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Abstracts

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A Longitudinal Nerve Sonography Study on Miller Fisher Syndrome

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The diagnosis of Miller Fisher syndrome (MFS) is mainly made clinically with cardinal features (ophthalmoplegia, ataxia, and hyporeflexia) while electrophysiological and cerebrospinal fluid analyses often show nonspecific findings at the onset. The availability of anti-GQ1b antibody assays is limited in many places. Nerve sonography provides a chance to evaluate the nerves morphologically. We measured the size of the facial nerves, cervical nerve root, and nerves in the limbs of patients with MFS (n=5) and control group (n=18) by sonography. Serial follow-up was performed before treatment, 2 weeks after disease onset, and 3 months after disease onset. The width of the facial nerve was significantly larger in the MFS group than in the control group (MFS: 1.19 ± 0.31 mm vs. normal: 0.67 ± 0.13 mm, P = 0.01). The size of the cervical roots and the nerves in the limbs were similar between the two groups. Two patients' facial nerve size subsided with time, but the decrease in other nerves' sizes were not obvious. Sonography analysis revealed enlarged facial nerves at the onset of MFS, but only two patients' facial nerve width decreased three months after the disease onset. Nerve sonography may serve as an objective tool to evaluate MFS.

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A Family of IBMPFD Showing Variable Clinical Features

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Inclusion body myopathy with Paget's disease of bone and frontotemporal dementia (IBMPFD) is an autosomal dominant hereditary disease with valosin-containing protein (VCP) gene abnormality. We experienced three cases of an IBMPFD family and examined their clinical characteristics.

Materials and Methods: We have evaluated clinical characteristics retrospectively of three cases in an IBMPFD family with VCP pArg155Cys mutation.

Result: Patient 1: Proboud 42-year old male. His limb-girdle muscle weakness started at age 38. He felt difficulty of climbing stairs at age 39. Serum CK elevation and myogenic change in needle EMG was found. Muscle biopsy from left Biceps Brachii showed fiber size variation, a few RRF and no vacuoles. He has been using wheelchairs since the age of 47. Patient 2: Sister of patient 1. 47-year old female. She felt weakness of both legs at age 39. Her serum CK is normal. Myogenic change in needle EMG was found. Muscle biopsy from left Biceps Brachii showed fiber size variation and one rimmed vacuole. Her muscle weakness has not affected her daily life 2 years after the diagnosis. Patient 3: Mother of patient 1&2. She was diagnosed of amyotrophic lateral sclerosis (ALS) at age 40, and passed away because of respiratory failure at age 54. She was also diagnosed Paget's disease of bone.

Conclusion: The clinical findings of IBMPFD varied within the same family, and it was revealed that various symptoms appear with age. Even if there are no inclusion bodies in a muscle biopsy, a detailed family history taking is very important. If IBMPFD is suspected genetic testing of VCP gene is required.

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Non-Motor Symptoms are Frequent in DM1 Patients

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Myotonic dystrophy type 1 (DM1) is a chronic progressive multi-system disorder with autosomal dominant inheritance, caused by a cytosine-thymine-guanine (CTG) repeat expansion in the DM1 protein kinase. Neurocognitive impairment is a well-known symptom in DM1 but lack of motivation in patients with DM1 has been less studied. The current study aims to characterize the non-motor profile of DM1. We study DM1 patients in a Spanish tertiary hospital from January to April in 2019. Demographic questionnaire included age, gender, and number of completed years of schooling. Clinical characteristics regarding DM1 were assessed. The following scales were tested: Hamilton depression rating scale (HDRS), apathy evaluation scale (AES), fatigue severity scale (FSS), Epworth sleepiness scale (ESS) and Barthel Index (BI).

We studied 14 patients (9 male, 5 female) with a mean age of 47.5 years (range: 30-56). The average age at diagnosis was 38.5 years (range: 18-51) and disease duration was 8.9 years (range: 5-12). The average repeat expansion was 110 (range: 50-160). Ten patients had secondary studies, two primary studies, and two university studies. The results for each scale were HDRS: 12.3, AES: 14.9, FSS: 33.5, ESS: 12.7 and BI: 86.8. There was no statistical significance between gender, age, disease duration, and CTG repeats, but there were differences in BI in patients with less (93.6) and more (72.5) than 10 years of disease duration (p: 0.029). A correlation was found between HDRS and BI (P: 0,541; p: 0,046); HDRS and AES (P: 0,541; p: 0,046); FSS and BI ((P: -0,613; p: 0,020); FSS and AES (P: 0,707; p: 0,005). No correlation was found between CTG repeats and any of the scales. In this small DM1 study, we found that depression, apathy, and fatigue are frequent in DM1 patients and they may influence in performing activities of daily living; therefore, more attention should be pay to non-motor symptoms when treating DM1 patients.

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Efficacy and Safety of IqYmune® in Patients with Chronic Inflammatory Demyelinating Polyneuropathy: PRISM Study Results

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This prospective, multicenter, single-arm, open-label phase 3 study aimed to evaluate the efficacy and safety of IqYmune® (10% liquid human intravenous immunoglobulin (IVIg)) in patients with chronic inflammatory demyelinating polyneuropathy (CIDP). Patients received one induction dose of 2 g/kg and then 7 maintenance doses of 1 g/kg at 3-week intervals. The primary efficacy endpoint was the responder rate at the end of study, defined as an improvement of ≥1 point on the adjusted INCAT disability scale. The responder rate was tested against the responder rate of a historical placebo group (33.3%) with an exact 1-sided binomial Clopper-Pearson test. Forty-three (43) patients with CIDP (21-79 years) were enrolled and treated. Among them, 42 were included in the efficacy set. The overall response rate at the end of study was 76.2% with a 95% confidence interval (CI) of [60.5 - 87.9%] (exact 2-sided Clopper-Pearson). The superiority of IqYmune® compared to the historical placebo control was statistically significant (p-value <0.0001). The median time to response was 15 weeks with a 95% CI of [8.9 - 19.1%] (estimated by the Kaplan-Meier method taking into account non-responder patients). The secondary efficacy endpoints included the changes from baseline to the end of study of adjusted INCAT disability score, grip strength in the dominant and non-dominant hand, Rasch-built overall disability scale (R-ODS) score, Medical research council (MRC) sum score, Rasch-modified MRC sum score and clinical global impression of severity of illness, global improvement and efficacy index. An improvement was shown for

all these secondary endpoints, supporting the result of the primary efficacy endpoint. This study included two subgroups of patients: 23 patients never previously treated with IgG (IgG-naïve patients) and 20 patients already treated with IgG but in clinical relapse following IgG therapy discontinuation (IgG-pretreated patients). Although no statistical tests were performed to compare both subgroups, we observed that the responder rate was numerically higher in IgG-pretreated patients than in IgG-naïve patients but CIs of these subgroups were largely overlapping (84.2% with a 95% CI of [60.4 - 96.6%] versus 69.6% [47.1 - 86.8%]). We also observed that the response occurred earlier in IgG-pretreated patients than in IgG-naïve patients (median of 7.9 weeks with a 95% CI of [3.4% - 12.1%] versus 19.1 weeks [12.1 - 24.1%]). A total of 156 treatment-emergent adverse events (TEAEs) were considered related to IqYmune® in 30/43 patients. The most common drug related TEAEs were headaches and pyrexia. All drug related TEAEs resolved without sequelae except an anemia. Nine serious TEAEs were reported in 7 patients and resolved without sequelae except a femur fracture unrelated to IqYmune®. No case of hemolysis was reported by investigators. No signs of renal or hepatic impairment were observed. These clinical results demonstrate that IqYmune® is an effective and well-tolerated treatment in patients with CIDP. Furthermore, safety results with IqYmune® were consistent with the known safety profile of this class of products.

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Frequency of Campilobacter Jejuni Antibodies in GBS Patients

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Background: Molecular mimicry and cross-reactive immune response play a key role in the pathogenesis of GBS. The aim of this study was to investigate the campylobacter as an agent of GBS and its correlation with ganglioside antibodies, type of GBS and severity of disease.
Material and Methods: The present cross-sectional study was conducted on 43 GBS patients present in to Al Zahra Hospital affiliated to Isfahan University of Medical Sciences, Isfahan, Iran in 2017-18. Serum samples were screened for immunoglobulin G(IgG), IgA and IgM antibodies against C.jejuni using the ELISA (ELISA kits, Serion, Germany) and anti-gangliosid antibodies, including IgG and IgM, were assessed for each of the antigens with the Euroimmun kit.
Results: The patients were 10-85 years old and had a mean age of 48.14±19.06 years. Infection was observed in approximately 30% of the patients, and acute inflammatory demyelinating polyneuropathy (AIDP) as the most prevalent type of GBS in 48.8%. Only 7% of the patients were positive for ganglioside antibodies and the patients positive for the campylobacter IgG antibody accounted for about 4.7% of the subjects and those positive for IgA antibody about 7%. Type of GBC was found not to be significantly related to Campilo IgG (P=0.7) and IgA (P=0.9). The relationships of gangiloside with Campylo IgG (P=0.7) and IgA (P=0.6) were also found to be insignificant.
Conclusion: The present findings suggested a low frequency of C.jejuni antibody in the GBS patients. Type of GBS was also found not to be correlated with positive serologic C.jejuni antibody and gangloside antibody.

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Autosomal Dominant Optic Atrophy Plus Due to the Novel OPA1 Variant c.1463G>C

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Introduction: OPA1 variants most frequently manifest phenotypically with pure autosomal dominant optic atrophy (ADOA) or with ADOA plus. The most frequent abnormalities in ADOA plus in addition to the optic nerve affection include hypoacusis, migraine, myopathy, and neuropathy. Hypertelorism and atrophy of the acoustic nerve have not been reported.
Case report: The patient is a 48yo Caucasian female with slowly progressive, visual impairment since childhood, bilateral hypoacusis since age 10y, and classical migraine since age 20y. The family history was positive for diabetes (father, mother) and visual impairment (daughter). Clinical examination revealed hypertelorism, visual impairment, hypoacusis, tinnitus, weakness for elbow flexion and

finger straddling, and generally reduced tendon reflexes. MRI of the cerebrum was non-informative but hypoplasia of the acoustic nerve bilaterally was described. Visually-evoked potentials revealed markedly prolonged P100-latencies bilaterally. Acoustically-evoked potentials were distorted with poor reproducibility and prolonged latencies. Muscle biopsy revealed reduced activities of complexes I, II, and IV. Genetic work-up revealed the novel variant c.1463G>C in the OPA1 gene.
Conclusions: This case provides novel information regarding the genotype of ADOA plus. The novel OPA1 variant c.1463G>C not only manifests with visual impairment, hypoacusis, migraine, and myopathy, but also with hypertelorisms and acoustic nerve atrophy.

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Severe Acquired Hypokalemic Paralysis in a Bodybuilder After Self-Medication With Triamterene/Hydrochlorothiazide

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Background: Severe hypokalemia with severe neurological impairment and electrocardiogram (ECG) abnormalities due to the misuse of triamterene/hydrochlorothiazide (HCTZ) in a bodybuilder has not been reported.
Case report: A 22-year-old bodybuilder acutely developed generalised muscle cramps, sensory disturbances of the distal lower and upper limbs, quadriparesis and urinary retention. These abnormalities were attributed to severe hypokalemia of 1.8 mmol/L (normal range 3.4–4.5 mmol/L) due to misuse of triamterene/HCTZ together with fluid restriction. He was cardiologically asymptomatic, but ECG revealed a corrected QT (QTc) interval of 625 ms. Upon intravenous application of fluids along with intravenous and oral substitution of potassium, his condition rapidly improved, such that the sensory disturbances, quadriparesis and bladder dysfunction completely resolved within two days after admission.
Conclusions: Self-medication with diuretics along with fluid restriction may result in severe hypokalemia, paralysis and ECG abnormalities. Those responsible for the management of bodybuilding studios and competitions must be aware of the potential severe health threats caused by self-medication with diuretics and anabolic steroids. Though triamterene is potassium-sparing, it may enhance the potassium-lowering effect of HCTZ.

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Exome Sequencing: Mutilating Sensory Neuropathy With Spastic Paraplegia Due a Mutation in the FAM134B Gene

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Introduction: Hereditary sensory and autonomic neuropathies (HSANs) are a clinically and genetically heterogeneous group of disorders involving various sensory and autonomic dysfunctions. The most common symptoms of HSANs include loss of sensations of pain and temperature that frequently lead to chronic ulcerations in the feet and hands of the patient.
Case report: In this case study, we present the clinical features and genetic characteristics of two affected individuals from two unrelated Saudi families presenting mutilating sensory loss and spastic paraplegia. We employed homozygosity mapping and exome sequencing which is an efficient strategy to characterize the recessive genes, thus obtaining a rapid molecular diagnosis for genetically heterogeneous disorders like HSAN. Subsequently, a nonsense mutation (c.926 C>G; p.S309*) in FAM134B was identified. In addition, we confirmed that the mutant FAM134B transcripts were reduced in these patients presumably disrupting the receptors of the degradative endoplasmic reticulum pathways that facilitate the autophagy processes.
Conclusions: we describe the second family with HSAN-II associated with HSP due to the mutation p.S309X in the FAM134A gene. However the pathogenetic role of FAM134A in sensory neuropathy with spastic paraplegia remains largely unknown and this study expands the phenotypic heterogeneity caused due to variants in FAM134A.

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Suboptimal Control of Myasthenia Revealed by Implementation of Systematic Follow-Up in A French-Canadian Community Practice

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Background: Little is published on actual management of generalized myasthenia gravis (MG) in community practice. According to a recently published American registry,[1] 7% of myasthenic patients are refractory. Participants were classified as having refractory MG if they met the three following criteria : 1 -past use of at least 2 immunosuppressant therapies (ISTs) for at least 6 months each OR past use of at least 1 IST for any duration AND repeated use of IVIg or plasmapheresis, 2 - ongoing treatment at enrollment, 3 - a MG-Activities of Daily Living (MG-ADL) total score at enrollment of at least 6. These refractory patients were experiencing worse scores on MG-15-item Quality of Life (MG-QOL-15).
Methods: From 19-10-24 to 19-12-20, 16 consecutive patients from Western Quebec, a mostly French-Canadian community, scheduled for regular follow-up with the author, were asked to complete both a MG-ADL and MG-QOL-15 instrument. The author, his nurse, and his EMG technician completed Quantitative Myasthenia Gravis score (QMG), Myasthenia Gravis Foundation of America Clinical Classification (MGFA), spirometry and dynamometry.
Results: Almost all scales were successively completed. Patients' age range between 28 and 82 years. Eleven patients are AARA positive on a standard laboratory essay (69%). Fourteen are using second line treatment of therapy and 12 (75%) are on continuous IVIg, plasmapheresis or rituximab. Two are MGFA = 4. The mean MG-ADL is 5.5 (7 equal or more than 6), MG-QOL-15 is 11.1 (6 equal or more than 15), QMG is 7.3 (7 equal or more than 10). Correlations have been found between MG-ADL and MG-QOL-15 ($r = 0.55$) and MG-ADL and QMG ($r = 0.56$). Five (31.3%) meet the definition of refractory generalized myasthenia according to American Registry and would be eligible for the phase-3 REGAIN study on eculizumab. Another is currently AARA seronegative and less than 12 months from initial diagnosis. Qol-15 and QMG were found to be worse in refractory patients.
Conclusion: Implementation of systematic follow-up is feasible in an out-of-hospital community general neurology practice. Many of the author's patients remain negatively impacted despite undergoing current clinical care guidelines. According to the American Registry definition, about one third of patients are refractory, considerably worse than the 7% reported in this registry and the 15% commonly cited in the literature,[2] and would fulfill criteria for the REGAIN Study.

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A Nationwide Survey on X-linked Myopathy with Excessive Autophagy (XMEA) in Japan

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X-linked myopathy with excessive autophagy (XMEA) is a very rare X-linked recessive vacuolar skeletal myopathy. XMEA is pathologically very similar to Danon disease. Causative mutations have been identified in the VMA21 gene on Xq28. However, the clinical features of XMEA have not been well established. Therefore, to evaluated the clinical features and management of XMEA, we sent questionnaires on XMEA to 2,617 hospitals in Japan that

have departments of neurology, cardiology, or pediatrics. We reviewed clinical histories, muscle specimens, and genetic analyses of the VMA21 gene.

As a result, we identified 12 XMEA male patients from 4 families in Japan. Onset was from birth to childhood. All patients showed progressive proximal muscle weakness of the extremities. Among the 9 patients who had died, all died of respiratory failure or pneumonia during the infantile period for 6 patients and the fifth decade for 3 patients. Cardiomyopathy was not evident in all, although 3 patients showed mild cardiomegaly. All patients showed autophagic vacuoles with sarcolemmal features (AVSF) in muscles. In addition, they showed depositions of complement C5b-9 over the surface of muscle fibers and multilayered basal lamina along the sarcolemma, which were not seen in Danon disease. All families had VMA21 gene mutations. We found c.164-6T>G in 2 families, c.161A>T in 1 family, and c.164-7T>G in the other family. Previously we reported one family with c.164-6T>G as a congenital autophagic vacuolar myopathy (CAVM) and the other as an infantile autophagic vacuolar myopathy (IAVM).

In conclusion, XMEA is an extremely rare disorder characterized by strictly skeletal muscle disease and may be primarily caused by lysosomal dysfunctions. None of the XMEA patients had cardiomyopathy except for 3 patients with cardiomegaly, which is critically different from Danon disease. In addition, we conclude that CAVM and IAVM are allelic to XMEA, caused by a severe VMA21 mutation. Our findings suggest that XMEA is more clinically variable than previously thought.

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Diagnostic Value of NGS in Distal Myopathies

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Distal myopathies (DM) are a heterogeneous group of muscle diseases caused by mutations in different genes. The new generation sequencing technology (NGS) has improved the diagnosis, although a proportion of patients remain still undiagnosed.

The objective was to evaluate the efficiency of a NGS approach using a self-costumed panel of neuromuscular genes in patients with DM.

Seventy-five patients who remained undiagnosed of a series of 125 cases with DM on follow up in a Neuromuscular Unit in the Valencia Country were studied. Thirty-five cases were sequence by PANEL1 (40 genes; Ion Torrent technology) during 2016-2017 and 40 cases were sequence by PANEL2 harboring of 272 genes based on Illumina technology from 2017-2019.

A definitive molecular diagnosis was reached in 45% of the investigated cases, being the frequency of genes as follows: 27% ANO5, 18% TTN, 9% DYSF, 9% MYOT, 6% GNE, 6% HSPB1, 6% MYH7 and a single case was detected of each of these genes: HNRPDL, VCP, COL6A2, BICD2, EMD, NEB and TPM2. A probable diagnosis was obtained in 16% cases, with the following yield: ANO5, TTN, TCAP, DYSF, POLG, CAPN3, COL6A1, BAG3, HNRPDL and LDB3. 39% of the cases remained unsolved.

Our results demonstrated the efficacy of NGS in the diagnosis of DM. This approach is also useful to diagnose atypical phenotypes in DM. However, this procedure provides a large amount of unprocessed data that requires experience and sometimes biological analysis in tissues or cells to confirm the pathogenicity of the variants found.

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Diagnostic Yield of an NGS Panel of Muscle Genes in a Neuromuscular Diseases Reference Unit

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Next generation sequencing (NGS) methods have become a fundamental tool for the diagnosis myopathies. However, its final performance must be evaluated in a global context taking into account clinical aspects and biomarkers, often requiring a multidisciplinary interpretation.

The objective is to evaluate the diagnostic performance of two home design gene panel in muscular

diseases. We studied 417 undiagnosed patients at a Reference Center in Valencia County. First we sequenced 253 cases by an Ion Torrent PANEL1 composed of 40 genes during 2015–2017 year period. An Illumina PANEL2 harboring of 272 genes was applied to 184 subjects (including PANEL1 unsolved cases) during 2017–2019.

PANEL1 gave a diagnostic outcome of 24% confirmed, 32% possible and 44% inconclusive cases; being ANO5, FKRP, DES and MYH7 the most frequent gene mutations. PANEL2 yielded 32% confirmed, 26% possible and 42% inconclusive cases; in this group the most frequent mutations were those related to metabolic myopathies and channelopathies genes.

The global performance rate was 28% with definitive molecular diagnosis, 27% of a possible one and 45% remained unsolved.

These results confirm NGS is a very useful tool in the study of neuromuscular diseases, especially when the panel contains a large gene list and hold high coverage. Nevertheless, this procedure provides many raw data that requires experience and sometimes biological analysis in tissues or cells to confirm the pathogenicity of the variants.

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TOPAZ: Phase 2 Study Evaluating Efficacy and Safety of Apitegromab in Later-Onset Spinal Muscular Atrophy

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Apitegromab (SRK-015) is an investigational fully human, high-affinity anti-proMyostatin monoclonal antibody that binds to human proMyostatin and latent myostatin and inhibits the tolloid-mediated proteolysis step for myostatin activation. As proMyostatin is the predominant form of myostatin in skeletal muscle, apitegromab inhibits myostatin activation directly in target tissues. The primary objective of the 52-week Phase 2 trial (TOPAZ) was to assess safety and tolerability of apitegromab, administered by IV infusion every 4 weeks, in subjects with later-onset Type 2 and Type 3 SMA, aged 2- 21 years old and measure changes in motor function. The primary endpoint was mean change in baseline Hammersmith Scale scores. Secondary objectives were to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) effects of apitegromab, therapeutic effects of low-dose (2 mg/kg) and high-dose (20 mg/kg) apitegromab, immunogenicity and other exploratory motor function measures. Subjects received apitegromab as monotherapy or with an approved SMN upregulator (nusinersen). The results of an interim analysis showed subjects in Cohort 1 (ambulatory Type 3, n=23), who received apitegromab (20 mg/kg) as monotherapy (n=11) or as an adjunctive treatment to nusinersen (n=12), had a pooled mean change in baseline Revised Hammersmith Scale (RHS) scores of 0.5 (-1.1, 2.2). Cohorts 2 (n=14) and 3 (n=18) included Type 2 and non-ambulatory Type 3 subjects, who received apitegromab (Cohort 2, 20 mg/kg; Cohort 3, 2 mg/kg and 20 mg/kg) as an adjunctive treatment to nusinersen. Cohort 2 had received nusinersen since they were 5 years old and Cohort 3 included subjects ≥2 years old receiving nusinersen, which was started before they turned 5 years old. Subjects in Cohort 2 achieved a mean change in baseline Hammersmith Functional Motor Scale Expanded (HFMSE) scores of 1.4 (0.1, 2.7). In the low-dose Cohort 3 group, the mean change in baseline HFMSE scores was 2.4 (-0.9, 5.8). In the high dose Cohort 3 group, the mean change in baseline HFMSE scores was 5.6 (2.5, 8.7).

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Hyperlipidemia in Patients with Myotonic Dystrophy Type 2

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Objective: Myotonic dystrophy is a multisystem disorder with high frequency of metabolic changes. Hypercholesterolemia and hypertriglyceridemia are well known condition in myotonic dystrophy and occurs up to 63 %. In general, the prevalence of hypercholesterolemia in the Czech population is about 40%. Patients with hyperlipidemia are at increased risk of cerebrovascular diseases, so the lipid lowering drugs have to be prescribed. In myotonic dystrophy (and other muscle diseases) is widely known that statins can cause muscle problems.

The aim of this study was to assess the frequency of hypercholesterolemia and hypertriglyceridemia and the frequency of using lipid lowering drugs in patients with myotonic dystrophy type 2 (MD2).

Methods: 58 patients with MD2 (mean age 53.6 ± 12.6; range 19 – 77 years) were involved in this study. The serum levels of total cholesterol, HDL and LDL cholesterol and triglycerides were measured by the standard laboratory methods during the routine screening tests.
Results: The total cholesterol level was elevated in 52 patients (89.7 %). High level of LDL cholesterol was found in 22 patients (37.9 %) and HDL cholesterol level was in normal range in all patients. The average level of total cholesterol was 6.19 mmol/L, the average HDL cholesterol level was 1.79 mmol/L and LDL cholesterol was 3.44 mmol/L. Increased serum triglyceride level was in 27 patients (46.6 %) and the average level was 2.28 mmol/L. Only 14 patients (24.1%) used some lipid lowering drugs (rosuvastatin > atorvastatin > ezetimibe > fenofibrate > simvastatin, PCSK9 inhibitors). In 5 patients (8.6 % of all patients; 26.3 % of patients used lipid lowering drugs) the statin therapy was stopped, when the myotonic dystrophy was diagnosed, although no evidence of adverse effects of statins was present in patients. For 31 patients (53.4%) the hyperlipidemia was a newly detected abnormality.
Conclusions: Hyperlipidemia is a frequent metabolic abnormality in myotonic dystrophy. It seems there are some fears of prescribing statins in myotonic dystrophy, although patients with hyperlipidemia without the treatment are at increased risk of cerebrovascular diseases.

