-coagulant solution and replacement fluid) with multiple infusion sets via three way taps. This risks inadvertent contamination and introduction of infections. We are currently working to customize this SVPE circuit into a continuous multichannel kit. Such a ready-made, cost-effective, continuous SVPE-kit, if successfully tested in additional studies, can potentially be used to treat not only GBS but also other neuro-immunological disorders that are currently untreated in under-resourced parts of the world.

References: None.

Keywords: Inflammatory

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Clinical spectrum of stiff person syndrome associated with glutamic acid decarboxylase antibodies

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**Background:** Stiff person syndrome (SPS) is an immune-mediated neurological disorder that can cause rigidity of the axial and limb muscles. About 80% of patient with SPS have had high-titer antibodies against glutamic acid decarboxylase (GAD), and 15% have antibodies to glycine receptors.

**Objective:** The aim of this study was to examine the clinical characteristics and associated diagnosis of the SPS.

**Methods:** Retrospective chart review of patients with SPS and positive GAD antibody who were seen over 5 years was performed. Demographics, detailed clinical information, and diagnostic data were recorded. Coexisting autoimmune diseases and serologies were reviewed.

**Results:** Nine patients were included in this study, 7 women and 2 men. The median age at symptom onset was 47 years. Six patients had positive Gad antibody and 3 were negative. Primary diagnosis was stiff person syndrome (n=4), cerebellar ataxia (n=2), PERM (n=2) and sensory neuropathy/neuronopathy (n=1). Commonly associated antibodies were islet cell antibody and neuronal voltage-gated potassium channel. Type 1 diabetes, seizures, and thyroid disease were commonly associated with the diagnosis. Three patients had an EMG finding suggestive of SPS and two of these patients had negative GAD antibody.

**Conclusion:** Women are commonly affected by the disease. There is a phenotypic variation of the disease as previously reported in the literature. EMG is helpful in the diagnosis of negative GAD antibody patients where clinical suspicion for SPS is high.

**References:** None.

**Keywords:** Inflammatory

**Grant Support:** None.
Peripheral neuropathy associated with neuroglial antibodies: clinical, electrodiagnostic and histopathological characteristics

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Introduction: Descriptions of aquaporin-4 (AQP4), glial fibrillary acid protein (GFAPα) and myelin oligodendrocyte glycoprotein (MOG) antibody associated neuropathies are limited. Furthermore, phenotypic and histopathological details are lacking.

Methods: We included patients from our institution's EMR and Neuroimmunology Laboratory database using the following criteria: 1) signs/symptoms of neuropathy, 2) electrodiagnostic/radiological evidence of peripheral nerve involvement 3) AQP4/GFAPα/MOG seropositivity 4) reasonable exclusion of alternative etiology. Clinical outcome was measured by change in Modified Rankin Score.

Results: Nineteen patients [42% females, age 12-78 years (median 63)] seropositive for AQP4-IgG (n=9) or MOG-IgG (n=5) or GFAPα-IgG (n=5) with neuropathies were identified. Twelve patients (63%; AQP4, 4; MOG, 4; GFAPα, 4) had neuropathies as the initial presentation. Polyradiculoneuropathy/polyradiculopathy were the most common phenotypic presentations (n=16, 84%). Other phenotypes included bilateral sciatic neuropathies (n=1) and subacute length-dependent neuropathy (n=2). Neuropathic pain was common (74%). The majority of cases had co-existing myelopathy (68%). Four patients (GFAPα-IgG, 2; MOG-IgG, 1; AQP4-IgG, 1) had demyelinating features (slow conduction velocity [n=2], prolonged/absent F-waves [n=1], conduction block [n=1]) on nerve conduction studies. CSF studies showed inflammatory changes in 87% (13/15) of cases. Four patients (GFAPα-IgG, 2; AQP4-IgG, 1; MOG-IgG, 1) had nerve biopsies. AQP4-IgG case had evidence of increased axonal degeneration and small to moderate sized epineurial and endoneurial perivascular inflammatory collections. GFAPα-IgG and MOG-IgG cases demonstrated increased rate of demyelination and axonal degeneration, along with individual to small collections of inflammatory cells. Seventeen patients received immunotherapy. Clinical outcomes varied based on antibody specificities; 60% of MOG-IgG and GFAPα-IgG cases had favorable outcome at last follow-up, compared to 44% of AQP4-IgG cases.