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Profiling Serum Antibodies Against Muscular Antigens in Facioscapulohumeral Muscular Dystrophy (FSHD)

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Facioscapulohumeral dystrophy (FSHD) is a complex (epi)genetic muscular disorder often inherited in an autosomal dominant fashion. Progressive muscular weakness and atrophy of facial, upper, and lower limb skeletal muscles are the disease clinical hallmarks, whereas FSHD histology is often characterized by inflammatory infiltrates whose nature is still far from clear. The FSHD mutation results in the expression of the otherwise epigenetically silenced Double Homeobox 4 gene (DUX4), a transcription factor, which is toxic to skeletal muscle cells by targeting multiple downstream genes. Both innate and adaptive immune genes are found among the DUX4 targets. We hypothesized that DUX4-induced aberrant expression of immune genes might trigger an auto-inflammatory reaction against skeletal muscle cells, thereby explaining the nature of the frequently described inflammatory muscle infiltrates. The aim of this study was to investigate the presence of autoantibodies against muscular antigens in FSHD patient sera. Autoantibodies directed against muscular antigens occurring in sera of 138 well characterized FSHD patients and in 11 healthy control (HC) sera were detected by immunoblotting and immunofluorescence. The reactivity of FSHD and HC sera was analysed with various muscular protein extracts (as a source of muscular antigens): healthy skeletal muscle, FSHD skeletal muscle, cultured healthy and FSHD myotubes, and cultured DUX4-expressing myoblasts. All protein extracts were used for immunoblotting analyses, whereas the immunofluorescence analyses were performed with the DUX4-expressing myoblasts. Although FSHD sera were found to be reactive with several muscular polypeptides, their reactivity with all the tested muscular antigen preparations did not significantly differ from that of HC sera. Therefore, this approach did not lead to the identification of a disease-specific autoantibody in the FSHD cohort. Moreover, the staining of DUX4-expressing myoblasts did not differ when incubated with either FSHD or HC sera. Importantly, the lack of specific autoantibodies in the tested cohort might exclude autoantibody-mediated pathology as a disease mechanism in FSHD. Nevertheless, exploring the role of inflammation in FSHD might have crucial therapeutic implications. Therefore, other immune pathways, both innate and adaptive, warrant further investigation.
Key words: autoantibodies, skeletal muscle antigens, inflammation, facioscapulohumeral muscular dystrophy

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PROMISE-MG: A Comparative Effectiveness Study of Myasthenia Gravis Treatments: Study Design, Demographics and Baseline Data

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Objective: To present the study design, demographics and baseline data of the PROMISE-MG study, a multicenter, prospective, observational comparative effectiveness study of treatments for MG.

Background: High-quality randomized controlled trials of immunosuppressive/ immunomodulatory (IS/IM) treatments for myasthenia gravis (MG) are sparse due to difficulties with patient recruitment/ retention and the heterogeneous nature of MG. Evidence for comparative effectiveness of IS/IM treatments for MG is not available.

Specific Aims: To compare outcomes at 24 months in:

- MG patients receiving azathioprine vs. those receiving mycophenolate
- Patients receiving vs. not-receiving azathioprine/mycophenolate at adequate doses/duration

Exploratory Aims:

- Effectiveness and adverse effects of high dose steroid initiation vs. low dose escalating regimens
- Comparative effectiveness of corticosteroids vs. no corticosteroids in preventing generalization of ocular MG at 24 -36 months of treatment
- Quantitative and qualitative analysis of discordance between clinician-reported and patient-reported outcomes
- Analysis of demographic patterns compared to clinical trial populations

Inclusion criteria: autoimmune MG, age >18 years, no IS/IM treatment or thymectomy prior to initial study visit.

Protocol: Patients are treated as in routine clinical practice with treatment choices, visit frequency and laboratory monitoring at physician discretion. De-identified data are entered into a central RED-Cap database.

Co-Primary outcomes:

- MG-Quality of life (MGQOL-15r)
- Achieving Minimal Manifestation status with no more than grade 1 adverse effects (Common Terminology Criteria for Adverse Events). Secondary Outcomes:
- MG-composite (MGC)
- MG-Activities of daily living (MG-ADL)
- MG-Manual Muscle Test (MG-MMT)
- Visual Analog Scale (VAS) for disease severity
- VAS for severity of side effects from MG treatments
- Hospitalizations for MG

Descriptive statistics were used for initial visit data; Pearson correlation was used to calculate association between outcome measures.

Results: One hundred sixty seven participants are enrolled from 19 USA/Canadian centers: male 62%, 93% White. Mean age at disease onset: 64±14 years (females 61±17, males 66±11). MGFA class: I (Ocular) - 40%, II - 37%, III - 21%, IV/V - 2%. Mean disease duration: 1.3±2.5 years; 76% AChR-Ab positive, 6% MuSK-Ab positive. Thoracic imaging: normal/involuted thymus in 88%, thymoma in 6.5%.

At initial visit, 57% were taking pyridostigmine and treatment was started or changed in 73.5% (66% pyridostigmine, 23% corticosteroids). Mean outcome measure scores± SD: MGQOL-15r - 10.9±8.2, MGC - 8.6±6.2, MG-MMT - 8.2±6.6, MG-ADL - 5.5± 3.2. Correlations between MGC/MG-ADL and MGC/MG-MMT were strong (r=0.79 and 0.71, respectively, $p<0.0001$); other measures correlated moderately with each other (r=0.54 to 0.68, $p< 0.0001$).

Conclusions: PROMISE-MG is a novel trial design evaluating treatments in real world settings. Participants are predominantly male, with disease onset in the 7th decade; this differs from the typically described demographics of MG – potential reasons will be discussed.

Correlation was moderate between the patient reported MG-ADL and MGQOL15r. Correlation was highest between MGC/MG-ADL and MGC/MG-MMT, probably because MG-ADL and MG-MMT are components of MGC. MG-MMT and MG-ADL correlated the least, likely because of differences between clinician-evaluated muscle strength and patient-reported functional assessments. Thirty-two percent of participants have completed 24 months follow-up; the study is ongoing.

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A New Mutation in the C12orf65 Gene Causes a Severe Predominant Motor Neuropathy

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Background: The C12orf65 gene is a nuclear gene that encodes a mitochondrial matrix protein contributing to mitochondrial translation. Deleterious mutations in the C12orf65 gene causes a phenotype of early onset optic atrophy, peripheral neuropathy and spastic paraparesis .

Next-generation sequencing techniques continue to expand genetic causes of neuropathy. These genes known to cause complex inherited disorders may present with an isolated neuropathy.

Methods: We studied a 34-year-old Honduran male with no consanguineous parents, motor neuropathy and optic atrophy. His delivery was normal, with normal motor and mental development in infancy. At the age of 5 years he developed insidious visual impairment and at 8 years he showed difficulty running due to bilateral foot drop without sensory impairment. He has at least 2 cousins with similar symptoms but none of them have a genetic diagnosis.

Neurological examination revealed loss of visual acuity with bilateral optic atrophy, pes cavus deformity with flexion contracture of the toes with severe atrophy of the distal leg muscles resembling a reversed-champagne bottle. Manual muscle examination revealed bilateral symmetrical weakness, worse distally. Toe and ankle flexors and extensors were 0/5 (Medical Research Council), knee flexors 4-/5, knee extensors 4/5 and hand intrinsics 4+/5. Deep tendon reflexes were brisk upper limbs and knees with absent deep tendon reflexes in ankles. Sensitivity to pinprick, touch, temperature, positioning, and vibration was normal in all the limbs. There were no other pyramidal signs, with normal muscle tone in upper limbs.

Nerve conduction studies were consistent with bilateral motor axonal neuropathy with absent compound muscle action potential (CMAP) and F waves in lower limbs and low-amplitude CMAP in upper limbs, sparing the sensory nerves (normal amplitude and velocity). Motor nerve conduction velocities (MNCVs) in upper limbs were mildly decreased. Needle electromyography revealed a neurogenic pattern mostly distal and symmetrical with large motor unit action potentials.

Results: We used exome sequencing and we identified in apparently homozygosis the frameshift pathogenic variant c.418_422del (p.R141Kfs*13) in the C12orf65 gene (NM_152269.4) which predicts a truncated protein lacking the C-terminal portion.

Conclusions: This novel frameshift variant in the C12orf65 gene cause a severe predominant motor axonal neuropathy with optic atrophy. Our finding extend the genotyping and phenotypic spectrum of the C12orf65 gene.

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Myotonic Dystrophy Type 1 Aassociated with the Brain's White Matter Abnormalities: A Case Report

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Introduction: Myotonic dystrophy type 1 (DM1) is an autosomal dominant multisystemic disorder that affects skeletal and smooth muscle as well as the eye, heart, endocrine system, and central nervous system (CNS). This disease is caused by CTG repeat expansion on chromosome 19q. Poor sleep quality, fatigue and daytime sleepiness have a big impact on the quality of life of DM patients.

Case report: We report a fifty-years-old woman with familiar history for DM1, manifested temporal, ocular and bulbar muscle weakness, slight flexor neck, distal limb weakness, mild intermittent myotonia, bilateral cataract and sterility. Deep tendon reflexes were absent. Also, she suffered a stroke-like episode, followed by right hemiparesis, six months ago. Equally important, the CK level was 274 U/l (reference range 22 U/L - 198 U/L). Moreover, generalized myotonia and myopathic changes were observed on electromyography (EMG). On the other hand, skeletal muscle biopsy showed myopathic changes: varied fiber size, endomysial connective tissue mildly increased, type I fiber predominance. Notably, MRI of the brain gave us this data: bilateral multifocal changes in white matter, periventricular and in brain steam, hyperintense on T2-weighted and proton-density-weighted MR images, as well as hypointense on T1-weighted scans. MRI of the cervical spinal cord and MRI cerebral angiography

were normal. Apart from that, cerebrospinal fluid (CSF) was normal, with no evidence of immunological activity. Electroencephalography (EEG) and evoked potentials were also normal. Neuropsychological testing showed mild cognitive impairment. To sum up, finding definite MRI abnormalities in this patient with DM1 is evidently. Surely, an examination of the CSF gave no evidence of an inflammatory process. The morphology underlying this leukoencephalopathy remains unknown. The MRI pattern suggests a process affecting the perivascular spaces or small pial vessels. As well, microangiopathy is another possible mechanism.

Conclusion: The causative relationship of these clinical features with the magnetic resonance imaging (MRI) white matter abnormalities remain to be established. Novel advances in the understanding of the molecular mechanisms involved in DM1 provide opportunities for new diagnosis perceptions and new therapeutic strategies.

Keywords: myotonic dystrophy type 1, MD1, magnetic resonance, leukoencephalopathy

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A Case of HNRNPA1 Gene Mutation with Multisystem Proteinopathy Presenting as Inclusion Body Myopathy

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Background: Multisystem proteinopathy (MSP) is a rare adult onset inherited degenerative disorder characterized by inclusion body myopathy (IBM), early-onset Paget's disease of bone (PDB) and premature frontotemporal dementia (FTD). In over 99% of cases when a genetic cause is identified, a pathogenic variant can be identified in the VCP gene. However, there are case reports of families presenting similarly with pathogenic variants in the HNRNPA1, HNRNPA2B1, HNRNPDL, MYH2, SQSTM1, and MATR3 genes. We identified a family with IBM and PDB, with pathogenic variant in the HNRNPA1 gene.

Case report: 46 year old male presented to our clinic with a 10 year history of asymmetric weakness of the right foot that worsened over the years to involve bilateral proximal legs leading to multiple falls per week. He did not have weakness of facial, neck, arm or trunk muscles, neither sensory deficits. Electrodiagnostic studies demonstrated myopathic changes proximally and distally in the lower extremities. A muscle biopsy of the left quadriceps muscle revealed chronic myopathy with rimmed vacuoles without inflammatory findings, consistent with hereditary hIBM. He underwent genetic testing for hIBM (GNE, HNRNPA2B1, MYH2, TTN, VCP), which was unrevealing. His mother was diagnosed with IBM at 60 years of age, after 10 years of carrying the diagnosis of PDB. Her diagnosis of IBM was confirmed by muscle biopsy. Given family history we pursued further genetic testing. A custom gene panel was created based on the recent advances in MSP genes (HNRNPA1, HNRNPDL, SQSTM1 and MATR3), which revealed a pathogenic variant (c.941A>T, p.Asp314Val) in the HNRNPA1 gene. This has been previously reported in a German family, with hIBM and PDB in six and three family members respectively.

Conclusion: To our knowledge, this is the second reported case of a family with a pathogenic variant in the HNRNPA1 gene manifesting with IBM and PDB. Unlike the prior case, distal asymmetric leg weakness was the initial presentation in our case. Cognitive impairment was not a part of the MSP in our case, consistent with the prior presentation. Here we also emphasize the importance of custom gene panel in cases with strong family history and unrevealing testing based on the existing panels.

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Long-Term Observation of Enzyme Replacement Therapy for Pompe Disease in Japan

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Introduction: Alglucosidase alfa received marketing approval for the treatment of Pompe disease in Japan in 2007. In accordance with the Good Post-marketing Surveillance Practice ordinance, we conducted a post-marketing surveillance study to monitor the long-term safety and effectiveness of alglucosidase alfa therapy among Japanese patients with Pompe disease.

Methods: The outcome data on the safety and effectiveness were collected as real-world data for up to 9 years following the initiation of treatment with alglucosidase alfa, without any intervention to

treatment strategies. The surveillance was targeting all the Pompe disease patients to whom alglucosidase alfa was administered during the surveillance period, and the data was collected from 92 patients. Among them, we here analyzed 73 patients' data with the permission of data usage for the publication. The safety of the drug was assessed in terms of the rate of drug-related adverse events, infusion-associated reactions, and anti-alglucosidase alfa antibody titers. The effectiveness was evaluated with the survival rate, pulmonary and motor function tests. We also evaluated whether the of antibody expression exerted negative impact on the safety and/or effectiveness of the enzyme replacement therapy.

Results: Drug-related adverse events were observed in 29 of 73 (39.7%) cases, and the cumulative adverse event rate during the 9 years of the study was 45.7%. Immunoglobulin G antibodies against alglucosidase alfa were positive in 59 of 61 cases in which the titers were not correlated with drug-related adverse events or infusion-associated reactions. Survival of infantile-onset cases was sustained for 9 years. The results of the physical function tests suggested that the treatment could have slowed disease progression. The antibody titer was also not significantly correlated with long-term pulmonary function outcome. Although the available data were limited, there was a tendency that the patients with larger temporal gaps between the disease onset and treatment initiation showed poorer trajectory of respiratory function.

Conclusion: Alglucosidase alfa was generally well tolerated in Japanese patients. No new concern of safety and effectiveness was found from this surveillance.

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Autoantibody Valency Dictates Their Pathogenicity in MuSK Myasthenia Gravis

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In myasthenia gravis, autoantibodies against proteins in the neuromuscular synapse cause fatigable skeletal muscle weakness. In ~5% of patients, these autoantibodies bind muscle-specific kinase (MuSK), a protein essential for establishment and maintenance of neuromuscular synapses. In serum, MuSK antibodies are predominantly of the IgG4 subclass. IgG4 antibodies are unique as they exchange half-molecules with other IgG4 molecules in a dynamic and continuous process called Fab-arm exchange. This results in bispecific antibodies and, consequently, functional monovalent antigen binding. To investigate whether the functional valency of MuSK antibodies (i.e. having one or two binding sites for MuSK) contributes to their pathogenicity in MuSK myasthenia gravis, we generated recombinant monoclonal MuSK antibodies (i.e. bivalent antigen binding) from patient-derived IgG sequences. To model Fab-arm exchanged functional monovalent serum IgG4 we digested these into Fab fragments or generated stable bispecific monovalent MuSK antibodies. In vitro characterization in C2C12 myotubes cultures revealed that monovalent anti-MuSK Fab fragments and bispecific antibodies inhibit agrin-induced MuSK activation and acetylcholine receptor (AChR) clustering, similar to polyclonal patient-purified IgG4. Surprisingly, bivalent MuSK antibodies act as (partial) agonist on MuSK signalling independent of agrin. In NOD/SCID mice, monovalent MuSK antibodies caused rapid and severe myasthenic muscle weakness, whereas the same antibodies in their parental bivalent form were less potent or did not induce a phenotype. Thus the functional monovalency of MuSK IgG4 autoantibodies amplifies their pathogenicity. MuSK autoantibody isotype switching and consequently Fab-arm exchange of anti-MuSK IgG4 in patients seem important steps in the pathomechanism in MuSK myasthenia gravis.

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Treatment of Myasthenia Gravis: Experience of Our Hospital

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Objective: Myasthenia Gravis (MG) is a treatable neurologic condition whose treatment must be individualized. There are few reports about real life treatment patterns of the disease. We describe the treatment patterns of MG in a third-level hospital.
Methods: We retrospectively reviewed the medical history of all the patients with diagnosis of MG in follow-up by our neuromuscular diseases unit in the period 1/1/2013-30/10/2019 and analyzed their therapeutic information.
Results: Information about 135 patients (68 males) was analyzed. 38 patients (28%) had ocular MG and 97 (72%) generalized MG. Anti-acetylcholine receptor antibodies were positive in 61.5% of all patients and Anti-muscle specific tyrosine kinase antibodies were positive in 1 patient. The mean age at diagnosis was 50.1 and 7 patients (5,2%) died in this period –known cause in 4: 2 infections and 2 neoplastic disease-. Current mean age is 60.8 and average follow up time since diagnosis of alive patients is 10.8 years. 45 patients (33.3%) were thymectomized. 8 patients had a thymoma. The first treatment was: 72% pyridostigmine alone, 20% pyridostigmine and corticotherapy, 1.5% pyridostigmine and intravenous immunoglobulins (IVIG) and 6,5% pyridostigmine, corticotherapy and IVIG.

All patients have been on pyridostigmine and 85% currently take it. 5% didn't tolerate it and it was ineffective in 2.5%. 10 patients (7.5%) have stopped pyridostigmine because they are asymptomatic -9 have ocular MG-. Current mean dose of pyridostigmine is 205 mg/day. 97 patients (72%) required immunosuppressive agents (IA) at some point of the disease. 96% received corticosteroids, 37% azathioprine and 7,2% mycophenolate mofetil. Other treatments used were tacrolimus, cyclosporine and rituximab in 3 patients each and methotrexate in 1 patient.

Nowadays, 76 patients (56.3%) are in treatment with IA: 77,6% are taking corticosteroids, 25% azathioprine, 6,6% tacrolimus and 3,9% mycophenolate mofetil. Cyclosporine, rituximab and methotrexate are now used by 1 patient each. 38 patients could stop corticosteroids due to a good control of the disease. The current mean dose of prednisone is 8.28 mg/day. The average time taking corticosteroids is 5.68 years.

Patients with generalized MG needed IA treatment more frequently: 14,5% of generalized MG never received IA, against 63,2% of ocular MG. 30% of generalized MG have stopped IA, against 79% of ocular MG.

28 patients (21%) received IVIG sometime: 16 (11.9%) once, 6 (4.5%) twice and 6 three or more times.
Conclusions: We present our data about 135 MG patients treated in our hospital since 2013. Pyridostigmine was used in all patients and it was usually effective and well tolerated. Corticosteroids are usually needed for more than 5 years in spite of the use of steroid-sparing agents, but usually at low doses (< 10 mg/day). The majority of generalized MG patients required IA. 21% of patients received IVIG at some point of the disease.

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Descriptive Analysis of Acquired Motor Neuron Diseases in the Northern Area of Tenerife

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Objective: To describe the basic epidemiological and clinical aspects of acquired Motor Neuron Diseases (MND) in the northern area of Tenerife.
Methods: We retrospectively reviewed the medical history of all the patients with diagnosis of Amyotrophic Lateral Sclerosis (ALS), Primary Lateral Sclerosis (PLS) or Progressive Muscular Atrophy (PMA) in follow-up by the Neuromuscular diseases unit of our hospital in the period 1/1/14-30/10/19, to do a descriptive analysis of their main epidemiological and clinical aspects. The reference population of our hospital is 396483 people.
Results: 63 cases of MND were found: 58 ALS (92%), 3 PMA (4,8%) and 2 PLS (3,2%). 33 (52,4%) patients were females and the mean age at diagnosis

was 60,9 years old. The current prevalence is 6,55 per 100000 people and the incidence in the 5 years period from October of 2014 to October of 2019 was 1,96 per 100000 people. 37 (58,7%) patients died in this period, with an average surveillance since diagnosis of 24,8 months. Alive patients currently accumulate an average of 4,6 years of follow-up since diagnosis.

Average time from the first symptom to diagnosis was 17 months. The most frequent first symptoms were monoparesis (39,7%), bulbar symptoms (28,6%) and paresis of more than 1 limb (19%). Nevertheless, 7 patients (11,1%) had a debut symptom that didn't include limb paresis or bulbar impairment: 3 muscle cramps, 2 isolated fasciculations, 1 bilateral phrenic nerve palsy and 1 abdominal muscles weakness.

69% of patients fulfilled Awaji-Shima criteria in the first electromyographic study performed, while 9,5% presented any generalized denervation signs, 18% had a study suggestive of an alternative diagnosis and 3,5% had a normal study. Available antiganglioside antibodies in our hospital – anti-GQ1b, anti-GT1b, anti-GD1b, anti-GD1a, anti-GM1, anti-GM2 and anti-GM3- were mesured in 35 patients. 2 patients had positive anti-GM2 IgG antibodies, but the rest (94,3%) didn't show any of them.

Respiratory support was required by 60,7% of patients, but only 2 were tracheostomized. Non-invasive ventilation was offered to 35 (55,5%) patients, but 6 didn't tolerate it and 1 rejected it. 33% had gastrostomy performed. 4 patients (6,3%) fullfilled diagnostic criteria for associated frontotemporal dementia: 3 frontal variant and 1 primary progressive aphasia. Riluzole -50 mg orally twice daily- was used throughout the disease in 80,6% of patients. Due to secondary effects, 2 patients needed a dosage reduction and 9 patients (14%) had to stop it completely. It was never started in 1 patient due to a previous hepatopathy.

Conclusions: We report, in the best of our knowledge, the first epidemiological and clinical data about acquired MND in the Canary Islands. Our results globally agree on those reported in other regions of the world. Atypical presentation without limb paresis or bulbar symptoms were observed in 11,1% of patients and the first electromyographic study didn't fulfill the Awaji-Shima criteria in 31%. Riluzole was globally well tolerated.

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Guillain-Barre Syndrome in the Northern Area of Tenerife

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Objective: To perform a descriptive study about Guillain-Barré Syndrome (GBS) in the northern area of Tenerife.

Methods: We retrospectively reviewed the medical history of all the patients diagnosed with GBS in follow-up by our neuromuscular diseases unit between 1/1/2013 and 30/10/2019, in order to analyze their epidemiological, clinical and prognostic information.

Results: 26 cases of GBS were identified, subclassified into the following variants: 18 acute inflammatory demyelinating polyradiculoneuritis (AIDP), 2 Miller-Fisher syndrome (MFS), 5 acute motor axonal neuropathy (AMAN) and 1 acute motor-sensitive axonal neuropathy (AMSAN). 6 patients suffered GBS before 2013, 8 from 2013 to 2016 and 12 from 2017 to 2019. 19 patients (73%) were males and the mean age at diagnosis was 45.4.

Based on the 20 patients identified since 2013, the incidence of GBS was 0,72 cases per 100,000 persons. Incidence measured in the last 3 years rises up to 1.01 per 100000 persons.

Most patients (52%) were admitted on the first 2 days after the onset of symptoms and 76% on the first week. 80,5% had a preceding infection (respiratory tract infection in 11 and gastrointestinal infection in 10). No cases associated with previous vaccination were recorded. Isolated motor symptoms (42%) and isolated sensory symptoms (31%) were the most frequent initial manifestations of the disease. Hyporeflexia or areflexia was described in 71% of patients.

Regarding the cerebrospinal fluid analysis of the first lumbar puncture, 48% of patients had hyperproteinorrachia (>50 mg/dL) and 87% had normal leukocyte counts (<10 leukocytes/mm3). The absence of hyperproteinorrachia appeared to be associated with an early lumbar puncture: all patients admitted after the first week had hyperproteinorrachia, compared to 12.5% of those admitted on the first day. Only 43,5% had albuminocytologic dissociation.

The first electromyographic study was compatible with GBS in 81% of cases. We didn't find a clear association between the early realization of the electromyography and the normality of the test. Only 8,3% of patients presented both a normal first electromyography and a first cerebrospinal fluid analysis without albuminocytologic dissociation. All patients were admitted to the hospital and received specific treatment of GBS. Intravenous immunoglobulins (IVIG) -0,4 g/Kg/day for 5 days- was the most used treatment (94,5% of patients). After the first IVIG, 2 patients repeated IVIG treatment and 1 received plasma exchange. Only 1 patient received isolated plasma exchange. 11 patients were admitted in our intensive care unit, but only 2 patients required intubation.

All patients survived the acute disease, but 1 patient with severe residual tetraparesis died 3 years later due to a respiratory infection. Nowadays, only 4 patients (16%) are completely asymptomatic. 32% present different degrees of weakness, 16% remain with cranial nerves symptoms and 12% have some degree of mixed sensory-motor deficit in their limbs. 37% required treatment of neuropathic pain after the GBS, but half of them could stop the treatment because of improvement.

Conclusions: We present, in the best of our knowledge, the second report about GBS in the Canary Islands. Our epidemiologic results are similar to those of other European regions.

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Unilateral Neuralgic Amyotrophy After Viral Infection. Cytomegalovirus vs Hepatitis E virus. Are There Any Differences?

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Introduction: Neuralgic Amyotrophy (NA) usually presents as unilateral shoulder pain with proximal weakness. It is preceded by an infection in about 40% of cases. Hepatitis E Virus (HEV) has been reported in association with peripheral nervous system diseases such as NA. The typical clinical course is a man with prodromic anicteric hepatitis (90% abnormal function liver tests) and asymmetric bilateral brachial NA (only 20% unilateral involvement). Cytomegalovirus (CMV) infections are rare in healthy patients. There are only five cases of NA associated with CMV described in literature. 80% have abnormalities in Function Liver Tests (FLT) and 20% unilateral brachial presentation. Our objective is to compare clinical characteristics, complementary tests and outcome after one year follow-up in patients with unilateral brachial NA associated with CMV or HEV in our hospital. We present a case associated with CMV and three with HEV. See details in table 1.

Results: Case-1: 40 year-old man, admitted because of severe pain and weakness in right shoulder within 24 hours. 10 days before he suffered from fever and malaise. Blood test: elevation of FLT. Serology results for CMV: High titer of IgM antibodies, low titer of IgG. Serology for HEV: negative. He was treated with Immunoglobulins and rehabilitation. One year later, there was partial weakness recovery.

Case-2: 53 year-old-man, admitted because of one day of severe pain and weakness in right shoulder. 6 days before he suffered from fever and malaise. Blood test: elevation of FLT and positive IgM against HEV. IgM test for CMV: negative. He was treated with Immunoglobulins and rehabilitation. One year later, total recovery happened.

Case-3: 56 year-old-man, admitted because of mild pain in right shoulder and distal weakness after 18 months. Complementary tests in the second week within the initial symptoms showed abnormal FLT. There was not any previous infection. In the moment of our evaluation, IgG test was positive for HEV. He received rehabilitation treatment. One year later, there was partial weakness recovery.

Case-4: 53 year-old-man, admitted because of weakness and mild pain in right shoulder and sensory disturbances in first three fingers for 12 months. He suffered diarrhea and malaise 10 days before initial symptoms. HEV IgG result was positive. One year later, total recovery happened.

Discussion and Conclusions: We present the second case described of unilateral brachial NA associated with CMV infection and three cases of unilateral NA associated with HEV infection. Case-1 (CMV) and Case-2 (HEV) are very similar in terms of clinical presentation, infectious antecedent, liver alterations and treatment given. They mainly differ in age, viral etiology and outcome. Case-3 (HEV) and Case-4 (HEV) are very similar in terms of clinical presentation, serology results and outcome. The main difference between them and Case-1 and Case-2 is the longer time to hospital attendance

because of way of presentation, which could involve the rest of differences.

We suggest investigating HEV and CMV serology in patients with unilateral NA, due to viral associations could be easily overlooked. Abnormalities in FLT could be a clue in patients with an abrupt onset.

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Myasthenia Gravis and Pregnancy: Descriptive Analysis of a Cohort of Women with Myasthenia Gravis

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Background and Aims: Myasthenia gravis (MG) presents a peak of incidence in women in the 2nd and 3rd decade of life, which overlaps with childbearing years. As pregnancy and MG can affect each other, a close follow-up in young women is key to optimize treatment before and during pregnancy. Our study pretends to analyze the clinical evolution, treatment and outcomes in myasthenic women during pregnancy.

Methods: We retrospectively reviewed pregnant women with MG assessed in our neuromuscular outpatient clinic between 2013-2019. We analyzed their clinical and therapeutic data before, during and after pregnancy.

Results: 32 women of childbearing age (16-44) were assessed in our outpatient clinic. 7 pregnancies were recorded from 5 MG patients, with a mean age of 31.5 years (25-38). All patients had a diagnosis of generalized MG. Mean time from diagnose to pregnancy was 6.8 years (3-13), only 3 were planned pregnancies. Antibodies against acetylcholine receptors (AchRAb) were detected in all patients and thymectomy performed in all of them before pregnancy (mean 6.2 years).

Before pregnancy, 1/7 did not have any pharmacological treatment (asymptomatic), 2/7 pyridostigmine alone, 1/7 pyridostigmine + corticosteroids and 3/7 needed also another inmunosuppressant (1 tacrolimus, 1 azathioprine (AZA) in her two pregnancies). Mean doses of pyridostigmine and corticosteroids were 180 mg/d and 19 mg/48h, respectively. During pregnancy, no acute exacerbations nor hospital admissions were noted. 6/7 were reviewed by a neurologist in 1st term. 2 patients referred mild worsening symptoms in 3 pregnancies. Regarding their treatment, pyridostigmine was increased in 1 patient and decreased in 2. Corticosteroids at low doses were started by Rheumatology in one patient because of mild conective tissue disease suspicion. AZA was stopped in both pregnancies by the patient's own decision in month 2 and 4, respectively, with increased corticosteroids doses and patient referred symptom improvement during both pregnancies. Tacrolimus was kept unchanged. Mean doses of pyridostigmine and corticosteroids were 186 mg/d and 18.4 mg/48h, respectively.

All patients had obstetric follow-up without incidences. 3 premature rupture of membranes were recorded. 6/7 pregnancies were delivered at term, 1/7 late premature at week 36+2. All pregnancies ended via normal vaginal delivery without instrumental extraction, all of them under epidural anesthesia. No prolonged labour were recorded. 1 neonatal myasthenia gravis was noted. On puerperium only 1 patient showed mild increase of systemic fatigability and ptosis. Dose of pyridostigmine was increased in 2 patients and decreased in another 2. Concerning inmunosuppression, corticosteroids dose was decreased in 1 patient and AZA was restarted. Mean doses of pyridostigmine and corticosteroids were 180 mg/d and 18.3 mg/48h, respectively.

Conclusion: As previously reported, MG presents high variability in pregnancies. All patients got pregnant at least 3 years after MG diagnosis. No severe MG exacerbations were noted. We emphasize the importance of an individualized treatment and follow-up in every MG patient, specially during pregnancy. A multidisciplinary approach with obstetricians and anesthesiologists is essential to achieve a proper disease management.

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Regulation of nNOS by Caveolin 3: Implications in the Pathogenesis Leading to LGMD1C

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Caveolins are 21- to 24-kDa integral membrane proteins and principal components of flask-shaped

invaginations of the plasma membrane known as caveolae. These proteins play important roles in signal transduction by binding to and regulating several molecules: including Ha-Ras, Src family protein kinases, G protein-coupled receptors, and type I TGF-β kinase receptor (Ohsawa, JCI 116, 2006). Caveolin 3 is muscle specific and form homooligomers in the muscle cells. We previously generated a mouse model of caveolin 3-deficient limb-girdle muscular dystrophy 1C (LGMD1C) by transgenic overexpression of a dominant-negative mutant of caveolin 3 (CAV-3-P104L) in mouse muscle (Sunada, Hum Mol Genet 10, 2001). The deficiency of caveolin-3 caused atrophic myopathy accompanied with the activation of subsarcolemmal neuronal nitric oxide synthase (nNOS) in the mice. In order to uncover the role of nNOS activation resulting from caveolin 3 deficiency, we generated the double-deficient mice (CAV-3-P104L+/+, nNOS-/-) by crossing the caveolin 3-deficient mice (CAV-3-P104L+/+) with nNOS-deficient mice (nNOS-/-). The double-deficient mice exhibited a significant ($p<0.05$) reduction in the muscle mass and the single myofiber area when compared to the caveolin 3-deficient mice. The mice were significantly ($p<0.05$) weaker than the caveolin 3-deficient mice both in grip strength and muscle tension. No compensatory upregulation of other NOS isoforms was observed in the double-deficient mouse muscle. These data indicate that the activation of subsarcolemmal nNOS could prevent muscle atrophy in caveolin 3-deficient LGMD1C. Underlying molecular mechanisms by which caveolin-3 inhibits activation of nNOS will be presented.

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Illness Identity Development in Young Adults with Neuromuscular Disorders

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Young adults with neuromuscular diseases have to cope with a lot of physical discomfort and psychosocial stressors during their transition into adulthood. Adolescence is an important phase in psychosocial development with the formation of personality and an own identity as outcome. Having a chronic disorder can influence this developmental stage as is demonstrated in adolescents with Type 1 diabetes and individuals with congenital heart disease. Illness identity development was introduced as an extra developmental task for adolescents with a chronic disease as a way to incorporate their disease into their own identity and personality with four possible outcomes: rejection, engulfment, acceptance and enrichment. Our study focusses on how adolescents with a visible disability like a neuromuscular disease differ on the four outcomes of illness identity compared with young adults with a non-visible chronic disease like Type 1 diabetes. Secondly, we are interested in how quality of life is correlated with illness identity.

To investigate these research questions, we conducted a cross sectional research design with self and proxy report questionnaires that measure illness identity and quality of life. 50 adolescents with a neuromuscular disorder and one of their parents filled in these questionnaires. We matched them for age and gender with a historic cohort of young adults with Type 1 diabetes. Statistical analyses are being done at this moment. First results are expected in April 2020, leading to conclusions we want to present in this poster.

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Sensory Neuropathy Associated with Familial ALS Type 16 Triggered by a Novel SIGMAR1 Gene Mutation

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Amyotrophic lateral sclerosis (ALS) involves the upper and the lower motorneurons. It leads to progressive generalized weakness and paralysis. Approximately, 90% of ALS are sporadic, while about 10% are considered as familial. Familial ALS shows a great phenotypic variability and autosomal recessive (AR) or dominant transmission. Familial AR ALS attributable to a homozygous SIGMAR1 mutation (ALS16, MIM# 614373) was only very rarely reported. We describe a 45-years old female patient being the first daughter of consanguineous

Morrocan parents (first degree cousins). Pregnancy and delivery were uneventful. Developmental milestones were normal until the age of 6 years, when she started to present a progressive gait disturbance with frequent falls. She was first evaluated at the age of 7 years: a thin muscle bulk and atrophy of the small muscles of the hands were observed. Muscle testing revealed a symmetric distal limb weakness. Dysarthria and tongue fasciculations were noticed during childhood. Sensory examination was normal. Reflexes were increased in the four limbs. Babinski sign was present bilaterally. Cognition was normal. EMG showed chronic neurogenic changes, brain and spinal MRI were normal. Over the 20 years following the first examination, disease course was slow. Examination at 33 years revealed a mild progression of distal atrophy and mild diffuse weakness. Sensory examination was normal, but the patient presented an unsteady gait. Nerve conduction studies revealed a sensory peripheral neuropathy. A clinical exome sequencing identified a novel homozygous mutation on exon 1 of SIGMAR1 gene. The c.19delC (pArg7Glyfs*16) variant is predicted to be pathogenic as it introduces a premature STOP codon early in the protein. The segregation study identified the mutated allele at heterozygous state in the patient's mother (the father being not available) and her three asymptomatic siblings. Mutations on SIGMAR1 gene are also associated with few cases with hereditary distal motor neuropathy. As far as we know, the association of ALS16 with sensory neuropathy was not previously reported. Overlapping ALS phenotypes with peripheral neuropathies are increasingly reported. Here, we provide additional evidence that SIGMAR1 gene is responsible for ALS type 16, in a patient with a sensory neuropathy as associated feature. Finally, we enlarge the molecular and clinical spectrum of SIGMAR1 related diseases.

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Clinical and Genetic Description of Charcot-Marie-Tooth in the Population of Alicante (Spain)

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Background: CMT disease is characterized by wide genetic heterogeneity, influenced by social and geographical characteristics of each population.
Objetive: To define the clinical and genetic characteristics of patients with CMT disease in the area of Alicante, a Spain southeast region.
Methods: This is a prospective descriptive study. We included all patients with clinical and neurophysiological diagnosis of CMT disease from the General Hospital of Alicante area between January 2015 and June 2018. Prevalence of CMT disease was calculated. CMT type was determined by the neurophysiological study (demyelinating, intermediate, axonal) and inheritance pattern. Relative frequency, diagnostic success rate and identified genes of each group were described.
Results: We registered 95 patients from 42 unrelated families. The prevalence of CMT disease was 33.23/100,000. CMT1 was the largest group (45.2%) with a higher frequency of autosomal dominant cases. The genetic clearance rate was 73.7% (14/19) and although most patients were diagnosed using diagnostic algorithms, the use of genetic panels was required in 3 families. The majority (52.3%) carried the PMP22 duplication, and point mutations in this gene and MPZ were also found. A novel EGR2 P397H mutation associated with the LITAF T49M polymorphism was identified in one family. Mutations in the SH3TC2 gene were described in the recessive forms. The CMT2 group included 18 index cases (42.9%), with a higher prevalence of sporadic cases. The molecular diagnosis was achieved in only one case (5.5%; 1/18) by finding a mutation in GADP1 gene. Although genetic panels were used in 10 cases, only variants of uncertain significance or negative results were obtained. 11.9% of index cases were classified as intermediate CMT (CMTI) with an X-linked inheritance and GJB1 positive mutations in 80% of them. One patient from a single family carried a de novo mutation in NEFL. The causative mutations were detected in all patients of this group (100%; 5/5).
Conclusion: The prevalence in our area is similar to the prevalence described in other areas of our country. The two main forms CMT1 and CMT2 similar frequency and the high number of sporadic patients in the CMT2 group determine the specific features of our region. In 76% of cases the mutations were found in the most frequent genes. The use of region-specific diagnostic algorithms is essential. However, the use of new diagnostic techniques as genetic panels enables to extend the diagnostic possibilities in selected cases saving unnecessary costs.

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The Efficacy of Amifampridine Phosphate in Patients with Congenital Myasthenic Syndromes (CMS)

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Background: Congenital myasthenic syndromes (CMS) are a group of heterogeneous inherited disorders caused by mutations in genes encoding proteins essential for the integrity of neuromuscular transmission. CMS is characterized by fatigable weakness of skeletal muscle (ocular, bulbar, limb muscles). The diagnosis and management of patients with CMS is challenging and response to treatment in CMS varies widely and depends on the type of defect. Currently, there is no approved treatment for CMS. In patients with CMS, treatment with amifampridine, a non-specific voltage-dependent potassium channel blocker that increases acetylcholine release, has shown benefit in case series, case reports, and clinical trials; however, these investigations lacked controls and were inconsistent in the use of sensitive and objective measures of motor and electrophysiologic outcomes.

This investigation was the first randomized, double-blind, placebo-controlled trial of amifampridine in genetically confirmed CMS patients that assessed the efficacy of amifampridine phosphate using the subject's global impression (SGI) and motor function measure (MFM20/MFM32). SGI was selected to record feedback on how patients feel and function in daily life, while MFM evaluated the severity and progression of motor function in ambulant and non-ambulant patients. MFM was also the only assessment validated for use in children ≥ 2 years of age, critical given the primarily pediatric CMS population.

Methods: A two-period, two-treatment crossover study design was used to evaluate the efficacy and safety of amifampridine phosphate in patients diagnosed with CMS. After an unblinded drug escalation period, 16 patients (14 with post-synaptic genetic subtypes and 2 with pre-synaptic genetic subtypes) were randomized to begin Period 1, an 8-day blinded treatment period with amifampridine or placebo. Patients then returned to open-label amifampridine treatment for 13 days, which was followed by the cross-over period (Period 2), an 8-day blinded dosing period with amifampridine or placebo.

Results: Treatment with amifampridine was well tolerated by patients. Analysis of the primary endpoint, SGI, demonstrated that while some subjects may have experienced an improvement in raw SGI scores while taking amifampridine phosphate versus placebo, the treatment effect was not statistically significant. A mixed model analysis showed the difference between groups in least square means was 0.56 (95% CI: -0.97, 2.09). Similarly, MFM-32 and MFM-20 assessments did not provide evidence of clinically meaningful improvements in CMS patients following treatment with amifampridine relative to baseline or compared treatment with placebo. A mixed linear model analysis showed that based on the change from baseline estimated mean difference for the MFM-32 was 1.14 (95% CI: 2.31, 4.58) and for the MFM-20 was 0.63 (95% CI: -5.25, 6.50). When analyzed by dimension, a statistically significant difference from baseline at the end of Study Period 1 was observed for MFM-32 Dimension 3 (p=0.01) suggesting a treatment benefit of an amifampridine with regard to distal motor function.

Conclusion: In contrast to previous clinical trials, case series, and case reports, when a randomized, double-blind, placebo-controlled trial in genetically confirmed CMS patients was conducted using validated efficacy measures, amifampridine treatment did not result in statistically significant or clinically meaningful improvements compared to placebo.

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Late-onset Pompe Disease (LOPD) in Belgium: Clinical Characteristics and Outcome Measures

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We studied epidemiological, clinical, brain imaging and genetic features of the Belgian cohort of Late-onset Pompe disease (LOPD) (N=52). This lysosomal disease is a rare, hereditary, progressive disorder that is usually characterized by limb-girdle muscle weakness and/or respiratory insufficiency. It is caused by mutations in the acid alpha-glucosidase (GAA) gene and can be treated with enzyme replacement therapy. We also explored the sensitivity of different outcome measures in these patients during a longitudinal period of seven years (2010-2017), including the activity limitations ActivLim score, 6 minute walking distance (6MWD), 10 meter walking test (10MWT), MRC sum score, and forced vital capacity (FVC) sitting/supine.

Prevalence was calculated, with 3.9 per million in our Belgian cohort (N=52). Mean age at onset was 28.9 years (SD: 15.8 y), ranging from 7 months to 68 years; mean diagnostic delay was 12.9 years. Clinically, 75% of the patients presented with limb-girdle weakness at first presentation, whereas in 13% respiratory symptoms were the only initial symptom. In 37% (N=19), non-invasive ventilation (NIV) was started, at a mean age of 49.5 years (SD: 11.9 y), with a mean duration of 15 years (SD: 10.2 y) after symptom onset. Small cerebral aneurysm(s) were found in two patients, vertebrobasilar dolichoectasia was found in another two patients. In total, brain imaging revealed abnormalities in 25% (N=8) of patients. The most prevalent mutation was c.-32-13T>G, present in 96%. All patients were compound heterozygotes. We identified two novel mutations in GAA: c.1610_1611delA and c.186dup11. We measured a significant decrease over time for the 6MWD, MRC sum score, FVC sitting and FVC supine ($p=0.0002$, $p=0.0001$, $p=0.0077$, $p=0.0151$), which was not revealed with the ActivLim score and 10MWT ($p>0.05$).

To conclude, because of the long diagnostic delay and implications for treatment, awareness on LOPD should even be further increased. In the follow-up of LOPD patients, the 6MWD, but not the ActivLim score, is a sensitive outcome measure.

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Inhibitory Core of Myostatin Prodomain Alleviates the Phenotype of Duchenne Muscular Dystrophy Model Mice

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Myostatin, a muscle-specific transforming growth factor-β (TGF-β), negatively regulates skeletal muscle mass. The N-terminal prodomain of myostatin noncovalently binds and suppresses the C-terminal mature domain (ligand) as an inactive circulating complex. We previously showed that overexpression of the prodomain reverses muscular atrophy in a rodent model of caveolin3-deficient muscular dystrophy (Ohsawa, J Clin Invest 116, 2006). In addition, the activity of a myostatin-inhibiting protein negatively correlates with the severity of motor impairment in patients with DMD (Franigan, Ann Neurol 73, 2013). Thus, the activation of myostatin/TGF-β in dystrophic muscles has been now drawn attention as a disease modifier and a therapeutic target of DMD without restriction of the types of mutations in the dystrophin gene. Here, we identified a 29-amino acid region that inhibited myostatin-induced transcriptional activity by 79% compared with the full-length prodomain. This inhibitory core (IC) resides near the N-terminus of the prodomain and includes an α-helix structure that is evolutionarily conserved among other TGF-β family members, but suppresses activation of myostatin and growth and differentiation factor 11 (GDF11) that share identical membrane receptors. Interestingly, the inhibitory core

co-localized and co-immunoprecipitated with not only the ligand, but also its type I and type II membrane kinase receptors. Systemic injection of the optimized IC peptide corresponding to the inhibitory core (p29) ameliorates the dystrophic pathology and increased the muscle absolute force in a rodent model of Duchenne muscular dystrophy (DMD). Our findings indicate a novel concept for this newly identified inhibitory core of the prodomain of myostatin: that it not only suppresses the ligand, but also prevents two distinct membrane receptors from binding to the ligand. This study provides a strong rationale for the use of the optimized IC peptide for a disease modification therapy of DMD.

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Prediabetes, Diabetes, Metabolic Syndrome and Small Fiber Neuropathy

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Introduction: The role of elements of the metabolic syndrome (MetS) in the development of small fiber neuropathy (SFN) has begun to emerge. However, the association between prediabetes (PD) and SFN remains controversial. This study was conducted to evaluate the association between PD, additional elements of the MetS and SFN.

Methods: 268 patients with SFN symptoms and normal electrophysiology underwent tests to assess small fibers. SFN was diagnosed based on abnormality of at least 2 among intraepidermal nerve fiber density (IEFND), quantitative sensory testing and quantitative sudomotor axon reflex testing (QSART). The definitions of diabetes mellitus (DM), PD and normoglycemia (NG) were according to the criteria set forth by the American Diabetes Association.

Results: There was no difference in IENFD or rate of skin biopsy abnormality between PD and NG groups, notwithstanding significant differences in measures of glycemic control between PD and NG. However, IENFD was significantly lower in DM than NG (mean 4.2 vs. 8.5, $p=0.013$). There was a negative correlation between HbA1C and IENFD ($r= -0.26$; $p<0.05$) but the association was observed only if DM patients were included. Other attributes of the MetS (body mass index(BMI), triglyceride (TG) and high density lipoprotein (HDL-C) level) were associated with the rate of skin biopsy abnormality, but not with QSART measures of autonomic dysfunction.

Discussion: Prediabetes alone does not appear to be sufficient to cause SFN. Other MetS elements (BMI, TG and HDL-C) appear to preferentially impact small fiber structure (IENFD) over small fiber function. In individuals presenting with SFN, clinicians should not ascribe causality to pre-diabetes alone, and should seek risk factors beyond pre-diabetes.

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An Outbreak of Botulism in Northeast Iran Associated with "Poost Yogurt"

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Here we report the largest outbreak of botulism on record in the northeast region of Iran which occurred during December 2019 and January 2020. Affected population included 64 patients with an age range of 8 to 62 years.

Initially, an 8-year-old boy was referred to our center presenting with dizziness, ptosis and shortness of breath 24 hours after ingestion of contaminated yogurt. Patient underwent mechanical ventilation in the first day of presentation. Two days later, two other patients – a 46-year-old male with primary diagnosis of Myasthenia Gravis and a 25-year-old male primarily diagnosed as Guillain Barre Syndrome – were referred to our neuromuscular department. Primary electrodiagnostic examinations did not confirm the diagnosis of GBS or MG. Another 6 cases of various ages were admitted during the next few days. All cases came from the same geographical region of Neyshabour.

Blood and stool samples were sent for further investigations. In the meantime all patients were started on poly-valant anti-toxin. Botulinum toxin was found in blood assays of all these patients. By the day 12 of the onset of the outbreak it was discovered that a total of 64 people, including one pregnant

woman, had been affected via the same unusual route: through consumption of a particular type of yogurt known locally as "Poost Yogurt". Poost is basically a pouch made from goat hide to contain condensed yogurt. Investigations conducted by our national center for disease control (CDC) confirmed the contamination of the mentioned container with Clostridium Botulinum bacilli and botulinum toxin.

Most common clinical presentations in the order of frequency were: dizziness, blurred vision, diplopia, droopy eyelids, dry mouth and dysphagia among admitted patients. Four patients were admitted to ICU because of severe respiratory symptoms, none of them died. All were discharged upon full recovery. This report describes the first ever outbreak of botulism traced to the intake of "Poost Yogurt" in Iran, and probably marks the highest number of cases intoxicated through consumption of dairy products globally.

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Glycogen Storage Disease 9D Presenting Recurrent Myalgia Induced by Handball Training

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Glycogen storage disease 9D is caused by mutations of PHKA1 gene which encodes α-subunit of skeletal muscle-specific phosphorylase kinase with X-linked recessive trait. Until now, seven cases have been reported, however, its precise clinical picture has remained largely unknown. Here we report a new GSD9D patient, a Japanese 18-year-old high school boy, who first had myalgia soon after he began practicing handball clubs. He experienced no muscle pain in swimming, soccer, gymnastics, and other sports. Although both aerobic and anaerobic exercise tests were normal, muscle biopsy exhibited accumulation of glycogen in the subsarcolemmal region of myofibers. He harbored a novel nonsense mutation of the PHKA1 gene (p.S1194*) which resides in the C-terminus of α-subunit of muscle-specific phosphorylase kinase. His phosphorylase kinase activity was relatively preserved in muscle (24% of the lower normal limit) when compared to previous cases. GSD9D should be taken into account in patients with recurrent myalgia occurring only after intense exercise.