Conclusion: Peripheral neuropathy with or without CNS involvement is a rare but severe manifestation of neuroglial antibodies. Neuropathies in these patients can contribute to substantial morbidity. Recognizing the inflammatory polyradiculoneuropathy/polyradiculopathy phenotype may help in early diagnosis and treatment.

References: None.

Keywords: Inflammatory, Pain

Grant Support: None.
Subcutaneous immunoglobulin (SCIg) represents an effective alternative to intravenous immunoglobulin (IVIg) for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Recently, SCIg administration via manual push technique (MPT) was presented as an option in a large cohort of PID patients requiring Ig replacement therapy. The aim of this study is to evaluate feasibility and (both clinical and laboratory) efficacy of a novel regimen of immunoglobulin administration, based on the delivery of lower volumes of SCIg administered daily using MPT in CIDP patients.

8 patients were randomly assigned 1:1 to receive SCIg either by MPT or pumps for 4 consecutive months at the same dose with crossover to the other. Clinical and laboratory efficacy parameters: IgG level, inflammatory neuropathy cause and treatment score (INCAT), medical research council scale (MRC), Martin vigorimeter handgrip strength test and the Rasch-built overall disability scale (RODS) were assessed monthly; while life quality index (LQI) was evaluated at the end of each treatment period.

The average plasma levels of IgG during the infusion period with pumps ranged from 1569.38±352.95 mg/dL (range 915-1866) to 1490.25±315.56 mg/dL (range 775-1743) while during MPT period ranged from 1556.63±337.8 mg/dL (range 775-1855) to 1554.13±340.64 mg/dL (range 1074-1866). Even if there is no significant difference between the two periods (p:0.70), there is an increase in IgG level at the end of the MPT period compared with the pump administration (from 1490.25±315.56 to 1554.13±340.64 mg/dL). LQI sub-scale I significantly improved (p:0.05), while no significant changes were observed in INCAT (p:0.99), MRC (p:0.78), grip strength test (p:0.62), RODS (p:0.96).

Our study reports a fluctuation of IgG after the MPT with a gradual increase of plasma levels probably due to the fact that serum IgG has a concentration-dependent catabolism. In conclusion our findings suggest that SCIg-MPT seems to have similar clinical efficacy and tolerability as SCIg weekly infusions administration.

References: None.

Keywords: Inflammatory, Clinical Trials, Other

Grant Support: None.
Characteristics and management of peripheral nervous system adverse events induced by anti-PD-1 or anti-PD-L1 immunotherapy

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• Introduction: Anti-programmed cell death 1 (PD-1) and anti-programmed cell death ligand 1 (PD-L1) antibodies are novel immunotherapies for cancer that can induce neurologic immune-related adverse events (n-irAEs). N-irAEs occurrence often leads to immunotherapy withdrawal, and guidelines are needed. In this retrospective monocentric study, we describe n-irAEs patients with emphasis on clinical features, morbidity, mortality and treatment strategy.

• Material and methods: Patients registered in a national referral database of suspected irAEs from 10/1/2014 to 1/1/2019 were included. N-irAEs probability was assessed using the Uppsala monitoring center causality scale. All cases were thoroughly investigated by oncologists and neurologists using an extensive diagnostic workup.

• Results: Twenty-five patients treated with anti-PD-1/PD-L1 antibodies and presenting with peripheral nervous system (PNS) symptoms (CTCAE grade I to V) were included. Eleven n-irAEs were scored grade II CTCAE, 11 grade III and 3 grade IV. Eleven patients (44%) presented with inflammatory demyelinating polyneuropathy (IDP), seven (28%) had both central and PNS involvement, four (16%) had radiculopathy, 4 (16%) had cranial nerve alterations, 4 (16%) had neuromuscular junction (NMJ) disorders, including 3 with myasthenia gravis (MG) and 1 with Lambert-Eaton myasthenic syndrome (LEMS), and 2 (8%) had length-dependent axonal polyneuropathy. Mean time of onset was 94 days after treatment was started. Three patients with IDP presented with anti-gangliosides antibodies in serum. Treatment was withdrawn in 23/25 cases, and reintroduced in 2/23 cases. Twenty patients were treated with corticosteroids, five with intravenous immunoglobulins, and 1 with TNF-alpha inhibitors. One patient died from LEMS.