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GM1-Glycopolymer Inhibition of Anti-GM1 Antibody Binding in a Mouse Model of Acute Motor Axonal Neuropathy

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Introduction: In the Guillain-Barré Syndrome (GBS) variant acute motor axonal neuropathy (AMAN), autoreactive antibodies are generated during a prior infection against bacterial lipo-oligosaccharides (LOS). These LOS are molecular mimics of neuronal gangliosides, notably GM1. GM1 is highly expressed along the axolemmal membrane and prominently exposed at the nerve terminals and nodes of Ranvier. Anti-GM1 antibodies bind peripheral nerve axons and trigger the complement cascade, thereby injuring the nerve sometimes beyond repair or regeneration. Currently, there has been no change in registered treatments for GBS since 1985. Recently, a high-molecular weight glycopolymer has been developed that presents multiple GM1 glycoepitope mimetics and thereby has the potential to sequester and eliminate autoreactive anti-GM1 antibodies. The aim of this study is to determine the efficacy of this glycopolymer in an established mouse model of AMAN.

Methods: The GM1 glycopolymer and control glycopolymer were provided by Polyneuron Pharmaceuticals. In order to determine the inhibition of anti-GM1 antibody binding to distal axons in the presence of GM1 polymer or control polymer, diaphragm from neuronal GM1-enriched mice was sectioned in 10 μm sections and incubated in PBS with both DG2 - a GM1 ganglioside specific IgG3 monoclonal antibody - and the respective glycopolymer. Triangularis sterni (TS) nerve-muscle preparations from the same strain of mouse were incubated ex vivo in Ringer's solution with both DG2 and the GM1 glycopolymer or the control glycopolymer. After incubation for 2 hours, antibody and glycopolymer were removed by rinsing. Following this,

the TS muscle or diaphragm was stained with bungarotoxin to visualize the nerve-terminal and an anti-mouse IgG3 antibody to measure DG2 binding. Images were captured using a Zeiss LSM 880 Confocal Microscope.

Results: Over a wide dose range, the glycopolymer bound DG2, thus preventing DG2 from binding to GM1 at the nerve terminus axonal network both in vitro and ex vivo. A significant decrease in DG2 signal occurs at the nerve terminals at concentrations of mimetic as low as 1 ug/mL in vitro and 35 ug/mL ex vivo compared against the control.

Conclusion: Here, we demonstrate the potential efficacy of a novel treatment of the AMAN variant of GBS. The further testing of this GM1 glycopolymer mimic in vivo may pave the way for clinical testing of this polymer, a significant step towards a precision medicine approach in the treatment of AMAN and other indications involving anti-GM1 antibodies. This project is funded by Polyneuron Pharmaceuticals.

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Using Human Pluripotent Stem Cells Derived Motor Neurons to Address the Pathogenesis of SMA

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Spinal muscular atrophy is the most common genetic cause of infant mortality characterized by the specific degeneration of lower motoneurons (MNs) in the spinal cord, leading to progressive paralysis and muscle atrophy. SMA etiology relates to an insufficient amount of SMN (survival motor neuron) protein, which results from mutations in the SMN1 gene. Despite the ubiquitous expression of SMN protein, it is still unclear why MNs are one of the most affected cell types. Understanding this specific cellular tropism is critical but requires access to the relevant cell type. MNs from mouse are difficult to isolate and are obviously impossible to access from human. The ability to reprogram somatic cells into human induced pluripotent stem cells (hiPSC) offers a unique opportunity to access normal and pathological neuronal populations in sufficient quantities for systematic analysis. In this present study, we demonstrated that the reduced expression of SMN lead to a decreased survival of hiPSC-derived MNs rather than a defect in their generation. We identified that this phenotype can be rescued by kenpaullone, an inhibitor of several CKDs as well as JNK, likely through a JNK dependent mechanism. By a transcriptomic approach, we identified SMA-specific changes in early MNs that include genes involved in synaptic plasticity. Interestingly, these genetic defects were rescued by kenpaullone treatment. These findings suggest that alteration in synaptic organization might be a new therapeutic target for SMA. Furthermore, several studies suggest that pathological changes of the neuromuscular junction (NMJ) precede the motor neuronal loss. Therefore, it is critical to evaluate the NMJ formed by SMA patients' MNs, and to identify drugs that can restore the normal condition. We thus developed an in vitro co-culture strategy to study the interaction between MNs and its skeletal muscle target. Altogether, our results demonstrate the potential offered by hiPSC to shed light on the cellular and molecular bases of selective MN vulnerability in SMA.

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Evidence of a New LAMA2 – Mutation Using Next Generation Sequencing

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Background: LAMA2 – associated muscle dystrophies (LAMA2 MD) are autosomal recessive diseases caused by mutations in the LAMA2 – gene. This gene encodes the alpha – 2 laminin subunit of the extracellular protein laminin – 211 (synonym: merosin), a basal membrane associated protein in muscle cells. The range of different clinical phenotypes associated with LAMA2 MD has increased during the last years through molecular genetic analysis. Clinical distinction is made between a severe progressing early – onset – type, the congenital muscular dystrophy type 1A (LAMA2 MD or MDC1a), and a more benign form, the late – onset limb girdle muscle dystrophy (LGMDR23). Patients with LGMDR23 usually show a delayed motor development but gain the ability to walk. Over time they often

develop scoliosis, a rigid spine, joint contractures and sometimes respiratory difficulties.

In the presented case study, two previously undiscovered likely pathogenic variants in LAMA2 have been identified using Next Generation Sequencing (NGS).

Methods: Extended genetic diagnostics using high – throughput sequencing is used in conjunction with immunohistochemical staining of merosin in the muscle biopsy specimen.

Results: A 41 years old patient presented with a slowly progressing muscular dystrophy. His first symptoms developed at an age of 3 to 4 years when he experienced difficulties getting up from a lying position. Since the age of 28 his walking became gradually impaired and several falls occurred. The clinical examination revealed a proximal paresis of both arms and legs, a weakness of thoracic muscles and severe muscle atrophy. CK levels were upregulates by four-fold above the normal threshold. The electromyography displayed myopathic changes and his muscle biopsy showed typical myopathic impairment including internalised nuclei and variation of the fiber size. Extensive immunohistochemical staining failed to produce a reliable diagnosis. Next Generation Sequencing of a panel for disease associated genes (TruSight One, 4813 Gene) showed two heterozygoteous mutations in LAMA2, which were classified as probably pathogenic (Class 4 according to ACMG – guidelines). To demonstrate the pathogenicity of the two mutations, an immunohistochemical staining of merosin was performed on the patients muscle biopsy. The result of the current muscle biopsy will be presented.

Conclusion: This case study underscores the value of a muscle biopsy in order to demonstrate the pathogenicity of a newly detected sequence variation. Despite the ease and value of NGS diagnostics, muscle biopsies have are highly relevant in diagnosis of genetic neuromuscular diseases. A correct diagnosis is of importance as new avenues for novel gene therapy become available for LAMA2 mutations.

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European Collaboration on the Clinical and Genetic Spectrum of Sarcoglycan-Deficient Muscular Dystrophy

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Background: Sarcoglycanopathies comprise four subtypes of autosomal recessive limb-girdle muscular dystrophies (LGMDR3, LGMDR4, LGMDR5 and LGMDR6) that are caused, respectively, by mutation in the SGCA, SGCB, SGCG and SGCD genes. In 2016, several clinicians involved in the diagnosis, management and care of patients with sarcoglycanopathies created a European network. The aim of this study in to determine the clinical and genetic spectrum of a large cohort of European patients with sarcoglycanopathy from this European network.

Methods: A total of 33 neuromuscular centers agreed to establish a European network on sarcoglycanopathies. A retrospective observational study was conducted. All sarcoglycanopathy patients followed in participating centers underwent an extensive clinical evaluation or review of medical records. Demographic, genetic and clinical data was provided to this European network.

Results: A total of 439 patients, from 13 different countries were collected. Fourty-three patients were not enrolled in the study because the genetics were not available or there was not enough clinical information. A total of 159 patients had a confirmed diagnosis of LGMDR3, 73 of LGMDR4, 157 of LGMDR5 and 7 of LGMDR6. Patients with LGMDR3 have a later onset and a lower severity of the disease. Cardiac involvement is most frequent in LGMDR4. Sixty per cent of SGCA patients carried one of the following mutations, either as homozygous or heterozygous: c.229C>T, c.739G>A or c.850C>T. Similarly, the most common mutations in SGCG patients were c.525delT or c.848G>A. In SGCB patients the most frequent mutation was c341C>T. In all sarcoglycan groups, patients who begin the disease after 10 years and have mutations that involve more than 30% of protein expression have a better prognosis.

Conclusions: This study reports clinical and molecular data of European patients with mutations

in the sarcoglycan genes. Sarcoglycanopathies are extremely rare disorders so that, development of international networks can result in an extended collection of clinical and genetic data that eventually will improve the knowledge of this disease. Our study provides important data on the clinical-genetic correlation that could be important in the design of natural history studies in view of the development of potential new therapeutic approaches for muscular dystrophies.

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Twenty-two months of nusinersen treatment in 16 adult patients with spinal muscular atrophy types 3-4

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Introduction: Spinal muscular atrophy (SMA) is a genetic neuromuscular disease, affecting the motor neurons in the spinal cord and leading to progressive muscular atrophy and weakness. Recently, we reported on the efficacy and safety of nusinersen treatment of 16 adult SMA patients over the course of 14 months. A few other studies on nusinersen treated adult SMA patients were recently published, but were limited to 10-14 months of follow-up.

Study objectives: To study the efficacy of nusinersen treatment in 16 adult SMA patients types 3-4 over a longer follow-up period of 22 months and to evaluate the evolution of neurofilaments and neuro-inflammatory biomarkers in blood and cerebrospinal fluid (CSF) under treatment.

Patients and Methods: In this prospective study, 16 adult patients with SMA types 3-4 were treated with intrathecal nusinersen at the neuromuscular reference centre at University Hospitals Leuven (Belgium) following the standard of care dosing schedule. Longitudinal measurements over 22 months of treatment included hand grip strength, 60-point MRC sum score, 6-minute-walk-distance (6MWD), Hammersmith Functional Motor Scale Expanded (HFMSE), Revised Upper Limb Module (RULM), Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF), and the patient-reported Activity Limitations Score (ActivLim). Phosphorylated neurofilament heavy chain (pNfH), neurofilament light chain (NfL), and biomarkers for neuro-inflammation will be analysed both in CSF and in blood.

Results: Hand grip strength significantly improved by on average 54% in both the right ($p<0.01$) and left ($p=0.02$) hand at month 22 compared to baseline. The MRC sum score also significantly improved from 36.9/60 points at baseline to 39.6/60 points at month 22 ($p<0.01$). Two of the seven still ambulatory patients experienced post-traumatic leg fractures during the study period, rendering them wheelchair bound at the evaluation at month 22. The average 6MWD in the other patients increased by 27.5 metres at month 22 compared to baseline, which is 9 metres less than month 14, however. After an initial non-significant improvement in HFMSE and RULM scores after the first year of treatment (+2.1 and +1.1 points, respectively), the evaluation at month 22 showed an overall return to baseline, with only a residual 0.5 point increase in HFMSE ($p=1$) and 0.3 point increase in RULM ($p=0.36$). In contrast, a sub-score of the RULM pertaining to hand motor function continued to show a significant improvement at month 22 compared to baseline ($p=0.03$). There was no significant change in FVC, but the PEF improved significantly at month 22 ($p=0.02$) compared to baseline. Finally, the ActivLim score showed an improvement of 0.5 logits at month 22, but this was not significant ($p=0.17$). The biomarker analysis is still ongoing.

Conclusion: Adult SMA 3-4 patients treated with nusinersen experience significant and continual improvements in hand grip strength, hand motor function, MRC sum scores and PEF over 22 months of treatment, corresponding to the previously reported results after 14 months of treatment. Other outcome measures showed (sometimes transient) improvements, but were not significant.

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Study of Comparative Epidemiology of ALS in Uruguay. Comparison of Two Incident Cohorts (2002-2003 2017-2018)

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The results of a comparative epidemiology work of the ALS in Uruguay in two different periods are presented: a prospective cohort of incident patients diagnosed between January 1, 2002 and December 31, 2003 (Period 1) and another of incident patients diagnosed between October 1, 2016 and September 30, 2018 (Period 2, in the framework of the LAENALS study).

Both cohorts correspond to population studies with similar methodology. Neurologists and laboratories of neurophysiology were used as data sources for the collection of patients.

The modified El Escorial criteria are used, and most of the patients were examined by the research team. Uruguay is a small country (3: 500,000 inhabitants), geographically accessible with a good network of neurologists (130) that facilitate this type of population-based studies. The majority of the population are descendants of European immigrants.

The population has remained relatively stable in the last 30 years. In Period 1 89 patients were prospectively enrolled while in Period 2 there were 92 patients. The estimated mean annual incidence rate for period 1 was 1.37 new cases per 100,000 inhabitants / year and 1.31 for period 2.

The geographical distribution of cases was homogeneous in the Uruguayan territory in the two periods, with no cluster areas found.

The average age of onset of the disease was below 60 years in both periods without gender differences. The clinical characteristics of the patients were similar during the two periods considered.

5% were family cases and 25% received Riluzol, the median survival since diagnosis was 23 months. The results of this research show the main characteristics of Uruguayan patients with ALS in two periods 13 years apart. The disease seems to behave in a stable manner and without significant differences in the main aspects evaluated with a similar methodology. We estimate that there was a low probability of losing cases in both studies (in Period 1 we apply the capture - recapture method with an estimate of very few lost cases)

Survival seems to also remain stable despite the fact that patient care has improved in some aspects in recent years in our country.

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C9orf72 ALS Human Neural Organoids for the Development of New Therapeutics and Disease Modeling

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Background and aims: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease. C9orf72 repeat expansion is the most frequent genetic cause of ALS (C9ALS) in Europe and North America. Partially owing to an incomplete understanding of disease etiopathogenesis, disease-modifying therapies in C9ALS still lack. A better insight into C9ALS pathomechanisms in reliable models is fundamental for developing new therapeutics. Here, we aim to model C9ALS pathology in 3D human neural organoids.

Methods: We differentiated iPSCs from C9ALS patients and healthy controls' fibroblasts using a free-floating 3D-culture method. We generated early cerebral-like organoids (COs) using standard methods and ventral spinal-cord like organoids (vSCOs) with a modified protocol inducing neural caudalization and ventralization. Then, we treated C9ALS COs and vSCOs with morpholino antisense oligonucleotides (MO) against c9orf72 repeat expansion. Finally, we evaluated the differentiation of organoids at different time points with immunohistochemical and qPCR analysis.

Results: We obtained control and C9ALS COs and vSCOs organoids displaying different co-existing neuronal subpopulations. COs exhibited progenitor (SOX2), forebrain (PAX6) and immature post-mitotic neuronal markers (TUJ1); vSCOs expressed SOX2, pan-neuronal markers (eg. TUJ1, Neurofila-

ment, MAP2) ventro/caudal marker (HOXB4) and motor neuron markers (ISL1 and SMI32). In addition, immunocytochemistry and a gene reporter assay showed HB9 and ChAT expression in vSCOs as markers of lower MNs. C9ALS organoids dissociated into single cells showed pBRCA1 and γH2AX foci, markers of DNA damage associated with c9orf72 expansion. Preliminary results on gene expression analysis using qPCR reported differential expression of genes involved in DNA damage response (GADD45A, CDKN1A) in MO treated C9ALS organoids.

Conclusions: Neural organoids represent an innovative in vitro system and a valuable platform for modelling aspects of C9ALS pathology, studying C9ALS pathomechanisms and potentially developing new treatments in vitro.

Nothing to declare.

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MuSK Antibody-Associated Myasthenia Gravis After Bone Marrow Transplantation and Graft-Versus-Host Disease

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Introduction: Myasthenia gravis is an autoimmune neuromuscular disorder, that may be a rare complication of bone marrow transplantation and graft-versus-host disease.

Objective: To present the case of a patient with MuSK antibody-associated myasthenia gravis after bone marrow transplantation and graft-versus-host disease and review literature.

Case report: A 56-year-old male, from non-consanguineous parents, with no significant family history of previous diseases, was diagnosed with the myelodysplastic syndrome - Refractory Anemia with Excess of Blasts 8 years ago. Chemotherapy was the treatment of choice and, after 2 years of diagnosis, an allogeneic bone marrow transplantation was carried out. On the 30th post-transplantation day, he developed graft-versus-host disease, which regressed with the administration of cyclosporine prednisone. After 5 years of transplantation, he developed dropped head and dyspnea. Fluctuation of symptoms, ptosis, diplopia and dysphagia were denied. Neurological physical examination revealed dropped head, with weakness of neck extensor muscle only. The other muscles had normal strength. Tendon reflex responses were normal. Electromyography demonstrated normal motor and sensory nerve conduction studies. Repetitive Nerve Stimulation at 3 Hz of the spinal accessory nerve evidenced a 27% decrement and needle electromyography revealed myopathic motor unit potentials. Laboratorial tests revealed normal CK levels, absent antibody against acetylcholine receptor and positive MuSK antibody. He was treated with Piridostigmine (60mg 4x/day) and Prednisone (80mg/day) with no response. He improved after being treated with human immunoglobulin 0,4g/Kg daily for 5 days. After some months he got dyspnea and cough and was diagnosed with lung graft-versus-host disease (bronchiolitis obliterans). Treatment was initiated with Mycophenolate mofetil but after 4 months, there was a recurrence of myelodysplastic syndrome.

Discussion: Myasthenia gravis is a treatable condition. The diagnosis is accomplished primarily through clinical, electrophysiological and laboratorial findings. The association of myasthenia gravis with bone marrow transplantation and graft-versus-host disease is rarely reported in literature.

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The Emery-Dreifuss's Phenotype in a New Pathogenic Variant of Titin Gene

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Introduction: Titin (TTN) is the largest known gene encoded by 363 exons. It's a central protein in muscle sarcomere responsible for structural integrity and elasticity. Mutations in TTN gene have a huge histological and genetic heterogeneity that makes the diagnostic a challenge.

Objective: We describe a patient with a new recessive phenotype of Emery-Dreifuss-like. Case: Female, 14 yrs, Brazilian. A severe scoliosis was observed at age 1. The milestones was delayed and walked with support at age 2. She developed contractures around 10 years old, being submitted to arthrodesis of the lumbar spine at age 12. She also

had recurrent pneumonias without invasive ventilation. Neurological exam: generalized amyotrophy, retroverted ears, prominent chin, scoliosis, scapula alata, elonged face, ogival palate, ankles and elbow contractures, axial, proximal and distal weakness: cervical 4/5, shoulder abduction 3/5, elbow flexion and extension 3/5, fingers flexion and extension 4/5, fingers flexion 4/5, fingers extension -4/5, hip flexor 3/5, knee extension 4+/5, hallux extension 2/5. Limited dorsiflexion. Plantar cutaneous reflex in flexion, deep osteotendinous reflexes abolished. No cognitive impairment. Family history: Paternal grandparents were first cousins. Parents are healthy. Her brother, 17 yrs presents foot deformities (flat feet), mild cognitive level; lower muscle proximal weakness (4/5), asymmetric scapula alata, scoliosis, ogival palate, and limitation on dorsiflexion. Muscle biopsy from deltoide (11 yrs) showed an end stage dystrophic pattern. Echocardiogram, creatine phosphokinase, profile of acylcarnitines, urinary organic acids: all normal.

Spirometry: FVC 26% VEF1 25%. (severe restrictitve disfunction). Muscle MRI show hypotrophy with signs of liposubstitution of: rectus femoris, vastus lateralis, vastus intermedius, biceps femoris, semitendinosus, longus adductor, tibialis anterior, extensor digitorum communis, extensors hallucis longus, long and brevis fibularis, soleus and flexors digitorum longus and hallucis longus bilaterally and symmetrically. Discreet edema of the left anterior tibial muscle with slight impregnation by the paramagnetic agent. NGS panel for myopathies (83 genes) revealed two variants in the TTN gene in compound heterozygous: c.27607G>T and c.669+1G>A. Segregation study was performed in their parents and her brother: One pathogenic variant (c.27607G>T) was found in the father and another one in the mother (c. 669+1G>A). The brother had only one pathogenic variant (c.27607G>T) and two variants of uncertain significance (VUS) from the mother.

Discussion: We found just one publication describing three cases of titinopathy showing a similar presentation: common age onset, respiratory impairment, contractures and no cardiac involvement. The previous three cases showed a recessive homozygous and compound heterozygous. There is no specific morphological pattern for titinopathy, so, making diagnosis more difficult. The two variants found in our patient were considered to be definitely pathogenic since they are absent in about 140000 individuals in the normal population. In addition, the variant c.27607G>T encodes a stop codon and the other one, c.669+1G>A, presents a mRNA processing defect. Titinopathy should be considered in patients with Emery-Dreifuss's phenotype with or without cardiomyopathy.

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Circulating Markers of Oxidative Damage Associated with Muscle Function in Patients with Duchenne Muscular Dystrophy

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Background: Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy generated by deficiency of dystrophin triggering different mechanisms as oxidative stress that contribute to muscle injury. Different studies have confirmed oxidative damage in patients with DMD compared with healthy, therefore it could be clinically useful to know if there is a relationship between circulating markers of oxidative damage and muscle function.

Objective: The aim of this work was to evaluate if oxidative damage and antioxidant markers are associated to muscle function in DMD patients.

Methods: Twenty-four patients with DMD were classified in two groups depending on ambulatory (n = 17) or non-ambulatory (n = 7) ability and muscle function was measured in lower limbs by Vignos scale in those groups of patients. The marker of oxidative stress total nitric oxide (NO), markers of lipoperoxidation malondialdehyde (MDA) and 8-Isoprostane (8-Iso), and marker of antioxidant response thiol were measured in plasma from DMD patients. mRNA Nuclear factor kappa B (NF-κB) and nuclear factor, erythroid 2 like 2 (NRF2) were measured in circulating leucocytes from DMD patients.

Results: Our findings show that NO, MDA and 8-Iso concentrations were significantly higher in non-ambulatory patients compared with ambulatory patients ($p < 0.05$). In contrast, thiol was lower ($p < 0.05$) in non-ambulatory patients compared with ambulatory patients. Moreover, we found a tendency of decreasing mRNA NRF2 expression in non-ambulatory patients ($p = 0.063$); nevertheless, we

did not observed differences in NF-κB mRNA expression ($p > 0.05$). Finally, a positive correlation between Vignos scale score and total NO ($r = 0.444$, $p = 0.030$), MDA ($r = 0.503$, $p = 0.012$), and 8-Iso ($r = 0.435$, $p = 0.049$) as well as a negative correlation between Vignos scale score and thiol ($r = -0.430$, $p = 0.036$).

Conclusion: Our results suggest a higher oxidative damage in non-ambulatory DMD patients, and it was confirmed by correlation analysis between Vignos scale score and circulating markers. Total NO, MDA, 8-iso, and thiol could be considered as good indicators of oxidative damage during DMD progression.

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Large Cluster of Autosomal Dominant Limb Girdle Dystrophy D3 HNRNPDL-Related in Uruguay

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Limb-girdle muscular dystrophy (LGMD) is a genetic disorder characterized by progressive weakness of pelvic and scapular girdles and great clinical variability. Autosomal dominant limb girdle muscular dystrophy D3 HNRNPDL-related is a rare dominant myopathy caused by mutations in HNRNPDL. Only three unrelated families have been described worldwide, a Brazilian and a Chinese carrying the mutation c.1132G>A p.(Asp378Asn), and one Uruguayan with the mutation c.1132G>C p. (Asp378His), both mutations occurring in the same codon. Recently, two unrelated Argentinean families carrying the previously reported c.1132G>C p. (Asp378His) HNRNPDL mutation have been described. We describe a large cluster of patients belonging to different families from the region of Colonia, Uruguay with the c.1132G>C p. (Asp378His) HNRNPDL mutation. A number of 25 patients belonging to four families with affected members in three or four previous generations were examined.

All affected individuals had normal birth and early motor development. The age of onset ranged from 20 to 60 years, with initial symptoms being proximal lower limb weakness in 80 % of patients. Scapular winging is a regular sign in all studied patients. Distal lower limb ankle dorsiflexion weakness was present in most patients. Atrophy and weakness of the posterior thigh compartment was noticed as well as abdominal weakness. Flexion limitation of fingers and toes, which was a typical feature reported in families of other origins, was not present. Cardiac and respiratory assessments were normal in most of the studied patients and cataracts were present in 9/25 patients. The disability progressed over the years and the prognosis was relatively benign, except in homozygous patients who also started their symptoms earlier in age. The course of disease of patients examined was from 1 to 40 years since the beginning of symptoms. The serum creatine kinase level was normal or mildly elevated. Prominent features of the muscle biopsy were rimmed-vacuolated myofibers. In fact, one patient was misdiagnosed as IBM before gene tests were available. A muscle MRI performed in two patients showed a striking involvement of most bilateral thigh muscles, partially sparing the rectus femoris and involvement of tibialis anterior.

Conclusions: Autosomal dominant limb girdle muscular dystrophy D3 HNRNPDL-related is probably the dominant LGMD most frequent in adult Uruguayan population and shows a typical and homogeneous phenotype with a slowly progressive scapular-pelvic-peroneal pattern.

We described a large cluster of patients in a small geographical region of Uruguay. The fact that all the families came from the same restricted region suggests the possibility of a common founder mutation.

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Design of a Phase 2/3 Study of Arimoclomol in Sporadic Inclusion Body Myositis

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Background: Sporadic inclusion body myositis (IBM) is the most common idiopathic inflammatory myopathy occurring in patients over the age of 45 years. IBM muscle displays both inflammatory and degenerative features, yet immune suppression has proven to be ineffective. Modulating the cytoprotective "heat shock response" (HSR) represents a therapeutic strategy targeting both inflammation and degeneration. Arimoclomol is an orally administered pharmacological agent that can up-regulate the HSR by amplifying heat shock protein expression. In a pilot Phase 2a study arimoclomol was safe and well tolerated and demonstrated a preliminary signal for potential therapeutic benefit in patients with IBM.
Objectives: To evaluate the efficacy in a phase 2/3 randomized controlled trial of arimoclomol in IBM and to gather data on safety and tolerability. We present herein the study protocol of NCT02753530.
Methods: In this international multicenter, double-blind, placebo-controlled trial, 152 subjects were randomized 1:1 to receive either arimoclomol citrate 400 mg or matching placebo capsules three times a day for 20 months. The primary outcome measure is the change from baseline to Month 20 in the IBM functional rating scale total score. The null hypothesis to be tested is that the mean value of this outcome variable is the same in the arimoclomol and placebo groups. Secondary outcome measures include Global Impressions of Severity and Change as assessed by the subject and the clinician, 6 Minute Walk Test distance, Modified Timed Up and Go, manual muscle testing of 24 muscles, bilateral quantitation of grip strength using the Jamar device and quadriceps muscle strength using the MicroFET, Health Assessment Questionnaire - Disability Index and Short-Form 36 health survey. Drug safety and tolerability will also be evaluated. Population pharmacokinetic studies and biomarkers such as the anti-cN1A antibody titer are collected. MRI of the lower extremities in a subgroup of participants is an exploratory assessment to characterize muscle signal changes.
Results: This is an ongoing study that fully enrolled. We anticipate that the last subject will be completing the study in January 2021 and that results will be available in mid-2021. On December 18, 2019, Orphazyme received fast track designation from the FDA for the development of arimoclomol specifically for IBM.
Conclusions: We present herein this pivotal study design and anticipate being able to share results in 2021.

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Gene Modifiers of Duchenne Muscular Dystrophy - Serbian Experience

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Duchenne muscular dystrophy (DMD) is genetically determined, progressive lethal disease that affects 1 in 5 to 10000 male births worldwide. There is increasing research trying to answer the question - what modifies the disease in patients with genetically confirmed DMD. It is well known that the type of mutation, type of affected dystrophin isoforms, can partly influence the phenotypic expression of the disease. More recent studies show that the single nucleotide polymorphisms (SNPs) of identified genetic modifiers - SPP1, LTBP4 and CD40 genes - play an important role. SNP rs28357094 G SPP1 gene, also known as oteopontin, affects the efficiency of transcription, bringing with it the possibility of early loss of gait. Haplotype 4 misense SNPs LTBP4 gene studied includes rs2303729, rs1131620, rs1051303 and rs10880 and describes two variant VTTTs and IAAMs. IAAM haplotype is associated with a later age of gait loss. SNP rs1883832 T CD40 gene was associated with one year earlier loss of self-walking ability.

We analyzed our patients with DMD for SNPs in genes mentions above. We tested SNPs of SPP1, LTBP4 and CD40 gens in 52 patients with retrospective data of loss of ambulation and 35 patients still independently mobile, using TaqMan assay. We

analyzed the association of selected SNPs with clinical disease progression and use of corticosteroid therapy. In univariate analysis, a log-rank test was used to test the association of each SNPs. Multivariate analysis was performed using Cox proportional hazard models, including SNPs that showed $p < 0.1$ in univariate analysis.

To our knowledge, this is the first study in the Serbian population of DMD patients to determine the association of genetic modifiers with clinical course and disease progression. The frequency of SNPs can be population-specific, while studies of genetic associations in rare diseases, such as DMD, cover relatively small groups of patients. For these reasons, replicative studies are needed to evaluate the clinical significance of SNVs in a given population. Patients identified as carriers of SNPs with negative effects could be monitored more regularly and advised in a timely manner about the possibility of early manifestation of expected complications of the disease. Also, carriers of specific SNPs gene modifiers in clinical studies could be considered at a more specific level depending on the form of SNPs gene modifiers, and finally in the future, gene modifiers could be a new target for clinical studies to find a new therapeutic response for DMD patients.

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Clinical Correlates of Variant KLRG-Expressing T cells in Inclusion Body Myositis

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Objective: To correlate disease behavior (disease phenotype and severity) in inclusion body myositis (IBM) with peripheral blood levels of variant killer cell lectin-like receptor G1 (KLRG1)- expressing T-lymphocytes.

Background: Recent published data has firmly highlighted the role of immune dysfunction as possibly the primary pathogenic mechanism in IBM, and clonal highly differentiated "immunosenescent" CD8+ T cells that phenotypically resemble terminally differentiated effector memory CD45RA+ T cells (TEMRA cells). The most striking surface marker of these cells is killer cell lectin-like receptor G1 (KLRG1).

Design/Methods: A prospective cross-sectional study, involving 51 IBM patients meeting the ENMC 2011 criteria for clinically defined or probable IBM, has recently been completed at the University of California, Irvine. The patients completed serological testing for the NT5C1A antibodies and analysis of markers of T cell subsets, including regulatory T cells, and T cell differentiation, including CD28, CD57 and KLRG1, in lymphocytes isolated from peripheral blood through multiplex flow cytometry. Clinical details, demographics, functional data (timed get up, manual muscle testing, hand grip, pinch grip, IBM functional rating scale, modified Rankin score, forced vital capacity, presence of dysphagia, use of assistive devices), and quality of life questionnaires were collected on all patients.

Results: The study has recently been completed and the data will be analyzed to evaluate the presence and relationship of TEMRA cells in circulating blood of IBM patients with disease phenotype, NT5c1A serological status, quality of life, functional disability and need for ambulatory devices in these patients.

Conclusions: Our study will evaluate whether increased frequency of KLRG1+CD8+ cells is present across the spectrum of IBM disease severity and how related biomarkers correlate with markers of disease severity in IBM patients. Identification of these KLRG1 expressing T cells in IBM and their associated clinical phenotype may give insight into the pathogenesis of IBM and potentially provide a therapeutic target, as currently there is no effective treatment to stop the progression of disease.

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Ataluren Delays Loss of Ambulation and Decline in Pulmonary Function in Patients with nmDMD

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Background: Duchenne muscular dystrophy (DMD) is a fatal, X-linked disease characterized by progressive muscle weakness. Approximately 10–15% of cases of DMD are caused by a nonsense mutation (nmDMD) in the dystrophin gene, resulting in the absence of functional protein that is essential for muscle function. Loss of ambulation (LoA) and decline in pulmonary function are major disease milestones and are prognostic of mortality. Oral ataluren (10, 10, 20 mg/kg [morning, midday, and evening]) targets the underlying cause of nmDMD, enabling the formation of full-length, functional dystrophin.
Aim: This phase 3, long-term safety study enrolled nmDMD patients from prior ataluren clinical trials (Study 019; NCT01557400) (N=95). The study was ~4.5 years in duration. We evaluated whether nmDMD patients receiving ataluren + standard of care (SoC; corticosteroid or palliative therapies) in Study 019 experienced a delay in LoA and a slower decline in pulmonary function compared with matched DMD patients receiving SoC in the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS; NCT00468832).
Methods: Propensity score matching (1:1) was performed to identify ataluren and CINRG DNHS patients with comparable indicators of disease severity: corticosteroid type (deflazacort or other), duration of corticosteroid use, and age at first symptoms. Kaplan–Meier analyses estimated the age at LoA and at decline in forced vital capacity (FVC) to <60%- or <50%-predicted or <1L.
Results: Age at LoA was delayed by ~2.5 years in nmDMD patients receiving ataluren in Study 019 compared with CINRG DNHS patients (median ages: ataluren, 15.5 years; CINRG DNHS, 13 years; p=0.0079 [each n=60]; Figure 1a). Ataluren was also associated with a delay in decline to %-predicted FVC <60% in non-ambulatory patients by ~2.5 years (median ages: ataluren, 18.1 years; CINRG DNHS, 15.5 years; p=0.0376 [each n=45]; Figure 1b) and a trend in delay in decline to %-predicted FVC <50% by ~1 year (non-significant).
Conclusion: Ataluren + SoC delays LoA and may reduce pulmonary function decline in nmDMD patients compared with DMD patients receiving SoC, although longer follow-up will be required to more fully assess this latter outcome.

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Demographics and Safety Data From Patients with nmDMD Receiving Ataluren in the STRIDE Registry

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Background: Duchenne muscular dystrophy (DMD) is a severe neuromuscular disorder caused by a lack of functional dystrophin. Ataluren promotes readthrough of an in-frame premature stop codon to produce full-length dystrophin and is indicated for the treatment of patients with nonsense mutation (nm) DMD. Strategic Targeting of Registries and International Database of Excellence (STRIDE; NCT02369731) is an ongoing registry providing real-world data on ataluren use in patients with nmDMD.
Objectives: To describe the demographics of the STRIDE population and the interim safety results as of the latest data cut-off date of 31 January 2019.
Approach: Data from enrolled patients are collected at the consent date; for patients who initiated ataluren as part of a commercial or early access program before enrollment, data for the period prior to enrollment are obtained retrospectively. Patients will be followed up for ≥5 years or until study withdrawal.
Results: At data cut-off, 220 boys were enrolled in STRIDE in 11 countries and received ≥1 ataluren

dose. Total mean±SD exposure to ataluren was 822±368 days, equivalent to 495 patient-years. Safety outcomes were consistent with the known safety profile of ataluren. Fourteen boys discontinued the study. Of 220 boys enrolled, 210 had genetically confirmed nmDMD, most of whom were Caucasian (66.7%), with mean age of 10.6±3.6 years at the consent date. Mean age at first symptoms was 2.8±1.8 years (n=193), and age at nmDMD confirmation was 5.2±2.9 years (n=200). Median time between first symptoms and nmDMD confirmation was 1.6 years (n=186). Most patients used concomitant corticosteroids (191/220 [86.8%]).
Conclusions: STRIDE constitutes the first drug registry for patients with nmDMD. Analyses of effectiveness data from STRIDE patients will provide insights into the real-world long-term effectiveness and safety of ataluren.

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Cardiac Findings in Children and Adolescents with Spinal Muscular Atrophy Types 2 and 3

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Background: A growing body of evidence suggests that spinal muscular atrophy (SMA) is a multisystemic disorder rather than just a motor neuron disease. Many reports show that the heart might be affected in SMA. However, it is still debatable whether patients with milder forms of the disease warrant cardiac evaluation.
Methods: We performed a cross-sectional study of 28 children and adolescents (median age, 7.3 years; range, 1.2–18.9 years) with genetically confirmed SMA (19 with type 2 and 9 with type 3 disease) to determine the prevalence and type of cardiac abnormalities. All patients were evaluated for the presence of structural heart diseases and disturbances in heart rhythm using transthoracic echocardiography, cardiac biomarkers (troponin T, NT-proBNP), standard electrocardiography, and 24-hour Holter monitoring.
Results: No structural heart abnormalities were found on echocardiography, except in one female patient with SMA type 2 who had mitral valve prolapse with mild regurgitation. None of the patients had impaired systolic or diastolic ventricular function. Troponin T and NT-proBNP levels were also within normal limits. No heart rhythm abnormalities were noted on standard electrocardiograms. The results of 24-hour Holter monitoring revealed only rare, isolated, and monomorphic ventricular extrasystoles in one male patient with type 3 disease. However, as many as 18 patients (64.3%), 11 of whom with type 2 and 7 with type 3 disease, had an increased minimum heart rate over the 24-hour period (median minimum heart rate, 79/min; range, 52–101/min).
Conclusion: It appears that children and adolescents with SMA types 2 and 3 do not exhibit clinically significant cardiac disease. However, the finding of increased minimum heart rate in the majority of patients may signify an imbalance in the autonomic nervous system, with increased sympathetic and decreased vagal tone.

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Deficient Expression of Apparently Intact GAA Alleles in Monoallelic Cases of Late-Onset Pompe Disease (LOPD)

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Pompe disease (PD, Glycogen storage disease II) is a rare (incidence 1:8,000-1:17,000) metabolic myopathy caused by inactivation of both alleles of the GAA gene, encoding lysosomal acidic alpha-glucosidase. PD is the prototypic lysosomal storage disorder, in which buildup of glycogen within lysosomes leads to impaired muscle function. The very severe

infantile form, due to nearly complete loss of enzyme activity, results in cardiomyopathy and generalized hypotonia; if untreated, the infantile form is lethal within the first year of life. In contrast, the late-onset (LO) form, which appears anytime from early childhood to adulthood, presents with a milder phenotype in which the cardinal sign is skeletal muscle involvement, slowly progressing to generalized muscle weakness, hypotonia and dyspnea. LOPD is usually due to hypomorphic mutations with a relatively weak pathogenic potential, sometimes located outside the coding sequence of GAA (e.g. deep intronic mutations affecting proper GAA splicing). In consequence, LOPD patients show a remaining, if abnormally low, acidic alpha-glucosidase activity. Although the infantile form is relatively easy to diagnose because of its unequivocal clinical presentation with nearly complete loss of enzyme activity, LOPD is insidious, with a varying clinical course, and in many cases, the results of enzyme activity assays are inconclusive. In such cases, genetic testing is essential to confirm a diagnosis of LOPD. However, in a significant number of cases with a clinical suspicion of LOPD, genetic tests only identify a single mutant allele (the so-called GAA monoallelic cases) and the cases remain thus unelucidated, which precludes treatment. We investigated a cohort of 21 GAA monoallelic cases with clinical suspicion of LOPD that were referred to us from hospitals in Spain and Portugal with the objective of identifying the second mutant allele and verifying the diagnosis. Genomic analyses and careful examination of clinical data by our expert committee confirmed LOPD in 2 cases and ruled out LOPD in 6 cases. Allele-specific analysis of GAA RNA expression among affected and unaffected family members (proband, parents and siblings) was instrumental in the elucidation of the remaining cases, as it unveiled abnormally low expression levels of apparently intact alleles (i.e. with no changes in the GAA coding sequence).

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POEMS Syndrome: A Case Report

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POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes) is a rare paraneoplastic disorder that occurs in the setting of an underlying IgA or IgG monoclonal gammopathy typically λ-light chain. It is characterized by multisystemic manifestations which exceed the ones originally described in the acronym. We report the case of a 57-year-old female who presented at our neurology department with a 13 months history of sensory-motor, distal and symmetric peripheral neuropathy, initially cataloged as a chronic inflammatory demyelinating polyneuropathy (CIDP), which does not respond to intravenous immunoglobulin treatment. In whom the further clinical and ancillary evaluation confirmed the diagnosis of POEMS syndrome, including the presence of polyradiculoneuropathy and monoclonal proliferation of plasma cells as mandatory criteria, the presence of high VEGF and four minor criteria (organomegaly, papilledema, skin changes and extravascular volume overload). She presented a good response to the treatment established, that was evidenced in the improvement of neurological symptoms and a marked decrease in VEGF levels. Since the debut with polyneuropathy and the differential diagnosis with CIDP are frequent, in this article we introduce a description of the case and a bibliographical review of the main aspects that should prompt the suspicion of this entity at the neurology consult.

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Pulmonary Function in Non-Ambulatory Patients with nmDMD: STRIDE Registry and CINRG DNHS Matched Cohort Analysis

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Background: Strategic Targeting of Registries and International Database of Excellence (STRIDE [NCT02369731]) is an ongoing, multicentre, observational registry providing data on ataluren use in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD) in routine clinical practice.
Aims: To examine whether patients with nmDMD receiving ataluren plus standard of care (SoC; corticosteroid or palliative therapies), who were non-ambulatory by their last assessment, experienced a lesser decline in pulmonary function compared with matched patients with DMD receiving SoC alone (Cooperative International Neuromuscular Research Group Duchenne Natural History Study [CINRG DNHS; NCT00468832]). Data cut-off was 31 January 2019.
Methods: Propensity score matching was performed to identify non-ambulatory patients from STRIDE and the CINRG DNHS with comparable predictors of disease progression: age at first symptoms; age at first corticosteroid use; duration of deflazacort use; and duration of other corticosteroid use. Patients from the CINRG DNHS who received any other mutation-specific investigational drug for DMD were excluded. Kaplan–Meier analyses estimated age at loss of ambulation (LOA) and age at pulmonary function decline.
Results: Median age at LOA (95% confidence interval [CI]) for the matched STRIDE vs CINRG DNHS cohorts (each n=22) was 12.4 (10.7,12.9) years vs 11.1 (10.0,12.5) years. Mean (95% CI) ataluren exposure for patients in STRIDE up to LOA was 302 (163,440) days. Median (95% CI) age at which patients reached %-predicted forced vital capacity (FVC) <60% (each n=22) was delayed for patients from STRIDE vs the CINRG DNHS (18.7 [17.7,18.7] years vs 15.6 [13.2,16.7] years). Mean (95% CI) ataluren exposure for patients in STRIDE up to %-predicted FVC <60% was 661 (495,826) days.
Conclusion: These data suggest that ataluren plus SoC treatment slows pulmonary disease progression in non-ambulatory patients with nmDMD.

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Translation, Cross-Cultural Adaptation and Validation of Spanish Version of the Revised 15-Item Myasthenia Gravis Quality-of-Life-Questionnaire

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Introduction: Myasthenia gravis (MG) is the most common autoimmune disease of the neuromuscular junction. Clinically it is characterized by muscle weakness and excessive fatigue involving voluntary muscles. Several attempts have been made to measure the quality of life of patients with MG. The 3-response version of the MG-QOL15 questionnaire (MG-QOL15r) has recently been shown to have improved clinimetric properties and is easy to use. There are no validated instruments in Spanish for the measurement of health-related quality of life in patients with MG. This work represents the translation of the MG-QOL15r into Spanish and the survey'scross-cultural adaptation and validation.
Methods: Subjects and Data Collection. The protocol of the study was approved by the local Ethics Committee, and all patients signed an informed consent. The study was conducted between March 2017 and May 2019 in Santiago, Chile. We recruited patients with MG, ≥18 years old and whose mother tongue was Spanish. They were enrolled from the Department of Neurology in Hospital Salvador, private clinics and from the Chilean Myasthenia Gravis Foundation. The data was obtained from a clinical evaluation and two self-administered questionnaires completed during a medical interview: the Spanish version of the myasthenia gravis activities of daily living questionnaire (MG-ADL) and the Spanish version of the MG- QOL15r.

Translation and Cultural Adaptation. The translation and cross-cultural adaptation were conducted according to current guidelines. A committee created an initial Spanish version of the MGQOL15r by reviewing translations and backtranslations. This version was tested in a pilot study that enrolled 30 MG patients. After reviewing these results and making further adjustments, the final version was produced.

Psychometric Testing. For psychometric testing, sample size was estimated as 83 subjects, considering a 95% confidence and 3% precision in the estimated values with a mean of 17.6 ± 12.9. A 15% sample loss was estimated. To assess the item-specific internal consistency of the Spanish MG-QOL15r, we used Cronbach alpha coefficient and corrected item total correlation. Reproducibility was evaluated with the test–retest method performed on

30 consecutive MG patients who completed the questionnaire between 1 to 4 weeks after the first interview. Correlations between the results on the 2 visits and concurrent validity were examined using Spearman correlation coefficients.

Results: A total of 83 MG patients (mean age 48.19 ± 17.25 years) were enrolled and 58 (69.9%) patients were women. The internal consistency of the Spanish MG-QOL15r was excellent (Cronbach alpha coefficient of 0.92). Reproducibility coefficient was 0.80, which was statistically significant ($p< 0.0001$). Regarding concurrent validity, the correlation between the Spanish MG-QOL15r global score and MG-ADL was 0.637 (p-value <0.001)

Conclusion: The Spanish version of the MG-QOL15r is valid and reliable. It provides a valuable new instrument for the measurement of health-related QOL in Spanish-speaking MG patients

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Measurement of Motor Capacities in Oculopharyngeal Muscular Dystrophy

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Intro: Oculopharyngeal muscular dystrophy (OPMD) is a neuromuscular disease characterised by ptosis, dysphagia and proximal muscular weakness. Muscular weakness in OPMD manifests after the age of 40 and is associated with walking limitations affecting quality of life. To date, few studies on OPMD addressed motor impairments such as walking endurance, hip flexion function and muscle strength using quantitative and standardized assessments. These date are necessary in the process of therapeutic clinical trials and anticipatory guidance with affected individuals.

Aims: The objective of this study was to document motor performances of adults with OPMD including upper and lower limbs muscle strength, walking speed and endurance, and functional capacities.

Results: Twenty-one participants were recruited at this time of the study, with a mean age of 64 years (57% men). All participants have the (GCN)13 expansion confirmed. Results show a muscle strength within the expected values for shoulder flexors and abductors, hip extensors, and knee flexors (127, 120, 96, and 110 %, respectively), while elbow flexors, hip flexors and knee extensors are below the expected values (66, 64 and 76%, respectively). According to walking abilities, a normal walking speed has been observed with a mean of 94% from the normative data, but the walking endurance is reduced with a result at the 6 minutes walk test at 66% of the expected value. Functional limitations have been found such as limited capacity to perform complete sit-to-stands (9 repetitions versus about 14 for community dwelling elderly of the same age) and longer time to climb (7.73 seconds) and descend (5.77 seconds) 10 stairs (compared to 3.36 and 3.38, respectively, in 28 healthy people with a mean age of 58 years).

Conclusions: This study highlights the progressive incapacities other than dysphagia that people with OPMD have to face. Muscular weakness and loss of endurance can cause significant functional limitations compared to individuals of the same age group. These objective measures will provide highly relevant data to plan for future therapeutic trials that may occur soon in this population.

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Gastrointestinal Complications in Dermatomyositis

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Objectives: Dermatomyositis (DM) is a systemic vasculopathy affecting skin and muscle, which may also affect the gastrointestinal tract (GI). The objectives of the present study are to compile the cases of severe GI compromise related to DM in our center and in the literature.

Material and methods: We retrospectively analyzed the clinical histories of patients with DM in our center, excluding those with other myopathies, autoimmune diseases or digestive compromise (dysmotility, ulceropic disease, Helicobacter pylori or CMV).

GI compromise included cases of perforation and upper or lower digestive hemorrhage (DH) associated with erosions/ulcers of the digestive mucosa. Cases of GI involvement in DM from 04/1990 to 04/2019 were reviewed exhaustively through PubMed / Medline and Cochrane (in English and Spanish).

Results: From our cohort (188 DM patients), only 3 presented GI compromise. All were women with age of onset at 10, 46 and 68 years-old. The initial symptom was abdominal pain and all had ≥ 2 episodes of digestive bleeding (HD) that required at least one surgery. As treatment they received corticosteroids, immunosuppressants (cyclosporine, azathioprine and cyclophosphamide) and intravenous immunoglobulins. All died, two of complications related to the GI involvement and one of sudden death. In histology, typical images of vascular ectasia were observed in the mucosa.

From the literature review, 48 cases of DM with GI compromise were identified, 77% women with a mean age of 49.04 years (16 children, 7 adolescents and 25 adults). 65% debuted with abdominal pain (20% acute abdomen). Other symptoms were diarrhea (14.5%), vomiting (16.6%), fever and macroscopic HD (12.5%). All presented muscular and cutaneous involvement. Twenty required surgery. The underlying lesion was spontaneous perforation or ulcer (gastric/intestinal) (n=22), thickening of the intestinal wall (n=2), macroscopic inflammation (n = 2), intestinal pneumatosis (n=15) or overlaps. In 13 cases vasculitis was described. Mortality was 41.7%.

Discussion: The presence of GI involvement in patients with DM denotes severity, so it is recommended to start an early intensive treatment. Pathological findings, as in muscle, suggest that the underlying pathophysiological mechanism is a vasculopathy and not a genuine vasculitis.

Conclusions: GI involvement in DM is exceptional and the underlying pathophysiological mechanism is probably a vasculopathy.

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When Should we Consider that CIDP Patient is Non-Responder to IVIg?

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For CIDP, IVIg treatment is often the first choice as improvement can be fast. However, there is no consensus on when considering alternative therapy (corticosteroids or plasma exchange) for non-responder patients [1]. In PRISM study (efficacy and safety of Iqymune® in CIDP), time to response was analyzed as secondary endpoint.

In this study, 42 patients with CIDP were treated with Iqymune® (8 courses at 3-week intervals) and included in the efficacy set. Among them, 23 were never previously treated with IgG (IgG-naïve patients) and 19 were already treated with IgG but in clinical relapse following IgG therapy discontinuation (IgG-pretreated patients).

Although no statistical comparison were performed between subgroups, we observed that responder rate at the end of study (24 weeks) was numerically higher in IgG-pretreated patients than in IgG-naïve patients but confidence intervals (CIs) of these subgroups were largely overlapping (84.2% with 95% CI of [60.4-96.6%] versus 69.6% [47.1-86.8%]). We also observed that the response occurred earlier in IgG-pretreated patients than in IgG-naïve patients (median of 7.9 weeks with 95% CI of [3.4-12.1%] versus 19.1 weeks [12.1-24.1%] estimated by Kaplan-Meier method taking into account non-responder patients). Before the 5th course of Iqymune®, 13/16 responders in IgG-pretreated subgroup versus 7/16 responders in IgG-naïve subgroup had achieved a response. In other words, 12/32 responders showed a "late" response (after 5 to 8 courses).