• Conclusion: PNS n-irAEs range from moderate to severe disorders involving roots, peripheral nerves, cranial nerves and NMJ. In our series of 25 patients, IDP represented 44% of n-irAEs cases, and only one patient died as a result of n-irAEs. In selected cases, n-irAEs may be managed without withdrawing immunotherapy.

References: None.

Keywords: Inflammatory, Clinical Trials

Grant Support: None.
Introduction

Antibodies to gangliosides play an important role in the pathogenesis of the Guillain-Barré syndrome (GBS). These antibodies and their effects have been characterized extensively, but relatively little is known about the cells that produce these antibodies. Recently, we observed that plasmablasts are increased in the peripheral blood of approximately one-third of the GBS patients at the time of hospital admission. In some patients the number of plasmablasts further increases in response to treatment with intravenous immunoglobulins. Our hypothesis is that these plasmablasts are also the producers of the anti-ganglioside antibodies in GBS. Here we aimed to investigate whether the plasmablasts are functional and able to secrete anti-ganglioside antibodies in vitro.

Methods

Naive B cells, memory B cells and plasmablasts were sorted from peripheral blood mononuclear cells (PBMC) using flow cytometry. PBMC were obtained from four GBS patients with elevated numbers of plasmablasts. Cells were cultured in vitro with cytokines. IgM and IgG levels in supernatants were measured by ELISA specific for human immunoglobulins. Anti-ganglioside antibodies in sera and supernatants were measured by ELISA.

Results

The frequency of plasmablasts in patients with GBS was 15.5 ± 5.3% of the total CD19-positive B cells. Plasmablasts spontaneously produced IgM (65 ± 30 ng/ml) and IgG (371 ± 289 ng/ml) in vitro. This was significantly higher as compared to naive B cells and memory B cells (p<0.05). Two patients were positive for anti-GM1 antibodies in the serum. Of these, one clearly demonstrated anti-GM1 antibody production by plasmablasts in vitro. In contrast to serum anti-GM1 antibodies, which were IgM and IgG, the in vitro produced anti-GM1 antibodies were only IgG.

Conclusion

Our data indicate that ganglioside-reactive plasmablasts can be present in the peripheral blood of patients with GBS, suggesting ongoing B-cell activation in a subset of patients.

References: None.

Keywords: Inflammatory

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Assessment of paranodal region in skin of Chronic Inflammatory Demyelinating Polyradiculoneuropathy patients

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Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) is a heterogeneous disease that critically lacks of diagnostic and prognostic biomarkers. The identification of anti-neurofascin 155 (Nfasc155), anti-contactin 1 (CNTN1) and contactin-associated protein 1 (Caspr1) antibodies in a subset of patients has widened the spectrum of CIDP phenotypes. Nfasc155/CNTN1/Caspr1 complex is expressed on the paranodal region, and play key roles on sodium channel clustering and glia-axon interactions. Besides the quantification of unmyelinated intraepidermal nerve fibers (IENF), skin biopsy allows the immunohistochemistry evaluation of dermal nerve fibers to investigate morphological changes of myelin sheath and node of Ranvier structure. Of the 31 CIDP patients who underwent skin biopsy at the lower limb, 7 had antibodies against one of the component of the Nfasc155/CNTN1/Caspr1 complex. Of all seropositive patients, 3 had IgG4 antibodies against Nfasc155, two had IgG1-3 antibodies against Nfasc155, one had antibodies against CNTN1, and one had IgG4 antibodies against Caspr1. Skin tissues from seronegative and seropositive CIDP patients was assayed using a panel of antibodies including anti-Protein-Gene-Product (anti-PGP) 9.5 to visualize axons; anti-Myelin-Basic-Protein (anti-MBP) to identify the sheath of myelin; anti-panNeurofascin (anti-panNfasc), anti-Nfasc155, anti-Nfasc186, anti-Caspr1, anti-CNTN1, anti-Nav and anti-Kv channels to identify nodal/paranodal/juxtaparanodal structures. CIDP patients showed a significantly lower IENFD at distal leg (DL) and proximal thigh (PTh) compared to normative values. All the parameters used to assess the paranodal symmetry significantly differed between CIDP and healthy subjects. The mean fluorescence intensity to Caspr1 protein appeared significantly lower in CIDP patients. Dermal myelinated fibers showed significant elongation of the paranodal regions and increase of the area in CIDP patients compared to healthy subjects. Myelinated nerve fibers in Nfasc155-positive CIDP patients showed lack of staining in the paranodal site where Nfasc155 is expressed. Findings could provide evidence in support of a pathology driven stratification of CIDP patients to be correlated with personalized treatment.

References: None.

Keywords: Node, Inflammatory

Grant Support: GBS/CIDP Foundation Non-profit Grant 2017 Grant code: 501(c)(3)
Body: A 33-year-old female presented to hospital with a 2-years history of bilateral leg weakness that began after flu, progressed, accompanied by cramping. Physical examination revealed poor strength in the musculus tibialis anterior and bilateral feet drop, absent Achilles and knee reflexes. Nerve conduction studies showed motor polyneuropathy with conduction blocks (CB) in multiple motor nerves of the lower extremities. CB also revealed in motor fibers of nervus ulnaris dextra. Conduction velocity was normal in sensory fibers of upper and lower extremities. Lab. values including ESR, ANA, ANCA, CRP were all negative. Anti-GM1 IgM ratio was 1:1800, confirming diagnosis of MMN. Patient received 5 doses of IVIG, along with physical therapy, and responded well with improvement in motor function.

Conclusion: MMN is a rare, treatable, immune-mediated neuropathy, often associated with CB with slowly progressive weakness, fasciculations, and muscle cramping without loss of sensation.

The pathologic mechanism is secondary to autoantibodies against the GM-1 ganglioside within the Ranvier nodes, causing nerve conduction block. The disease could be detected according to clinical criteria, EMG studies and these antibodies in the blood. IVIG is the first choice of treatment with the hope of suppressing the over activity of the immune system, but other pharmacological therapies are available. Response to IVIG may occur quietly rapidly, but the dose and frequency may need to be individualized depending on the length and benefits.

We presented a 33 years old female with MMN. Diagnosis was based on EMG tests, clinical features, lab. values and positive treatments with immunoglobulins. MMN typically begins in elderly people; most patients are affected between the ages of 40-60 years and preferably in men.

It is important to consider MMN as the differential diagnosis of demyelinating disorders as MMN causes significant disability but does not shorten life, and the prognosis is generally good.

References: None.

Keywords: Other

Grant Support: None.
Intravenous Immunoglobulin (IVIG) Therapy in Idiopathic lumbosacral plexopathy: Report of two cases

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Introduction

Idiopathic lumbosacral plexopathy (ILSP), also called lumbosacral plexitis or non-diabetic lumbosacral (radiculo)plexus neuropathy is a rare clinical entity. Some studies suggest that the condition has an immune-mediated etiology. We report documented case of ILSP, which to dramatic response to intravenous immunoglobulins (IVIG) treatment.

Methods:

Case 1: A 36-year-old woman presented to the medical admissions unit with progressive weakness of her right limb, pain and areflexia. Complete blood count, erythrocyte sedimentation rate (ESR), chemistries, hemoglobin A1c, fasting blood sugar, a 2-hour glucose tolerance and autoimmune screen were normal. Magnetic resonance imaging (MRI) of the lumbosacral plexus revealed gadolinium enhancement of mainly L5 on the right. The patient was started on intravenous immunoglobulins IVIG for 5 days repeated at monthly intervals. A dramatic response to IVIG within three months.