These efficacy results are in line with the results from previous clinical study [2]. Both results may suggest that CIDP patients, IgG-pretreated and mainly IgG-naïve, should be maintained under IVIg for longer time (6 months) before considering other alternative therapy as indicated by EMA guideline [3].

Ref:

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Registry of Patients with Generalized Myasthenia Gravis Treated with Alexion C5 Inhibition Therapies: Methodology Overview

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Introduction: Generalized myasthenia gravis (gMG) is a complement-mediated disorder of neuromuscular transmission. The complement component 5 (C5) inhibitor eculizumab is approved for the treatment of gMG, and other complement C5 inhibitors are currently in development. Real-world data on the effectiveness and safety of C5 inhibitors and on the patterns of their use in patients with gMG are needed to expand the evidence from clinical trials and inform clinical practice.

Objective: The Alexion gMG Registry is a new, long-term, multicenter, observational registry of patients with gMG in the USA who are receiving, or have ever received, Alexion C5 inhibition therapy (C5IT) at enrollment. The objective is to gather real-world data on the effectiveness and safety of Alexion C5IT in patients with gMG, as well as on treatment patterns in clinical practice and their impact on patients' lives.

Registry Participants: Up to 500 adults (≥ 18 years of age) with gMG and historic or current exposure to C5IT will be enrolled, and data will be collected for a maximum of 5 years from first patient enrollment. Participants must be capable of giving signed informed consent and have historic data available for: Myasthenia Gravis Foundation of America class; Myasthenia Gravis Activities of Daily Living profile score; and Myasthenia Gravis Composite score. Exclusion criteria for the Registry include current participation in clinical trials.

Data Collection And Statistical Analyses: Data from patients' medical records will be collected using an electronic data capture system during routine clinical care. Physicians may enter data at any time after a patient visit but will be required to complete an electronic case report form (eCRF) at least every quarter for the first year and every 6 months thereafter. Data relevant to gMG (both physicians' evaluations and patient-reported outcomes) will be recorded retrospectively at enrollment and prospectively following enrollment. Data will be collected on the effectiveness (clinical outcomes) and treatment patterns (treatment schedules and concomitant myasthenia gravis [MG] treatments) of Alexion C5IT and the impact of Alexion C5IT on quality of life (QoL), healthcare resource utilization (MG-related hospitalizations and gMG exacerbations) and employment status. Serious adverse events, infections, meningococcal immunizations, comorbidities, and pregnancies and pregnancy outcomes will also be recorded (Figure 1).

If Alexion C5IT is discontinued, interrupted or changed, data collection will continue until the end of the Registry period to record reasons for treatment changes and to provide information on clinical outcomes and QoL (Figure 1). Study monitors will perform ongoing source data verification to ensure data accuracy and completeness. Analytical principles, patient cohorts and statistical techniques will be specified before data analyses in an epidemiological and statistical analysis plan.

Conclusion: Real-world data from the Alexion gMG Registry will enhance the understanding of the burden of gMG, the treatment patterns used in clinical practice and the long-term effectiveness and safety of Alexion C5IT. It is expected that these results will help to inform treatment decisions for improved clinical outcomes in patients with gMG.

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Multiplex Assay for Analysis of Mitochondrial DNA Depletion, Deletions and Oxidative Phosphorylation Defects in Muscle

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Mitochondrial DNA (mtDNA) deletions and depletion are found in the skeletal muscle of patients with primary mitochondrial disease (mtD), inflammatory myopathies and ageing. Quantitative real time PCR is currently the method of choice for quantifying mtDNA deletions and mtDNA copy number in skeletal muscle homogenates. A key limitation is an inability to detect high-level accumulation of mutant mitochondrial genomes or copy number depletion in single myofibres. The main aim of our project is to develop a complimentary multiplex in-situ hybridisation-immunohistochemical (ISH-IHC) assay allowing multiparametric assessment of mtDNA deletions, copy number and oxidative phosphorylation (OXPHOS) deficiency in entire skeletal muscle frozen sections, within an intact spatial and pathological context. In a pilot proof-of-concept approach, we employed a 20ZZ RNAscope probe (Hs-MT-ND5-sense) targeting the reverse compliment sequence of MT-ND5 (NC_012920.1: m.12337_14148). As mtDNA lacks histones, and the hybridisation protocol does not employ DNA denaturing and histone unpacking steps, the sense probe can bind to the non-coding/negative strand of mtDNA. Antibodies to TOMM20 (mitochondrial mass), MTCO1 (mitochondrially-encoded complex IV sub-unit) and laminin (myofibre basal lamina) were titrated and tested on control sections with and without protease pre-treatment which is integral to the ISH protocol, to ascertain effects on immunolabeled signal and its specificity. All antibodies showed robust signal comparable to untreated sections. Three mitochondrial disease (mtD) biopsies (TK2-mtDNA depletion, mtDNA single deletion m. 7938_13416, mtDNA single deletion m. 8483_13447 and a histologically normal biopsy (mtD excluded) were recruited to the pilot assay. The ISH assay was developed initially on 7 microns thickness frozen sections cut transversely, followed by multiplex immunolabeling with TOMM20, MTCO1 and laminin antibodies. COX-SDH histochemistry was performed on the next serial section. Both the ISH probe and antibodies were tagged to fluorescent reporters. Multiplexed labelled sections were scanned digitally (Zeiss Axioscan). The minimal change sample showed a physiological mosaic pattern of colocalised TOMM20-MTCO1-sense-ND5 signals. In all three mtD samples, we observed a striking colocalised marked-to-complete loss of sense-ND5 and MTCO1 signal, with preserved TOMM20 signal. In the serial COX-SDH-stained section these same fibres appeared COX-negative/SDH-blue. A subset of fibres showed subsarcolemmal enhancement of sense-ND5-MTCO1-TOMM20 composite signal, but marked loss of sarcoplasmic sense-ND5-MTCO1, and frequently corresponded to the ragged-blue fibres. An overall mosaic distribution of these abnormal samples was observed in all 3 mtD samples, ranging from 5% in the two mtDNA deletion biopsies to over 50% in the TK2-mtDNA depletion case. The latter showed remarkable intra-, inter-fascicular and regional heterogeneity in the distribution of the abnormal fibres. In summary, we have developed a multiplex ISH-IHC assay that is able to demonstrate colocalised expression of mtDNA and mitochondrial OXPHOS proteins at the single-fibre level in entire transverse frozen sections of skeletal muscle. In mtDNA single deletion and mtDNA depletion samples, the assay detects colocalised loss of mtDNA and complex IV over a wide range. Work is ongoing to develop differentially targeted ISH probes to the mtDNA major arc, minor arc and D-loop regions that will allow simultaneous analysis of mtDNA depletion versus single deletions and their correlation with mitochondrial OXPHOS defects.

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Multiplex Assay Detecting exon 44-48 Junctional Transcripts and Dystrophin Expression in Becker Muscular Dystrophy Biopsies

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The aim of many Duchenne muscular dystrophy (DMD) clinical trials is the induction or increase in

sarcolemmal dystrophin and emulate a Becker muscular dystrophy (BMD)-like molecular and clinical phenotype. Exon skipping therapies aim to modulate the pre-mRNA splicing of the DMD transcript using antisense oligonucleotides to restore the open reading frame, leading to a BMD-like internally deleted, partially functional dystrophin protein. There is a growing need to develop precise quantitative tools for multiparametric analysis of dystrophin expression in clinical trial biopsies. Our aim was to develop protocols for a multiplex in situ hybridisation-immunohistochemical (ISH-IHC) assay allowing quantitative analysis and correlation between junctional mRNA transcripts due to in-frame deletion of exons 45-47 and sarcolemmal dystrophin expression in entire frozen sections of three skeletal muscle biopsies from BMD patients with similar, moderate levels of dystrophin expression and a histologically normal control. Using Basescope (ACD Biotechne) technology we custom-designed a highly specific short-length (6647-6694) chromogenically-tagged mRNA probe targeting E44E48 of DMD transcript variant Dp427m (NM_004006.02). Two proprietary versions of the probe were tested in parallel with housekeeping-gene positive and negative control probes. Four commercial antibodies to dystrophin (DYS-1, DYS-2, DYS-3 and ab15227) were initially tested in parallel on sections subjected to and without the ISH protease pretreatment conditions to verify the effects on immunolabeled signal and its specificity. ab15277 and DYS-3 performed robustly with no discernible difference in signal strength, producing uniform and even sarcolemmal labelling in both protease-treated and untreated sections. DYS-1 and DYS-2 showed moderate and complete loss of signal respectively following protease pretreatment. Subsequent dual E44E48-DYS2 or E44E48-ab15227 labeling was successful with similar low-level perinuclear or subsarcolemmal E44E48 dot labelling and moderate sarcolemmal DYS-3 or ab15227 expression in all 3 BMD samples. The new E44E48 probe formulation was more sensitive, giving enhanced signal, without non-specific background. Work is in progress for automated digital quantitation of the multiplex ISH-IHC labelled sections, and comparison of the BioTechne DMD E44E48 junctional probe with another commercial platform using LNA technology in their junctional DMD E44E48 probe design. In summary, by systematic testing of commercially available ISH probe platforms and dystrophin antibodies, developing optimised protocols for a multiplex ISH-IHC assay could be a useful complementary tool in correlative assessment of the amount of in-frame exon skipping and dystrophin expression in DMD clinical trial biopsies.

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A Novel PRPS1 Mutation in a Japanese Patient with CMTX5

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X-linked Charcot-Marie-Tooth disease type 5 (CMTX5) is a very rare hereditary neuropathy and characterized by deafness, optic atrophy, and polyneuropathy. It is caused by missense mutations in phosphoribosyl pyrophosphate synthetase 1 (PRPS1).

PRPS1 catalyzes the first step of nucleotide synthesis. The phenotypes associated with PRPS1 mutation include X-linked nonsyndromic sensorineural deafness (DFN2) (mild PRPS-1 deficiency), CMTX5 (moderate PRPS-1 deficiency), Arts syndrome (severe PRPS-1 deficiency), and PRS-1 superactivity.

We report a first Japanese patient with CMTX5. The patient was a 33-year old Japanese man. Neurological examination showed bilateral reduced visual acuity, optic atrophy, and hearing loss. He had ape and claw hands. Distal muscle atrophy was recognized in the upper and lower extremities. Nerve conduction studies revealed severe motor sensory neuropathy. Systemic DNA tests for CMT were performed. The patient was found to be a hemizygous for the PRPS1 c82G>C (p.G28R) mutation. To reveal the significance of this mutation, we measured PRS-I enzymatic activity in the patient's erythrocytes, and it was reduced to 7.4 nmol/hr per mg hemoglobin. We conclude that his PRPS1 mutation is responsible for CMTX5.

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FIREFISH Part 2: 24-month Efficacy and Safety of Risdiplam in Infants with Type 1 SMA

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Objective: To determine the efficacy and safety of risdiplam in infants with Type 1 spinal muscular atrophy (SMA) treated for 24 months during the confirmatory Part 2 of the FIREFISH study (NCT02913482).

Background: SMA is a severe, progressive neuromuscular disease caused by reduced levels of survival of motor neuron (SMN) protein due to deletions and/or mutations of the SMN1 gene. A second gene, SMN2, produces only low levels of functional SMN protein. Risdiplam is a centrally and peripherally distributed, oral SMN2 pre-mRNA splicing modifier that increases the levels of functional SMN protein. Risdiplam (EVRYSDI™) has been approved by the FDA for the treatment of patients with SMA, aged 2 months and older.

Design/Methods: FIREFISH is a multicenter, open-label, two-part study of risdiplam in infants with Type 1 SMA and two SMN2 gene copies (inclusion criteria: aged 1–7 months at enrollment). Part 1 (N=21) assesses the safety, tolerability, pharmacokinetics and pharmacodynamics of different risdiplam dose levels (plus exploratory efficacy outcomes). The pivotal Part 2 (N=41) assesses the efficacy and safety of risdiplam at the dose selected from Part 1. The primary endpoint of Part 2 was the proportion of infants sitting without support for ≥5 seconds after 12 months of treatment, as assessed by item 22 of the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III).

Results: The primary endpoint of Part 2 at Month 12 was met (data-cut: 14th November 2019); 29% (12/41) of infants were able to sit without support for ≥5 seconds, as measured by Gross Motor Scale of the BSID-III (item 22; P<0.0001, performance criterion=5%). This milestone was never achieved in natural history cohorts. After 12 months, risdiplam treatment also resulted in a significantly higher percentage of infants surviving, demonstrating improvements in motor function and achieving motor milestones compared with natural history cohorts. No treatment-related safety findings leading to withdrawal were reported in Part 2. Here we will present efficacy and safety data from FIREFISH Part 2 after 24 months of treatment.

Conclusions: FIREFISH Part 2 is ongoing globally and will provide important data on the long-term efficacy and safety of risdiplam in infants with Type 1 SMA.

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Anti-Ganglioside Antibodies Classification and Correlation with the Clinical Manifestations in Patients with Inflammatory Peripheral Neuropathy

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In this study we investigated the relationships between anti-ganglioside antibodies and the inflammatory peripheral neuropathy including Guillain–Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN). We used a multiplex immunochromatography to search for anti-ganglioside antibodies.

Methods: Samples from 113 patients diagnosed with CIDP(89), GBS(9) and MMN(8) were prospectively enrolled.

Results: In the GBS patients, 75% were classified as having acute inflammatory demyelinating polyneuropathy (AIDP). Serum IgG anti-ganglioside antibodies were detected in 9.7% of the CIDP patients and in 12.5% of the GBS patients by ELISA; 1.4% of the 89 CIDP patients were IgG antibody positive, and 2.8% were IgM antibody positive by immunochromatography. Compared to ELISA method, immunochromatography showed lower detection rate. This will be affected by blood sampling time which after acute stage with treatment and accuracy of method.

Conclusions: These results suggest that IgG anti-GM2 antibodies are associated with CIDP and AIDP, and that IgM antibodies against GM1 are associated with CIDP.

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Pregabalin for Muscle Cramps in Patients with Liver Cirrhosis: A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Muscle cramps in patients with cirrhosis are common in clinical practice and found to show a poor physical condition when they had a history of muscle cramps, and this is probably related with frequent pain episodes and resultant sleep disturbances.

Objective: We aimed to assess efficacy and safety of pregabalin against frequent muscle cramp with liver cirrhosis and to investigate the relationship of muscle cramps with quality of life (QOL) using SF-36 and LDQOL-K.

Method: In this randomized, double-blind, placebo-controlled study, patients with liver cirrhosis were enrolled from Boramae medical center. Patients were eligible if they were diagnosed with liver cirrhosis of under 75 years of age and muscle cramps occurred more than 2 times a week over the last month. Patients were randomly allocated to receive oral pregabalin or placebo for 75 mg twice daily during the first 1 week (titration period), 150 mg twice daily for 4 weeks (standard dose treatment period), and 75 mg twice daily during the last 1 week (tapering period). The efficacy of pregabalin for muscle cramp in patients with cirrhosis measured by the difference in the rate of reduction of the number of muscle cramps, the mean change in the average cramp pain intensity, quality of sleep as measured by mean change in the number of muscle cramps during sleep. We monitored adverse events in all participants. This study is registered with ClinicalTrials.gov, number NCT01271660.

Results: Between July 2011 and December 2017, 109 patients were screened for eligibility and 83 went through a 4-week run-in period, of whom 60 were randomly assigned to either pregabalin (n=30) or placebo (n=30). Of those patients, 56 were randomly allocated to receive either pregabalin or placebo (29 in the pregabalin group and 27 in the placebo group) and were included in the full analysis set. Patients who received pregabalin had a significantly greater reduction in cramp frequency: 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 no differ between the pregabalin and placebo group (% vs.%). There were no significant differences in the mean changes of pain intensity and number of cramps during sleep between the pregabalin and placebo groups.

Conclusion: Our findings suggest that pregabalin is safe and effective for the treatment of muscle cramps in patients with cirrhosis and that it can influence the QOL of these patients.

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SUNFISH Part 2: 24-month Efficacy and Safety of Risdiplam in Type 2/non-ambulant Type 3 SMA

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Objective: To determine the efficacy and safety of risdiplam in patients with Type 2 or non-ambulant Type 3 spinal muscular atrophy (SMA) treated for 24 months during the confirmatory Part 2 of the SUNFISH study (NCT02908685).

Background: SMA is a severe, progressive neuromuscular disease caused by reduced levels of survival of motor neuron (SMN) protein due to deletions and/or mutations of the SMN1 gene. A second gene, SMN2, produces only low levels of functional SMN protein. Risdiplam is a centrally and peripherally distributed, oral SMN2 pre-mRNA splicing modifier that increases the levels of functional SMN protein. Risdiplam (EVRYSDI™) has been approved by the FDA for the treatment of patients with SMA, aged 2 months and older.

Design/Methods: SUNFISH is a multicenter, two-part, randomized (2:1, risdiplam:placebo), placebo-controlled, double-blind study in patients with Types 2 or 3 SMA (inclusion criteria: 2–25 years at enrollment). SUNFISH is comprised of two parts: Part 1 (N=51) is assessing the safety, tolerability and pharmacokinetics/pharmacodynamics of different risdiplam dose levels in patients with Types 2 or 3 SMA (ambulant and non-ambulant); Part 2 (N=180) assesses the safety and efficacy of the Part 1-selected dose of risdiplam versus placebo in Type 2 and non-ambulant Type 3 SMA. Individuals were treated with risdiplam or placebo for 12 months; all individuals then received risdiplam until Month 24. At Month 24, patients were offered the opportunity to enter the open-label extension. The primary objective of Part 2 was to evaluate the efficacy of risdiplam compared with placebo in terms of motor function as assessed by the change from baseline in the 32-item Motor Function Measure (MFM32) total score at Month 12.

Results: The primary endpoint of SUNFISH Part 2 was met; showing a statistically significant difference in the change from baseline in MFM32 total score at Month 12 between patients treated with risdiplam (n=120) compared with those who received placebo (n=60). No treatment-related safety findings leading to withdrawal were reported.

Here we will present efficacy and safety data from SUNFISH Part 2 after 24 months of treatment.

Conclusions: SUNFISH Part 2 is currently ongoing and will provide further data on the long-term efficacy and safety of risdiplam in a broad population of children, teenagers and adults.

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Subcutaneous Immunoglobulin in Myasthenia Gravis: Results of a North American Open Label Study

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Objectives: To assess efficacy, safety and tolerability of subcutaneous immunoglobulin (SCIg) in the treatment in myasthenia gravis (MG) patients who are on IVIg as part of routine clinical care.
Background: IVIg has been demonstrated to improve the MG status as compared to placebo and in another study to be equally efficacious to plasma exchange. In routine care, SCIg might be preferred to administer over IVIg.
Methods: This multi-center North American open label prospective investigator-initiated study had 2 components: IVIg Screening Phase (ISP; Weeks -10 to -1) followed by Experimental Treatment Phase (ETP; Weeks 0 to 12). We hypothesized that more than 65% of the patients entering the ETP would have a stable a QMG score (primary outcome) at Week 12. We recruited 23 patients in the ISP and 22 entered the ETP. 12/22 (54.5%) were females and 18 cases were white; mean age 51.4 ± 17 years. We had complete ETP QMG data on 19/22; one subject withdrew from ISP owing to worsened condition, and two subjects who disliked needles withdrew before Week 4. The per protocol primary statistical analysis was conducted for n=22 subjects using a one-sided z-test of proportions at the 5% significance level. Sensitivity analyses were conducted using a cohort of n=22 subjects using 'worst-case' imputation scenario as well as post hoc analysis.
Findings: On primary analysis, 19/22 (86.4%; 95% CI:0.72-1.00) were treatment "successes" (p=0.018). Sensitivity analysis using the 'worst-case' imputation resulted in 17/22 (77.3%;0.60-0.95) declared as treatment success (p=0.114). Post hoc analysis of the primary outcome confirmed treatment success in 17/20 (85%;0.69-1.00) (p=0.0304). There was no difference in the secondary outcome measures although MG composite performed better at Week 12. SCIg was safe and well tolerated in this population.
Conclusion: Most MG patients who were doing well on IVIg maintained disease stability for another 12 weeks once transitioned to 1:1.2 dosage of SCIg.

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JEWELFISH: Safety and Pharmacodynamic Data in Non-Naïve Patients with SMA Receiving Treatment with Risdiplam

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Objective: To assess the safety, tolerability and pharmacokinetic/pharmacodynamic (PK/PD) relationship of risdiplam in non-naïve (previously treated with other SMA therapies) patients with spinal muscular atrophy (SMA) who have been treated with risdiplam in the ongoing JEWELFISH study (NCT03032172).

Background: SMA is a severe, progressive neuromuscular disease caused by reduced levels of survival of motor neuron (SMN) protein due to deletions and/or mutations of the SMN1 gene. A second gene, SMN2, produces only low levels of functional SMN protein. Risdiplam is a centrally and peripherally distributed, oral SMN2 pre-mRNA splicing modifier that increases the levels of functional SMN protein. Risdiplam (EVRYSDI™) has been approved by the FDA for the treatment of patients with SMA, aged 2 months and older.

Design/Methods: JEWELFISH is a multicenter, open-label study evaluating the safety, tolerability and PK/PD relationship of daily oral risdiplam in non-naïve patients with SMA (inclusion criteria 6 months–60 years at enrollment). JEWELFISH participants previously received RG7800 (RO6885247), nusinersen (SPINRAZA®), olesoxime or onasemnogene abeparvovec-xioi (ZOLGENSMA®).

Results: We have previously presented safety data from 173 patients with SMA (data-cut: 31st January 2020) who received risdiplam for up to 32.8 months (patients previously received RG7800 [n=13], nusinersen [n=76], onasemnogene abeparvovec [n=14] or olesoxime [n=70]). No treatment-related safety findings leading to withdrawal were reported. The overall adverse event profile of risdiplam treatment in non-naïve patients was consistent with that of treatment-naïve patients. Previously presented JEWELFISH PD data showed a ≥2-fold increase in median SMN protein levels versus baseline (data-cut: 1st June 2020), which was consistent with PD data from the SUNFISH study (NCT02908685) in treatment-naïve patients with Type 2 and 3 SMA. Here we will present updated safety and PD data from the JEWELFISH study.

Conclusions: JEWELFISH is ongoing in sites across Europe and the US and will provide important data on the safety and PD of risdiplam in non-naïve patients with SMA.

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A Novel Dystrophin-Related Protein-2 (DRP2) Exon Deletion in a Family with Intermediate Charcot–Marie–Tooth Disease

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Charcot–Marie–Tooth disease (CMT) is the most frequent form of inherited neuropathy with great variety of phenotypes, inheritance patterns, and causative genes. Mutations in the DRP2 gene are associated with Intermediate CMT (I-CMT) forms with recessive X-linked pattern of inheritance. To date, two hemizygous variants in the DRP2 gene found by whole-exome sequencing have been reported: a c.805C-T transition in exon 5, resulting in a gln269-to-ter substitution in a patient with I-CMT, and a "TTC" deletion on chromosome X from nucleotide 100510203 to 100510205 (GRCH37/hg19) in a consanguineous family with slowly progressive polyneuropathy and cardiomyopathy (there is no available electrophysiological data).

Herein we describe a 21-year-old male with axial spondyloarthritis HLA B27+ who was evaluated at Neurology clinic after performing an MRI of sacroliliac joints where marked neural thickening of sacral plexus was observed. He was born of healthy non-consanguineous parents and was asymptomatic from a neuropathy point of view. On examination he showed just mild atrophy of intrinsic muscles of the feet and generalized areflexia without pes cavus or thickening of the nerves. An electrophysiological study was conducted showing slowing of the nerve conduction velocities in the intermediate range (40m/s). A muscular MRI of the lower limbs was performed showing subtle decrease of volume at intrinsic musculature of the feet and flattening of the EDB muscles. Initially, the CMT1A duplication was discarded by MLPA analysis. Then, through a

custom gene panel sequencing we identified a novel single-exon deletion of exon 6 in the gene DRP2, which was validated by analysing the mRNA pattern of expression in peripheral blood lymphocytes from the patient. Both progenitors were asymptomatic. The electrophysiological study in the mother was normal, and she carries the deletion in heterozygosis. **Conclusions:** Mutations in the DRP2 gene are extremely rare. Here we describe a young male with a mild phenotype of I-CMT and a novel single-exon copy-number variation (CNV) in the DRP2 gene identified by targeted next-generation sequencing.

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High Resolution Ultrasound is Superior Than Clinical Examination and Electromyography in Detecting Fasciculations in ALS

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Introduction: High resolution ultrasound (HRUS) is an emerging complementary tool to electrophysiology in the diagnostic evaluation of various neuromuscular disorders. It can visualise static and dynamic anatomical details of muscles with precision. The first description of the role of ultrasound in detecting fasciculation was in 1988, subsequent studies reported that myosonography is more sensitive in detecting fasciculation in lower motor neuron diseases. We aimed to study the utility of HRUS compared to conventional methods: clinical examination and electromyography (EMG) in detecting a fasciculation in patients with amyotrophic lateral sclerosis (ALS).