Case 2: A 56 year old woman started felling sensation, pain, weakness, and numbness in her lower limb. On subsequent days the weakness was more progressed in lower extremities. In the examination performed, the left knee extension was found to be 4/5. Hypoesthesia was detected in left L4, L5 and S1 dermatomes. Left patellar reflex could not be taken when the patient was atrophic on the left thigh. Electromyography (EMG) findings were evaluated as compatible with dominant motor axonal degeneration in the upper part of lumbosacral plexus. Our patient responded to IVIG within two months which in view of her clinical findings.

Conclusions:

ILSP is characterized by an abrupt onset of sensory disturbances, weakness, and loss of deep tendon reflexes of lower extremities. The diagnosis requires clinical and electrophysiological demonstration of lesions affecting multiple nerves and root levels in the absence of other causes of lumbosacral plexopathy e.g. trauma, radiation, diabetes or mass lesions. Small series have reported response to intravenous immunoglobulin and steroids in high doses either alone or in combination.

References: None.

Keywords: Inflammatory

Grant Support: None.
Poster 183

Characteristics of Late-Onset Val30Met Transthyretin Amyloidosis with Polyneuropathy from the Transthyretin Amyloidosis Outcomes Survey

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Introduction: Transthyretin amyloidosis with polyneuropathy (ATTR-PN) is a clinically heterogeneous disease caused by mutations in the transthyretin (TTR) gene. The most common mutation is Val30Met which manifests as an early-onset or late-onset disease.

Methods: The Transthyretin Amyloidosis Outcome Survey (THAOS) is an ongoing, global, longitudinal, observational survey of patients with ATTR amyloidosis, including both inherited and wild-type disease, and asymptomatic patients with TTR mutations. This descriptive analysis compared symptomatic Val30Met ATTR-PN patients with late-onset (age ≥50 years) versus early-onset (age <50 years) disease in THAOS (data cut-off: January 16, 2019).

Results: Of 1327 Val30Met ATTR-PN patients in THAOS, 451 (34.0%) had late-onset disease. Regional differences were observed with late-onset more likely than early-onset patients to be from Sweden (28.8% of all late-onset versus 5.3% of all early-onset), Japan (8.9% versus 6.1%), or Spain (9.3% versus 6.5%) and not from Portugal (26.4% versus 62.1%) or Brazil (8.0% versus 10.4%). Late-onset patients: were more likely to be male (65.2% late-onset versus 53.4% early-onset); had an higher mean (SD) age at disease onset (62.6 [7.5] versus 33.3 [7.1] years); and had a longer time from onset to diagnosis (3.8 [3.5] versus 2.6 [4.0] years), potentially associated with more severe neurological impairment at enrollment (mean [SD] derived neuropathy impairment score in the lower limbs, 31.1 [24.3] versus 19.2 [21.9]; neurologic composite score, 58.7 [55.6] versus 38.1 [45.9]). Cardiac manifestations were more prominent in late-onset patients (versus early-onset), with 72.1% (versus 44.3% early-onset) having an overall interpretation of ECG as abnormal and 69.1% (versus 13.5%) having left-ventricular septum thickness of ≥12mm.

Conclusions: In THAOS, late-onset Val30Met ATTR-PN is relatively common, presenting with more severe neurologic and cardiac disease manifestations at enrollment but, due to heterogeneity of disease, may be more difficult to diagnose. Increased recognition of late-onset ATTR-PN could improve earlier diagnosis and patient outcomes.

References: None.

Keywords: Amyloidosis

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A 35-year-old man, with a history of hypertension since adolescence, presented with clinical features of erythromelalgia and small fiber neuropathy. In addition, he showed small stature with disproportionately small hands, feet and lower limbs. His father and brother had a similar, but less severe phenotype. All three were found to harbor a gain-of-function mutation in SCN9A (G856D; c.2567G>A). Functional analysis showed the mutation hyperpolarizes (-9.3 mV) channel activation, depolarizes (+6.2 mV) fast-inactivation, slows deactivation and produces a remarkable 10-11X enhancement of persistent and ramp current. During follow-up the patient developed an episode of confusion and myoclonic jerks as a result of a syndrome of inappropriate antidiuretic hormone secretion (SIADH). An X-ray showed an osteoporotic vertebral fracture. Subsequently, the patient's father was admitted to the hospital with SIADH. The family has expanded to include daughters with abnormal stature, and symptoms of erythromelalgia and small fiber neuropathy. One daughter has already been treated for hypertension beginning at age of six. Additional whole exome sequencing in the index patient did not reveal any other genetic causes for this remarkable phenotype. The finding of this mutation has extended the spectrum of SCN9A related human pain syndromes.