Objectives: 1. To study the yield of fasciculation by three methods in various muscles – Clinical examination, EMG and HRUS 2. To compare the times taken to detect fasciculation by Clinical examination, EMG and HRUS

Material and Methods: Study site: CARE hospital, tertiary care centre, Hyderabad, South India; Study Period: Jan 2019 and Dec 2019; Study technique: Clinical examination was performed by trained neurologist, HRUS was performed using Philips HD15 with linear 12-3 probe; EMG was performed using Synergy system; Study cohort: Nine patients of ALS were enrolled; Subjects were noted for fasciculations by three methods - Clinical examination, EMG and HRUS; 80 sites from 9 subjects were sampled, sites was chosen by treating neurologist; Parameters studied: Number of sites with fasciculation; time duration (in seconds) to recognise fasciculation; detection rate in different muscles; time duration (in seconds) to detect fasciculation in different muscles

Results: Technique 1: Clinical Examination, Technique 2: EMG, Technique 3: HRUS. Age (Mean±SD): 50.8±7.0; Sites with detectable fasciculation n (%): 34(42.5) vs. 49(68.1) vs. 68(85) ($p<0.05$); Time (seconds) to recognise fasciculation (median & range): 20 (3-120) vs. 25 (3-150) vs. 9 (1-88) ($p<0.05$); detection rate in various muscles (%): Biceps: 47.1 vs. 70.1 vs. 100 ($p<0.05$), Triceps:78.5 vs. 78.5 vs. 100 ($p<0.21$), Flexor digitorum superficialis: 100 vs. 100 vs. 100 ($p<0.99$), External digitorum communis: 50 vs. 100 vs.100 (p0.01), Quadriceps: 30.8 vs. 46.2 vs. 92.3 ($p<0.01$) Tibialis anterior: 16.7 vs. 66.7 vs.100 ($p<0.05$), Gastronemius: 0 vs. 33.3 vs.83.3 ($P<0.05$); time (seconds) to detect in various muscles: Biceps: 15 vs. 45 vs. 5 (p0.04), Triceps: 16 vs.20 vs.8 (p0.46), Quadriceps: 6.5 vs.17 vs. 4 (p 0.03).

Conclusion: HRUS is an easy, safe, convenient, painless, non invasive and repeatable and therefore superior tool to detect fasciculations than needle EMG.

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Incidence and Clinical Features of Adulthood Guillain-Barré Syndrome in Uruguay

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Objective: To establish the incidence and clinical features of Guillain Barré syndrome (GBS) in a well-defined geographical area of Uruguay.

Patients and Methods: All patients older than 16 years of age who were diagnosed with GBS between

June 1st, 2018 and December 31th, 2019 were prospectively enrolled. For case ascertainment, multiple sources of information were used, including records from specialties potentially involved in GBS diagnosis. All patients were examined by neurologist of our team. A standard questionnaire was used to collect the patient's demographic data, clinical history, neurological and laboratory findings, and treatment details. Clinical examination included MRC scoring (Medical Research Council), where score 0 = total paralysis, and 5 = normal strength, with a maximum score of 60. Functional levels were assessed using the Hughes Functional grading scale. To estimate the incidence, patients recruited during the first year of the study were considered.

Results: A total of 40 patients between 17 and 97 years old (mean age of 55) were diagnosed with GBS during our period of study. Of these, 27 were men (mean age of 56) and 13 women (mean age of 57). Four patients had MFS, four had AMAN-AMSAN, and all others were diagnosed with AIDP. History suggestive of infection prior to the illness was present in 25 (62%) patients, respiratory being the most common. Mean MRC score was 37,8 (range 0–60) and 10 patients had a Hughes score ≤2. Ten (25%) patients were mechanically ventilated. Raised protein levels (>0.5 g/L) in the spinal fluid was found in 29 (72%) patients and antibodies to the gangliosides in 12 (30%). The clinical factors associated with mechanical ventilation were the presence of autonomic dysfunction, a Hughes score ≤2, MRC≤40, and bulbar involvement. Intravenous immunoglobulin was given to 28 patients as the initial treatment and plasma exchange to 6. One patient (2,5%) died during in-hospital stay. Age specific rate incidence for the population over 16 years of age in the period between June 1st, 2018 and May 31th, 2019 was 1.68/100000 person year; 2/100000 person year for men and 1.40/100000 person year for women.

Conclusions: This study is the first prospective population based study of GBS in Uruguay. During the one year period, 24 GBS cases were reported and the age adjusted incidence was 1.68 per 100 000 population.

The reduced number of cases and the limited period of time must be taken into account when interpreting the incidence. Nevertheless, complete case ascertainment is highly probable due to our system of multiple sources used for the identification of GBS cases from a stable reference population living in a well and small defined geographical area. It is probable, although, that mild or very elderly cases that did not receive medical attention could have been missed.

The incidence observed in our study is in the range of the estimated incidence rates reported in European and North American studies. The clinical presentation, subtypes, treatments, variables associated with the need of mechanical ventilation and mortality are similar to other series.

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Childhood-Onset Limb-Girdle Muscular Dystrophy Type 2A or Calpainopathy: Clinical Spectrum and Long-Term Follow Up

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Introduction: Limb-girdle muscular dystrophy (LGMD) type 2A or calpainopathy, the most prevalent form of LGMD, is an autosomal recessive disorder caused by a deficiency of the calpain-3 protein (calcium-activated neutral protease-3), a muscle-specific enzyme involved in "sarcomere remodeling". LGMD2A is characterized by progressive weakness of the pelvic and shoulder girdle muscles with great variability in the clinical course.

Material and methods: Retrospective descriptive study. Clinical, pathological, radiological and genetic characterization of 21 genetically confirmed calpainopathy patients with childhood or adolescent age at onset.

Results: The average age at onset of muscle symptoms was 9.3 years (range 3-18). The main presenting symptom was muscle weakness in the lower extremities (n=12, 57%). Other clinical findings in the first stages of the disease were toe walking, exercise intolerance, and rhabdomyolysis. The clinical exam revealed winged scapula (n=12), adductor weakness and "hip abduction sign" (n=10), Achilles tendon contractures (n=14) and calf muscle

pseudo-hypertrophy (n=4) as the main early distinctive features. Laboratory tests revealed elevated serum CK levels in all patients, with a range between 1500 to 11000IU/l (average: 6200IU/l) and peripheral blood eosinophilia in 50% of the patients. Muscle MRI, disclosed gluteal muscle, adductor magnus and posterior compartment muscle involvement. (n=10, 90%). Paravertebral muscles were also frequently affected (n=5, 45%). The muscle biopsy was consistent with myopathic pattern, dystrophic findings consisted of variability in the size of the fibers with grouped or isolated regenerative-degenerative fibers and occasional necrotic fibers. The presence of high proportion of fiber splitting was one of the main findings. Fiber 1 type predominance and defects on stain in the intermyofibrillar pattern were also found. In one patient (clinically affected) the muscle biopsy was unremarkable. Calpain-3 immunoblot was performed using 2 antibodies to detect deficiencies in its different subunits, showing normal amount of protein in two patients. Genetics findings are summarized in table 1, the most frequent mutation was p.Arg788Serfs*14 (known pathogenic). During the follow-up period, six patients became wheelchair-bound from 7 to 38 years after the clinical onset, averaging 25 years. Decreased FVC (<80%) was rarely observed (n=3, 14%) exclusively in non-ambulant patients, with nocturnal non-invasive positive pressure ventilation requirement in two patients. None of the patients had cardiac dysfunction.

Conclusions: Limb-girdle muscular dystrophy (LGMD) type 2A or calpainopathy should be suspect in children or adults presenting with progressive low extremities weakness in association with a winged scapula and early joint contractures, increased CPK and eosinophilia. Typical and selective muscle involvement in both, clinical examination and muscle imaging may be used to address the diagnosis.

Muscle biopsy is consistent with nonspecific muscular dystrophy with a predominance of fiber splitting. The finding of lobulated fibers seems to be uncommon in children compared to adults. Normal muscle biopsy do not rule out the possibility of calpainopathy. Western-Blot has to be performed in a correctly processed muscle biopsy, otherwise the protein calpain-3 may be degraded as it has autolitical activity. Taking into account the progressive course of the disease, the respiratory function should be regularly evaluated, especially in non-ambulant stages, considering non-invasive ventilation.

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Clinical Molecular Study and Deflazacort Treatment in Becker Muscular Dystrophy

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To investigate deflazacort effect and role in Becker muscular dystrophy (BMD) to modulate inflammation. Becker muscular dystrophy (BMD) is a rare X-linked recessive inherited disorder, due to an in-frame mutation in dystrophin gene and results in progressive decline in muscle functions when left untreated. Deflazacort is a synthetic corticosteroid characterized by the insertion of a fused methyloxazolidine ring in the structure of prednisone. Deflazacort has been used in DMD but not so far in BMD. MicroRNAs (miRNAs) are small non-coding RNA molecules approximately 22 nucleotides in length. A group of miRNAs are highly expressed in skeletal and cardiac muscle and they are called myomiRs. The myomiR family includes miR-1, miR-133a, miR-133b, miR-206 which are used as non-invasive serum biomarkers in neuromuscular diseases. In a preliminary trial we have used deflazacort (60 mg/ alternate day) in BMD patients and have monitored their weight, MRC, spirometry and echocardiography and as biomarkers, serum microRNA versus untreated BMD and control. We have compared results of myomiRNAs in 2 deflazacort treated BMD cases versus 3 untreated BMD patients.

The most highly dysregulated serum miRNA in BMD was miR-206, a skeletal muscle-specific miRNA. We also observed an elevation of miR-133b and a slight up-regulation of the other miRNA, compared to the control group. Two deflazacort BMD patients presented stabilization of proximal weakness, MRI alterations with gastrocnemius hypertrophy.

Deflazacort was beneficial in treating the two patients by modulating inflammatory response in muscle stabilizing their clinical condition and functional outcomes and a spirometric data. Cardiac ejection fraction was 55-60 %. There was no effect on their weight and only a slight decrease in bone densitometry. These data highlight the potential use of

miRNA as biomarkers of BMD that seem to correlate with both clinical and MRI imaging changes.

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Abnormalities of Brain Gyrification in Early-Onset Myotonic Dystrophy Type I Patients

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Myotonic Dystrophy type 1 (DM1) is a progressive multi-systemic neuromuscular disorder caused by an abnormal cytosine-thymine-guanine (CTG) repeat expansion and characterized by anticipation phenomena. Central Nervous System (CNS) involvement includes brain abnormalities, cognitive and psychiatric dysfunctions that have an important impact on patients' quality of life. A new classification provided in 2016 underlined five different DM1 categories, based on age onset, clinical symptoms, and CTG length. The variability of CTG repeat expansion in DM1 is commonly associated with the severity of the disease. Surface base morphometry (SBM) analysis offers a new approach to evaluate brain cortex allowing to capture morphological proprieties such as gyrification. We used gyrification analysis to test the hypothesis that changes in gyrification are characteristic in DM1 patients. Comparing early-onset (EO) and late-onset (LO) we assessed if differences between subgroups are present and if these abnormalities partially overlap with those detected with the techniques previously used (VBM or cortical thickness). Twenty-eight patients with a genetic diagnosis of DM1, according to the International Consortium for Myotonic Dystrophies guidelines (IDMC, 2000), were recruited between 2013 and 2015. All patients underwent a psychological and clinical evaluation and a brain MRI exam. Patients were grouped on the age of symptoms onset and divided into two subgroups: EO with disease onset between 10 and 20 years and LO with an age of onset after 21. Healthy Control (HC) group was retrospectively selected from our database and 14 matched HC were included for MRI analysis. Considering the whole DM1 group, we detected deficit in attentional and working memory performance and in particular in the digit span forward, in the Raven Coloured Progressive Matrices, in the Trail Making Test (A and B task), and in the categorization ability of Wisconsin Card Sorting Test. Comparing EO and LO subgroups we observed that attentional and working memory dysfunctions were predominant in EO compared to LO, while executive dysfunctions were prominent in LO. Gyrification analysis revealed a lower local gyrification index (LGI) in frontal, parietal and temporal cortex in EO compared to LO while no differences in LGI were detected in between LO and HC. Abnormalities in the cognitive profile are present in DM1 patients (both subgroups). A different pattern of cognitive impairment can be underlined between EO and LO patients. Differences in gyrification were common in EO compared to LO. No differences were detected between LO patients and HC.

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Molecular and Protein Biomarkers in ALS Muscle

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MicroRNAs are small non-coding RNAs that regulate the expression of specific genes by binding to the 3' untranslated region of the target mRNA. HDAC4 belongs to the class IIa of HDACs (histone deacetylases) family and plays an important role during the denervation and regulation of miR-206 in ALS pathophysiology.

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease characterized by the degeneration of upper and lower motor neuron and the progressive loss of synaptic connection between nerve and muscle. While the majority of ALS cases are sporadic (SALS), about 10% of ALS cases have a familial inheritance (FALS). The most frequent genetic cause of ALS is associated with an expanded repeat in the 3' untranslated region of C9orf72 gene (C9-ALS). Another frequent genetic cause is due to mutation in the gene SOD1, coding for a superoxide dismutase enzyme (SOD1-ALS). A different form of ALS is upper motor neuron disease (UMN).

We analyzed the expression levels of muscle-specific myomiRNAs (miR-1, miR-133a, miR-133b,

miR-206), inflammatory microRNAs (miR-27a, miR-221, miR-155) and HDAC4 protein content by Western Blot in muscle cryostat sections of 18 ALS patients: 8 genetic forms (C9-ALS and SOD1-ALS), 5 SALS and 5 UMN. Our results show a strong up-regulation of miR-206 in C9-ALS and SOD1-ALS patients, a decreased expression of HDAC4 protein levels. We also observed an increase of inflammatory miRNAs in genetic ALS. The different expression of miRNAs and HDAC4 in genetic ALS versus SALS and UMN cases might be correlated to different pathogenic mechanisms.

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Clinical Evolution in Two Families with LGMD D2

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To study two families affected by LGMD D2, an autosomal dominant form of LGMD due to a mutation of TNPO3 gene. This rare disorder was firstly identified in a large Italo-Spanish family (mother and daughter) and we present another family with a congenital myopathy-LGMD phenotype in a child and his mother of Hungarian origin. Clinical data, MRI imaging and quality of life were performed and compared in two families with transportinopathy.

The onset of symptoms was often characterized by difficulty in walking or climbing stairs, collected by a standard LGMD questionnaire. Muscle MRI was done 1.5 Tesla Philips apparatus using Mercuri score. The assessment of Quality of Life(QoL) was done in the mother of Hungarian family by an Individualized Neuromuscular Quality of Life(INQoL) test.

In the Italo-Spanish family, the mutation was identified in a single nucleotide deletion (c.2771delA,p.X924C,exon22) in the TNPO3 gene while in Hungarian family the causative mutation of LGMD D2 is due to a heterozygous frameshift deletion c.2767delC. in exon 23. The age of onset in our cases was either in the early teens or from the third decade. Mother and daughter of Italian-Spanish family presented marked atrophy of upper girdle muscles. The child of Hungarian family and his mother presented difficulty to stand from the floor. Muscle MRI showed pronunced atrophy in posterior thigh muscles of daughter and mother of Italo-spanish family. Son and mother of Hungarian family showed generalized muscle atrophy. We observed that with age progression, connective and fat tissue increased, involving mostly posterior thigh (i.e. semitendinosus).

Data derived from longitudinal MRI study in two patients of a previously reported family and in two cases of a new family confirm two patterns of early onset and a late onset a proximal muscle involvement. Muscle MRI represents an valuable tool to document disease progression.

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Upper and Lower Limbs Motor Performance of LAMA2-Related Congenital Muscular Dystrophy Patients

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Introduction: Motor assessment of LAMA2-related congenital muscular dystrophy patients (LAMA2-CMD) represents a challenge to physical therapists due to the decreased whole-body mobility and limbs muscle shortening and weakness. There are no specific scales to assess upper and lower limbs motor impairment in these population. Measurement tools should quantify the impact of muscle impairments on motor development and daily living activities.
Objective: Transversal and prospective upper and lower limbs motor assessment of LAMA2-CMD in a Brazilian reference center.
Methods: Twenty three children (8.7±4.7 years old; 13 female\10 male) had motor impairment measured by functional tools. The dominant upper limb functional performance was measured by Revised Upper Limb Module (RULM) – 20 items of shoulder, elbow and wrist daily functions – with a maximum score of 37. Motor function was evaluated by Motor Function Measure (MFM) – with a maximum score of 20 (from 2 to 7 years old) or 32 (from 6 years old). Statistica 13.0 (Statsoft, USA) was used in all descriptive statistics.
Results: The mean score achieved for RULM was 13.6±5.5 points (min: 5; max 27). The MFM showed the highest impairment in orthostatism\transfers domain (1.5±2.6; min: 0; max: 1), followed by proximal function domain (16.1±6.8; min: 0; max: 25).

Distal function domain and total score showed similar mean scores – 31.3±3.8; min:7; max:19 and 31.3±7.9; min:14; max:44, respectively.

Conclusions: The sample exhibited difficulty to complete upper and lower limbs items with proximal muscle demand compared to distal demand, which performed better. Activities related to orthostatism and transfers represent the greatest challenge for LAMA2-CMD. Follow-up assessments with these scales are suggested to better understanding of the natural history and as a clinical parameter for therapeutic interventions in LAMA2-CMD.

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Case Report of Giant Axonal Neuropathy in a 6-Year-Old Girl with Gait Difficulties

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Introduction: A 6-year-old girl presented with progressive difficulty in walking since the age of two. Clinical examination showed muscle weakness in the lower limbs and trunk, positive Gower's sign, waddling gait, absence of deep tendon reflexes, nystagmus and tightly curled hair.

Methods: The clinical presentation of the child led to a series of exams. Full blood testing (including CPK) was ordered. The patient was also submitted to electroneurography (ENG) and whole exome sequencing analysis (WES). The parents also underwent genetic testing.

Results: Blood test results were normal (including CPK). The ENG findings showed no sensory deficits in the upper and lower extremities. Motor nerve conduction studies for peroneal and tibial nerves indicated reduction of amplitude of the motor action potentials. Furthermore, a slightly prolonged latency was recorded, accompanied by a slightly reduced motor conduction velocity. The above findings were consistent with axonal neuropathy of the motor nerves in the lower extremities.

WES analysis revealed two compound heterozygous variants c.370T>A;p.Phe124Ile and c.1412A>G;p.Tyr471Lys in GAN gene, maternally and paternally inherited, respectively. The variant c.370T>A;p.Phe124Ile was absent in control population databases, while the variant c.1412A>G;p.Tyr471Lys was present in very low frequency (MAF:2/251482) in gnomAD exomes. Both amino acid changes involve highly conserved residues and in silico tools predicted a pathogenic role.

Conclusion: The results of ENG and WES led to the diagnosis of a very rare polyneuropathy, Giant Axonal Neuropathy (GAN), which has been described in about 50 families. GAN is an inherited neurodegenerative disorder which affects both central and peripheral nervous system. It is an autosomal recessive disorder caused by mutations in the GAN gene, which provides instructions for the making of gigaxonin protein, a subunit of E3 ubiquitin ligase. Gigaxonin plays a role in the breakdown of neurofilaments, which comprise the structural framework that establishes the size and shape of axons. As a result, the affected giant axons do not transmit signals properly and eventually degenerate, resulting in the death of neurons.

GAN is a disease with an expanding clinical and genetic spectrum. The condition is underdiagnosed because its early symptoms resemble those of other more common disorders such as Charcot-Marie-Tooth disease and myopathies. Although there is no effective treatment at present, diagnosis is important for genetic counseling.

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25 Years of Co-creating the International Landscape in NMD Research: The Paradigm of the ENMC

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Thirty years ago, the causes for progressive and often fatal neuromuscular disorders (NMDs) were gradually being discovered. Treatments to stabilize or even cure these diseases were still far out of reach. Before that time research was done in a very isolated and fragmented way. Since most of the NMDs are rare according to the European Commission definition[1], it was vital to start joining forces and collaborate at the international level to speed up the

development of effective treatments. Parents from children affected by NMD and leading neurologists discussed and co-created a unique concept to bring researchers and clinicians together[2]. As a result, the European Neuromuscular Centre (ENMC) was founded in 1992. More exchange of knowledge, sharing of (unpublished) data and bio-samples, and collaboration in multinational studies was needed to improve the diagnosis and treatment of NMDs. This became the ultimate mission of the ENMC.

To achieve this, the founders believed in the strategy of organizing interactive and low-threshold workshops with a maximum of 20 participants on application basis. Applicants were 2-4 organisers from the researchers- and scientific community who submitted workshop proposals on topics with a high unmet need. European patient organisations and foundations (POs) were attracted to join and steer the ENMC via its Executive Committee and to secure income to support the workshops. As of today, 10 POs are forming the steady basement of the ENMC. In parallel, a multidisciplinary group of researchers and clinicians from varying countries was asked to form the ENMC Research Committee, chaired by the Research Director. This rotating committee assesses the workshop applications and advises the Executive Committee, establishing a close collaboration between POs and scientists within the ENMC.

As of today, more than 250 workshops were organised and about 2500 NMD experts from over 65 countries were included in the ENMC network. Each workshop is recorded in a lay and a scientific report; ENMC-derived papers are actively cited by the scientific community[3].

In the last 10 years, the ENMC brought patient-researcher collaboration to the next level by involving people affected by NMDs in every workshop. Giving voice to patients often completed the discussions and is now an essential component of each workshop. This further evolved in 2018: Patient involvement, co-creation in different areas of neuromuscular research and shared decision-making were the topics of a workshop held in Milan[4,5]. The overall conclusion of this meeting was that active inclusion of patients at all levels of neuromuscular research and care requires changing attitudes of the different stakeholders. Informed and trained ambassadors are needed who inspire and empower others about the benefits of patients' participation. A White Paper was written to identify more specific actions for each topic discussed at this meeting and will be presented at the ICNMD patient symposium.

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Acute Ocular Motor Mononeuropathy and Peripheral Polyneuropathy in Patients with Abnormal Glucose Metabolism

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Introduction: The association between acute ocular motor mononeuropathy and polyneuropathy in patients with abnormal glucose metabolism has not been studied. Most studies on acute ocular motor mononeuropathy are related to differential diagnosis and it relation with diabetes. To elucidate If there is an association between these two entities could be useful for the management of patients with abnormal glucose metabolism. In order to do this we carried out an electrophysiological conduction studies in patients with acute ocular motor mononeuropathy, abnormal glucose metabolism and without known diagnosis of polyneuropathy.

Material and Method: Prospective descriptive study of patients with acute ocular motor mononeuropathy and abnormal glucose metabolism, without diagnosis of polyneuropathy. The study was carried out between September 2013 to January 2015, in the Neuro-Ophthalmological Unit of the Instituto de Neurocirugia and Departamento de Ciencias Neurologicas, Facultad de Medicina, Universidad de Chile, Santiago, Chile. Patients with acute ocular mononeuropathy were recruited if they had an abnormal glucose metabolism, and did not have any other disease that can produce neuropathy, nor any structural cause of ocular mononeuropathy on a brain CT scan or MRI, and were willing to sign an informed consent. The diagnosis of diabetes or pre-diabetes were made based on diagnostic criteria of the American Diabetes Association. All patients

were submitted to motor and sensory conduction studies.
Results: Twenty two patients fulfilled the inclusion criteria, 77% of the subjects were men. Mean age (±SD) was 67 ±8 years. The average duration of diabetes or pre-diabetes was 7 years.There were 6 pre-diabetics, 8 non insulin requiring diabetics and 8 insulin requiring diabetics. Thirteen patients (59%) had involvement of the III cranial nerve, 7 (31%) had the VI cranial nerve, one the IV cranial nerve and another had involvement of more than one cranial nerve. None of the patients had pupillary involvement. Thirteen patients (59%) had abnormal electrophysiological studies, twelve of whom were diabetics. All acute ocular mononeuropathies showed complete recovery and the average time for recovery was 3.4 months (all patients) and 4.3 months in insulin requiring diabetic patients. In patients who had normal conduction studies the recovery time was 2.6 months compared with 3.6 months for those with abnormal conduction studies.
Conclusions: We found a strong association between acute ocular mononeuropathy in patients with abnormal glucose metabolism and polyneuropathy. The presence of clinical electrophysiological evidence of polyneuropathy and abnormal metabolic glucose status are associated with a longer time of recovery in acute ocular mononeuropathy. Further studies with a larger number of patients would be useful to confirm our findings.