References: None.

Keywords: Small Fibers, Pain, Human Genetics

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A Comparative Study of Human Hairy and Glabrous Skins

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Most human peripheral neuropathy and neuropathic pain studies using skin biopsy focus on hairy skin while experimental rodents and non-human primate models concentrate on glabrous skin. Differences in innervation patterns and distribution of nerve fiber subgroups between hairy and glabrous skin are poorly characterized. In the current study, we compared unmyelinated and myelinated nerve fiber innervation in human glabrous and hairy skin in normal healthy control subjects.

Three mm distal leg skin biopsies (hairy skin) and plantar foot biopsies (glabrous skin) were obtained from healthy control subjects (n=15). Immunohistochemistry for pan-neuronal marker (PGP 9.5), neurofilament H (NFH), peptidegic sensory nerve marker (CGRP) was performed. Quantification of intraepidermal nerve fiber density (IENFD) and subepidermal nerve fiber density (SENFD) were carried out using conventional counting method and unbiased stereology protocol with CE<0.1, respectively. Double immunohistochemistry of PGP9.5 with NFH or CGRP was carried out to examine co-localization of markers.

We observed prominent differences between plantar and glabrous dermal and epidermal innervation. Glabrous skin had significantly lower (p<0.0001) PGP 9.5 IENFD than distal leg hairy skin while NFH+ innervation was significantly higher in plantar glabrous skin than hairy skin (p<0.0001). Similarly, CGRP+ dermal nerve fiber density was significantly higher than distal leg hairy skin (p<0.05). There are prominent differences between hairy and glabrous epidermal innervation. This may account for some of the disconnect between preclinical models and human neuropathic pain studies.

References: None.

Keywords: Small Fibers, Axonal Biology, Pain, Other

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Diagnostic Performance of Sudoscan in Young Patients Evaluated For Small-Fiber Neuropathy and Healthy Controls

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Introduction: Sudoscan is a rapid non-invasive screening device cleared by US FDA to aid in assessing sudomotor function (sweating) in the hands and feet, which often decrements in small-fiber polyneuropathy (SFN). It measures electrochemical skin conductance (ESC) of the hands and feet. It has reported utility in identifying diabetic neuropathy in adults, but there is only one study of normal children, and none of youngsters with neuropathy. We tested the hypothesis that Sudoscan can effectively screen for SFN in children and teenagers, where noninvasive testing is particularly desirable.

Methods: With consent and/or assent of all volunteers and/or parents to an IRB-approved protocol, we have thus far studied with Sudoscan 39 patients aged 4-19 years being evaluated by neurologists for SFN. 120 community-recruited screened healthy children aged 2-20 years provided controls. Outcomes were based on manufacturer’s interpretation of ESC. Among the patients, 30 had SFN confirmed by lower-leg PGP9.5 immunolabeled skin biopsies (epidermal neurite densities ≤5th centile of predicted) and/or autonomic function testing (AFT) interpreted as SFN by consensus criteria. 115 healthy controls had interpretable Sudoscan results.

Results: Among all 39 SFN-evaluated patients, none were interpreted by Sudoscan as “elevated risk” of peripheral neuropathy. 5 (13%) measured as “moderate risk”, among whom 2 had objective confirmation. Among the 30 with confirmed SFN, 28 had normal ESC and 2 were measured as “moderate risk”. Among 115 healthy controls, 15 (13%) were measured as “moderate risk”; the rest had normal results. Mean ESCs in patients were very close to those in healthy controls: hand ESC averaged 76.5µSi vs. 75.5µSi; p=0.65, and feet ESC 85.5µSi vs. 83.2µSi; p=0.16.

Conclusions: Sudoscan did not differentiate children and teenagers with neuropathy from demographically matched healthy controls. Sudoscan thus should not yet be used with current interpretive scales to screen for SFN in youngsters under age 21.


Keywords: Small Fibers

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Dynamic Sweat Test (DST) in Small Fiber Neuropathies

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A sweating impairment has been described in painful small fiber neuropathies (SFN). Quantitative sudomotor axon reflex test (QSART) has been described as abnormal in 74% of SFN patients. Among functional testing, the sudomotor assessment may be an objective and sensitive tool to detect a small fiber pathology. Quantitative sensory testing (QST) abnormalities, associated to SFN symptoms contribute to reach a definite diagnosis of SFN. However, QST is not objective because implies patient collaboration. DST compared to QSART, provide a dynamic assessment of the sweating output, the number of activated sweat glands and the volume of produced sweat. We tested the hypothesis that autonomic sudomotor dysfunction may occur early in the course of SFN and can be revealed before the occurrence of intraepidermal nerve fibers (IENF) degeneration.

We recruited 138 patients (94 male, mean age 51±15 years) with symptoms and signs of SFN and normal NCV study. We assessed IENF density from distal leg and quantified sweating output with the DST on 2 body sites (leg and forearm), after stimulation with 1% pilocarpine by iontophoresis.

We found a sweating impairment in 77% of patients at the forearm and in 86% at the leg, while only 51% of patients showed an IENF density below the 5th percentile cut-off. Eighteen patients with normal IENF density and abnormal sudomotor function repeated skin biopsy over time, showing a reduced IENF density and therefore reaching a definite SFN diagnosis.

DST appears to be an objective and easy-to-perform test to assess autonomic function in SFN. In our population, it showed to be more sensitive than skin biopsy. The assessment of sudomotor function using a test as sensitive as DST may be able to detect a SFN even before the IENF loss. The DST should be considered to diagnose and to monitor SFN over time during disease-modifying treatment

References: None.

Keywords: Small Fibers, Pain

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Mutations in Cell Adhesion Molecules Belonging to the CADM Family Cause Charcot-Marie-Tooth Disease

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CADM family of proteins consists of four neuronal specific adhesion molecules (CADM1, CADM2, CADM3 and CADM4) that mediate the contact interaction between axons and glia. In the peripheral nerve, axonal-Schwann cell interaction is essential for the structural organization of myelinated fibers and it is primarily mediated by the binding of CADM3, expressed in axons, to CADM4, expressed by myelinating Schwann cells. We have identified by whole exome sequencing three families with axonal Charcot-Marie-tooth disease (CMT2) sharing the same private variant in CADM3 and one autosomal dominant CMT2 family with a private variant in CADM4. Although all families have CMT2, CADM3 and CADM4 families developed distinct subclinical features. The CADM3 families share the same peculiar phenotype consisting of axonal motor neuropathy affecting mainly the upper limbs with pyramidal features. In contrast, the CADM4 family developed a more typical length dependent CMT. The variant identified in CADM3, Y138C, was found to be de novo in two families, while in the third family the variant shows dominant segregation. High resolution mass spectrometry analysis coupled with nanoflow UPLC detected disulfide bonds modifications in the mutant CADM3 potentially modifying the native protein conformation. In addition, we observed a significant increased protein retention of the mutant in the endoplasmic reticulum leading to activation of the unfolded protein response (UPR). Interestingly, ablation of CADM4, but not CADM3, in mouse results in myelination abnormalities and impaired motor function. We are currently studying a CADM3 knockin (KI) mouse carrying the same variant observed in our patients to better mimic the human phenotype and its pathological mechanism. Preliminary results indicate increased muscle weakness in the CADM3-KI mouse compared to the wild-type. Our findings indicate a novel molecular pathway involving axon-glial interaction abnormalities in patients with CMT.

References: None.

Keywords: CMTR, Axonal Biology, Human Genetics, Schwann Cell

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