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Study of the Imaging Pattern in Laing Myopathy in a Large Series of Patients

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Introduction: Clinical and pathological heterogeneity in Laing distal myopathy can made the diagnoses challenging.
Methods: A study of the imaging pattern (MRI /CT) in a large series of patients with Laing myopathy due to different mutations in MYH7 gene in a single centre.
Results: 42 patients (29 females) with Laing myopathy due to different MYH7 mutations were studied. They displayed a variable current age, age at onset, myopathy extension scale and GMW scale, including 5 subjects with minor symptoms or signs of the disease. All the patients showed changes in muscle imaging with the exception of two presymptomatic/minimally symptomatic subjects. The more frequent and severely affected muscles were tibialis anterior (TA) and extensor hallucis longus (EHL) (92.9%) followed by extensor digitorum longus (EDL) (85.7%), vastus lateralis (78.57%), adductor magnus (73.8%), cervical paraspinal (71.8%), gluteus maximus (71.43%), vastus intermedius and medialis (69.05%) and lumbar paraspinal (68.3%). Muscles of the feet were involved in 8 out of 19 patients studied, being the involvement generalized in 6. A length-dependent pattern of involvement was not detected in any case. The MRI cumulative score ranged from 0 to 2.9, being ≥ 2 in 5 patients. Disease duration, myopathy extension scale and GMW scale were associated with a higher score. A second imaging study done in 24 patients showed variable progression of the involvement but the increase was ≥ 0.5 in 12 and 10 patients reached a score > 2.
Discussion: The study confirmed that the anterior compartment of the lower leg is systematically affected in Laing distal myopathy and may be restricted to EHL muscle in early stages. Nevertheless, involvement of other muscles (mostly of the thighs, but also of pelvic and axial regions) is common even in early stages. Feet muscles were affected in nearly half of the evaluated patients without manifesting a length-dependent pattern of involvement. The progression of the disease is documented by the increment of muscle fibrosis observed in the longitudinal study.

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A Case Report of Very Early Onset Friedreich's Ataxia with Severe Neurological Manifestations and Cardiomyopathy

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Introduction: Friedreich's ataxia is an autosomal recessive neurodegenerative disease. It is the most common in the category of inherited ataxias and it affects Caucasians with a frequency of 1:29000. In

about 98% of these patients the disorder presents due to homozygosity for a GAA trinucleotide repeat expansion in intron 1 of the frataxin gene. Friedreich's ataxia typically presents during adolescence (mean age 15 years). In one fifth of the patients it appears under the age of 5 years old. It is a multisystem disease, affecting both the central and peripheral nervous systems, as well as the cardiovascular, musculoskeletal and endocrine systems. The major neurological clinical features of Friedreich's ataxia are progressive trunk and limb ataxia, dysarthria, loss of lower limb reflexes and peripheral sensory neuropathy. During the course of the disease cardiomyopathy, scoliosis, deformities of the lower limbs and diabetes mellitus also appear (in 10% of the cases cardiomyopathy is present at onset). Most common symptom at onset is unsteadiness of gait. The ataxia is due to a combination of cerebellar and spinocerebellar degeneration, peripheral sensory neuropathy and vestibular nerve involvement. Patients usually become wheelchair-bound after a mean disease duration of 11-15 years. We submit the case of a child with very early onset Friedreich's ataxia, presenting with severe clinical symptoms from the nervous and cardiovascular systems.

Methods: A ten year old female patient of Asian (Syrian) descent was referred to our hospital for investigation of tetraparesis mostly affecting the lower limbs, since the age of 2,5 years old. Her perinatal & family history and early psychomotor development were normal. Regarding past medical history, spinal injury after bombing is reported, which had never been investigated. The patient is bed bound and the full neurological examination revealed ataxia of the upper limbs, spastic tetraparesis, absent tendon reflexes, extensor plantar responses, dysarthria, nystagmus, scoliosis and proprioception deficits bilaterally. Due to the history of injury and to exclude cerebral palsy, despite the normal perinatal history, she underwent a brain and spinal cord MRI scan. A full metabolic profile, as well as a caryotype were ordered. Due to the clinical presentation, the presence of a neuromuscular disorder was suspected, with Friedreich's ataxia being at the top of the diagnostic considerations, therefore further investigation with cardiac consultation, neurophysiological testing with electroneuromyography (EMG) and the relevant genetic testing were conducted.

Results: The MRI scans and the metabolic testing rendered no abnormal results. The caryotype was normal. The cardiac consultation, including ECG and echocardiogram, revealed hypertrophic cardiomyopathy and mitral regurgitation. The EMG study showed severe sensory axonal neuropathy, with findings of mild chronic neurogenic lesion in the level of the biceps and the quadriceps. The genetic testing was positive for Friedreich's ataxia.

Conclusion: Friedreich's ataxia must always be taken into consideration in case of any young patient presenting with chronic onset ataxia and cardiomyopathy. Earlier onset and cardiac involvement are usually associated with faster disease progression and smaller life-expectancy.

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Benign Tumors of Peripheral Nerves in Children at a Tertiary-Care Pediatric Hospital

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Tumors affecting peripheral nerves in children are rare. A prompt and accurate diagnosis can ensure that management is appropriate and timely. We review the clinical presentation of children (<18 years old) who were diagnosed with intrinsic tumors affecting a peripheral nerve or nerve root at the Children's Hospital of Eastern Ontario (CHEO) over a 10 year period. We report the utility of neurophysiological testing and the key features on magnetic resonance imaging (MRI) that assisted with diagnosis.

From 2009-2019, 14 children were diagnosed with a mononeuropathy associated with an intrinsic tumor affecting a peripheral nerve including: lipomatosis (2 cases), perineuriomas (6 cases), intraneural ganglionic cysts (2 cases), neurofibromas or plexiform neurofibromas (4 cases).

The mean age of symptom onset was 8.2 years old (range 0.3 to 17.3 years old) although patients with perineuriomas had an earlier mean age of symptom onset (6.7 years old) compared to intraneural ganglionic cysts (14.5 years old) or neurofibromas (8.5 years old). Overall, the main presenting symptoms included painless muscle wasting (2/14), focal muscle weakness (7/14), contracture (1/14), pain (1/14) or the identification of a painless, palpable mass (3/14). MR imaging was performed for all patients.

Nerve conduction studies (NCS) or electromyography (EMG) were performed in 11/14 patients permitting correct localization in all cases. Biopsies were performed in 9 patients (5/6 perineurioma and 4/4 with symptomatic neurofibroma or plexiform neurofibroma). Four patients underwent surgery including: 1 intraneural ganglion decompression, 2 nerve grafts (perineurioma) and 1 resection (neurofibroma causing cervical cord compression). Children were followed for an average of 2.5 years after diagnosis.

MRI was useful at differentiating these benign pediatric nerve tumors, and MRI diagnosis was congruent with biopsy in all cases where they were performed. Peripheral nerve lipomatosis demonstrated a classic "spaghetti string" appearance on MRI, obviating the need for surgical biopsy. Six patients with perineurioma showed MRI evidence of enhancing, nodular lesions that were later confirmed on a fascicular nerve biopsy in (5/6 patients); the latter patient has not had a biopsy but is followed with serial clinical and ultrasound evaluations. Intraneural ganglionic cysts have a unique appearance of a cystic lesion within the nerve. Neurofibromas and schwannomas present as slow growing masses, associated with neurofibromatosis type 1 or 2. MRI can provide clues to differentiate between neurofibromas and schwannomas: neurofibromas appear like a "bag of worms" while schwannomas are more eccentrically positioned around the nerve.

The rare nature of peripheral nerve tumors in children can pose diagnostic challenges. NCS/EMG can be important to assist with localization, and MRI important at distinguishing these benign tumors affecting peripheral nerves and roots. Key MRI, clinical and NCS features can in some cases guide management, possibly avoiding invasive procedures (eg lipomatosis) or prompting surgical intervention.

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RAINBOWFISH: A study of Risdiplam in Infants with Presymptomatic SMA

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Objective: To determine the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics of risdiplam in presymptomatic infants with genetically diagnosed spinal muscular atrophy (SMA) in the ongoing RAINBOWFISH study (NCT03779334).

Background: SMA is a severe, progressive neuromuscular disease caused by reduced levels of survival of motor neuron (SMN) protein due to deletions and/or mutations of the SMN1 gene. A second gene, SMN2, produces only low levels of functional SMN protein. Risdiplam is a centrally and peripherally distributed, oral SMN2 pre-mRNA splicing modifier that increases the levels of functional SMN protein. Risdiplam (EVRYSDI™) has been approved by the FDA for the treatment of patients with SMA, aged 2 months and older.

Design/Methods: RAINBOWFISH is an open-label, single-arm, multicenter global clinical study enrolling infants aged from birth to 6 weeks of age (at first dose), regardless of SMN2 copy number. Infants will receive risdiplam for 24 months, followed by a 36-month extension. Primary analyses will be conducted at 12 months of treatment in infants with two SMN2 copies and compound muscle action potential (CMAP) ≥1.5mV at baseline. The primary objective is to evaluate the efficacy of risdiplam in these infants as determined by the proportion of

infants sitting without support for ≥5 seconds after 12 months of treatment (as assessed by item 22 of the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development, Third Edition). Secondary endpoints include the development of clinically manifested SMA, survival and permanent ventilation, achievement of motor milestones, motor function, growth measures, nutritional status, CMAP, PK, safety monitoring, and other clinical parameters.
Results: The median age at first dose (range) for the first seven enrolled infants was 35 (16–40) days. Here we will present updated baseline demographics and baseline SMN protein data in enrolled infants with presymptomatic SMA. Additional preliminary data will also be presented.
Conclusions: RAINBOWFISH will provide valuable information about presymptomatic administration of risdiplam alongside the ongoing FIREFISH (Type 1 SMA, NCT02913482), SUNFISH (Types 2 and 3 SMA, NCT02908685) and JEWELFISH (patients with SMA who have previously received olesoxime, onasemnogene abeparvovec-xioi (ZOLGENSMA®) or therapies targeting SMN2 splicing, NCT03032172) studies. The RAINBOWFISH study is currently recruiting at selected sites worldwide.

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SMA-LED 1: Two Case Reports and a Systematic Review

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Introduction: Predominant lower limb spinal muscular atrophy (SMA-LED1) is characterized by muscle weakness and wasting of lower limbs with a dominant pattern. It is caused by mutation in the DYNC1H1 gene (OMIM#158600) which encodes cytoplasmic dynein heavy chain 1, a microtubule motor protein in the dynein-dinactin complex responsible for retrograde axonal transport in neurons.
Objective: To report two cases of unrelated patients presenting pathogenic variants not previously described followed by a systematic literature review. Case 1: A Caucasian male, 4 yrs, presented a delay in milestone. He walked at age 2 although with frequent falls. Currently he cannot run, jumping and he presents a Gowers's sign. No cognitive impairment was found, however an attention deficit hyperactivity disorder (ADHD) was present. Neurological exam: he has a scapula alata, scoliosis, lombar hyperlodosis and myopathic gait and not able to walk in heels. The muscle strength in upper limbs was preserved. There was a marked proximal and distal wasting of lower limbs: quadriceps strength 3/5 and tibialis anterior 4/5. Sensitive exam showed no abnormalities. Conduction studies and EMG were normal. Creatine kinase (CK) was also normal. Muscle biopsy from left biceps showed a mild fiber size variation and type 1 predominance fibers. NGS found a variant c.752G>A in heterozygosis probably pathogenic in the DYNC1H1 gene. Case 2: A Caucasian male, 49 yrs, noticed at age 10 muscle atrophy of both legs. At the age 20 he presented difficult to go down and upstairs, running and get up from a chair or floor. No family history. Neurological exam: right peripheral facial palsy, steppage gait and difficulty to walk in tiptoes and heels. The muscle strength in upper limbs was preserved. There was a marked proximal and distal wasting of lower limbs: quadriceps strength 4/5 and tibialis anterior 4/5. Sensitive exam showed no abnormalities. Neuroconduction studies were normal and EMG showed a motor neuronopathy. A panel for hereditary neuropathies found a heterozygous pathogenic variant c.13384C>T in the DYNC1H1 gene. From a systematic review we select 13 studies about SMA-LED1. Most of them revealed developmental delay (62%), with the onset of symptoms in the first decade of life (82%). There are no sensory symptoms (0%) however the upper limbs can be affected (9%). Other symptoms such as contractures (31%), foot deformities (44%), scoliosis (8%), lumbar lordosis (17%), arthrogyposes (4%) intellectual disability (23%), epilepsy (5%), scapula alata (1%) and CNS malformations (13%) were also found (Graphic 1).
Conclusion: The diagnosis of SMA-LED1 should always be included as a differential diagnosis in children with delayed motor development even so in the cases with upper limbs symptoms. Also, the central nervous system involvement should not be exclusion criteria for this disease as previous articles have been described different involvement of central nervous system resulting in a combined peripheral neurodegeneration and brain abnormalities.

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Symptomatology and Prevalence of Pompe in Cohort with Proximal Muscle Weakness and High CK Levels

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Introduction: Neuromuscular diseases have a great phenotypic variability and sometimes nonspecific clinical signs and symptoms, such as proximal muscle weakness and elevated creatine phosphokinase (CK) levels. Therefore, it is required a diagnostic confirmation with genetic testing.
Objective: Evaluate the prevalence and symptoms of late-onset Pompe disease (LOPD) in a patient cohort with proximal muscle weakness and elevated CK.
Methods: In a cohort of 48 patients a NGS panel for 10 types of limb-girdle muscle dystrophies (LGMD) was performed for the genes: Anoctamin 5 (ANO5), Dysferlin (DYSF), Glucosidase alpha acid (GAA), Sarcoglycan beta (SGCB), Sarcoglycan gamma (SGCG), Sarcoglycan alpha (SGCA), Sarcoglycan delta (SGCD), Calpain3 (CAPN3), Fukutin-related protein (FKRP), Telethonin (TCAP). It was performed proportionality test in order to evaluate the relevance of the results found in this study comparing with large cohorts.
Results: 18 patients (37.7%) were diagnosed with LGMD being divided in 27.7% CAPN3 (5/18), 27.7% DYSF (5/18), 16.6% GAA (3/18), 11.1% FKRP (2/18), 11.1% TCAP (2/18) and 5.5% ANO5 (1/18). Clinical, histological and laboratory findings from LOPD patients are showed in table 1.
Conclusions: Although the NGS panel is restricted for limb-girdle muscle dystrophies, it was useful because it diagnosed 18 patients (37.7%) from the cohort. There are different data in the literature about the prevalence of this disease: 2.4% (74/3076) in Europe, 4.2% (1/24) in Brazil and 0.8% (38/4656) in the United States. The variability of the prevalence may be the result of methodological variations among the studies, epigenetic aspects and the unfamiliarity with the disease by health professionals. The c.-32-13 T>G variant is present in Caucasian patients being related to respiratory dysfunction and LOPD. One of the patients did not present typical alterations in the muscle biopsy and showed a normal spirometry. Thus, the absence of typical findings does not rule out the possibility of LOPD.

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How Important of p62/SQSTM1 Distribution Pattern in Neuromuscular Diseases

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Introduction: P62/ SQSTM1 is a shuttle protein transporting poly-ubiquitinated proteins for the proteasomal and lysosomal degradation pathways. It is one of the proteins found in inclusion body myositis (IBM) and currently was consider the best marker of neurodegeneration in this pathology. However, p62 presence does not appear to be unique to s-IBM. Few studies have shown p62 positivity in other neuromuscular diseases.
Objective: Evaluate the distribution (quantitative and qualitative) of p62 in patients with neuromuscular diseases.
Materials and Methods: Skeletal muscle samples of 22 patients with IBM, 17 with other idiopathic inflammatory myopathies (OIIM) and 22 with other neuromuscular diseases (ONMD). The group IBM was divide: definite (d) and possible (p) by the following criteria of d-IBM: presence of rimmed vacuoles (RV), inflammatory infiltrate (II) and non-necrotic invaded fibers (NNIF). p-IBM: presence of two of previous criteria. Epidemiological and morphological data: age, sex, disease onset, duration of disease (ΔT), creatine kinase (CK) values, atrophic fibers (AF), nuclear clumps (NC), no rimmed vacuoles (NRV), major histocompatibility complex class I (MHC) and complement membrane attack complex (C5b9) immunohistochemical and cytochrome oxidase (COX) stain. Continuous serial cross-sections of hematoxylin and eosin (H&E), p62/ SQSTM1 were perform in order to get morphological findings. H&E staining was used to classify the grade of injury of muscle fibers, using scores from 0 to 2. HE0: normal fiber; HE1: presence of internalized nuclei; HE2: presence of vacuoles, necrosis or regeneration. The immunohistochemical pattern of p62 was classify diffuse, dots or granular. Mann-Whitney, Spearman correlation, Dunn's Pairwise

Comparison and Kruskal-Wallis's tests were use.
Results: The CK values among the groups show a significance p value (IBM x OIIM: p= 0.0008; IBM x ONMD: p= 0.0105). Morphological findings in patients with IBM demonstrated a significant p value in relation to: atrophic fibers, invaded non-necrotic fibers, rimmed vacuoles, inflammatory infiltrate, negative COX fibers and positive MHC. Also, the distribution pattern of p62 showed a significant p value in the granular pattern comparing d-IBM with the other groups (p-IBM p=0.0170; OIIM p=0.0146 and ONMD p=0.0007) according Dunn's Pairwise Comparison. In relation to score lesion demonstrated by HE it was observed: IBM= 11(73.33%) OIIM= 4(44.44%) and ONMD= 1 (33.33%) frequency of HE0. These data are summarized in table 1.
Conclusion: p62/SQSTM1 presence it's not pathognomic feature in IBM as the protein is closely related to autophagic process in different neurodegenerative disorders. Although p62 aggregates were associated with an abnormal increase in the onset of selective autophagy, unlike the other inflammatory myopathies. We must always correlate the clinical data and other pathological findings to define a neuromuscular disease. Therefore, the predominant presence of the granular pattern in IBM samples could help to get the diagnosis in doubtful cases. Also, our data suggest that the "dots" distribution pattern indicates that this pattern is the beginning of lesion fiber highlighting that the simple presence the protein it is not a specific maker of a specific disease.

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ACTA1 Mutation in a Woman with Facial and Distal Muscle Weakness

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Background: ACTA1 encodes a skeletal and cardiac muscle protein, actin, critical for muscle contraction. We report a case of a woman with chronic weakness with a variant in ACTA1.
Results: A 21-year-old woman with symptoms suspicious for congenital myasthenia, had longstanding difficulty holding her arms overhead, playing sports, running, performing fine motor tasks and fatigued easily. She had reduced muscle bulk, mild weakness of facial, and distal more than proximal limb muscles, and was hyporeflexic. The wrist and finger extensors were selectively weak. Her father and paternal grandfather had similar symptoms, and were diagnosed with a form of muscular dystrophy. The serum creatine kinase level was normal. The EMG showed myopathic features with no repetitive compound muscle action potentials with a single stimulus and no decrement with 2 Hz repetitive nerve stimulation. A single fiber EMG study was mildly abnormal. A deltoid muscle biopsy showed a nemaline myopathy, associated with type 1 fiber preponderance. Whole exome sequencing revealed a c.197T>G (pI66S) variant in ACTA1.
Conclusions: The patient highlights that the mutations in actin can mimic symptoms and signs of congenital myasthenia or an autosomal dominant distal muscular dystrophy.

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Label-Free Imaging of Abnormal Lipid Accumulation in Degenerated Muscle Fibers From Inclusion Body Myositis Patients

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Background: Inclusion body myositis (IBM) is the most common late-onset myopathy. It is characterized by progressive asymmetric weakness predominantly affecting the quadriceps and/or finger flexors. Loss of ambulation and dysphagia are major complications of the disease. Muscle biopsy usually shows inflammatory cells surrounding and invading non-necrotic muscle fibers, rimmed vacuoles, congophilic inclusions, and protein aggregates. Disease pathogenesis remains to be elucidated and it is hypothesized to include inflammatory and degenerative aspects.
Objective: In this study, we aimed to measure molecular vibrational spectra of rimmed vacuoles in muscle fibers from IBM patients. Vibrational spectra obtained using Raman spectroscopy provides vibrational information characteristic of chemical groups or bonds in a molecule without any labeling procedures. Measuring vibrational spectra enables us to locate and quantitate accumulated lipids within tissues in a molecular specific manner.

Methods: Hematoxylin and eosin staining, modified Gomori trichrome staining and p62 immunohistochemistry were used to pathologically diagnose three IBM patients. Vibrational spectra of frozen sections of muscles biopsied from the IBM patients were obtained using spontaneous Raman microspectroscopy and compared with the spectra in the local database of major lipid species measured in vitro.
Results: All three cases showed rimmed vacuoles in hematoxylin and eosin staining and Gomori trichrome staining, which is compatible with the diagnosis of IBM. The degenerated muscle fibers from all cases were confirmed to be p62-positive in immunohistochemistry. We found that the Raman spectra measured in the internal edges, i.e., the "rim" of rimmed vacuoles showed prominent peaks such as 1305cm^-1, 1450cm^-1 and 1650cm^-1, which is typical of phospholipid backbone structures. From detailed correlation analysis of its spectral pattern with the spectral database, phosphatidylcholine showed the highest correlation.
Discussion: Previous reports have shown that rimmed vacuoles found in IBM are associated and colocalized with various protein aggregates, such as β-amyloid, α-synuclein and TDP-43, which is considered as an evidence of degenerative aspect of the disease. These protein aggregates are usually co-stained immunohistochemically with p62 and LC3B, which are the marker molecules of autophagosome. In our observation, Raman spectra of rimmed vacuole demonstrated a pattern of phospholipid backbone structures, lacking any spectral signature indicative of protein, such as Raman shift of phenylalanine breathing mode at 1000cm^-1. Because peak intensity in Raman spectrum reflects stoichiometric amount of material, our result showed the primary component of rimmed vacuole is probably phospholipids, supporting the idea that rimmed vacuoles are disrupted autophagosomes.
Conclusions: Raman spectroscopic observation showed the primary molecular species constituting rimmed vacuoles in muscle fibers from IBM patients are phospholipids, and its major component is phosphatidylcholine. This result supported the idea that rimmed vacuoles are disrupted autophagosomes and IBM has a degenerative aspect in its disease pathogenesis.

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Child-to-Adult Healthcare Transition for Genetic Muscle Diseases: A Single-Center Study in Suburbs of Tokyo, Japan

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Background: Improvements in medical care for patients with genetic muscle diseases have made their lifespan longer. It should be important to provide multidisciplinary child-to-adult transition for better life of them.
Methods: We reviewed medical records of patients with genetic muscle diseases who visited our clinic for transition between November 2012 and October 2016, and analyzed current status and issues of child-to-adult healthcare transition.
Results: We accepted 31 patients with muscular dystrophy and 4 with congenital myopathy for transition in 4 years; mean age was 19.3±4.6 years (range 11-32). Twenty-five of them were referred by pediatric neurologists in university hospitals. The immediate reasons for referral were graduation of school (11), getting specialized management for muscle diseases (7), retirement of referred physicians (7), becoming adults(6), and preference of patients (4). Transition has completed in 19 patients. There was no difference between completed and uncompleted cases of transition by medical interventions as medication of steroids, mechanical ventilation, tracheostomy or tube feeding. Multiple logistic regression showed that involvement of primary care physician was the only factor for successful transition.
Conclusions: It might be cumbersome for patients and their families to visit segmentalized clinics for adults, which might make them nervous. It was suggested that participation of primary care physician should be helpful for successful transition between pediatric and adult specialists for clinical myology. It might be effective to plan and prepare transition since early childhood.

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Early Motor Development in Duchenne Muscular Dystrophy Compared to Typical Development: A Pilot Study

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Duchenne Muscular Dystrophy (DMD) is an X-linked inherited neuromuscular disorder caused by mutations in the dystrophin gene. The main feature is progressive muscle weakness, which follows a proximal to distal gradient and upper limb weakness generally occurs at a later stage compared to lower limb problems. Delayed motor milestones and gait disturbances are the first presenting symptoms. Early and accurate recognition of these symptoms plays a crucial role in the effective management of patients.

The goal of this study was to evaluate motor development in DMD boys between 2 and 6 years old and compare their scores to an age-matched typically developing (TD) control group. The Mann-Whitney U test was used to compare both groups.

Thirteen boys with DMD (mean age: 4y 0mo; SD: 1y 4mo; range: 2y- 6y) and 26 age-matched typically developing controls (mean age: 3y 11mo; SD: 1y 5mo range: 2y- 6y) were assessed with the Motor Function Measure (MFM-20), North Star Ambulatory Assessment (NSAA), Timed Function Tests (TFTs), three-minute walk test (3MWT) and Performance of Upper Limb Function (PUL 2.0).

Overall, significant differences in motor performance were found between the DMD and TD boys. Regarding the MFM-20, none of the DMD boys received the maximum score, whereas all but four of the TD children received a maximum score ($p< 0.001$). Similar results were found for the NSAA, none of the DMD boys scored maximum, while all TD boys of 4 years and older received the maximum score of 34 points ($p<0.001$). One DMD boy scored maximum on the PUL 2.0 shoulder dimension and three on the elbow dimension, the weakest scores were seen on the wrist dimension, no DMD boy received a maximum score. Also, none of the DMD boys reached the distance expected for his age on the 3MWT, whereas most of the TD boys did ($p=0.005$). The median percentage walked for the DMD group was 82.7% of the expected distance (IQR: 71.7%-93.1%). Finally, the DMD boys needed more time than the control group to perform the TFTs ($p<0.001$-0.005). Median (IQR) percentages of the expected times for the DMD group were: time to rise from floor: 188% (119.4%- 205.0%); 10m run: 134.5% (109.0%- 176.3%); climb 4 stairs: 146.5% (103.4%-243.6%); descend 4 stairs: 153.9% (137.2%-253.7%).

Performance of DMD boys on different motor outcome measures is already less starting from the age of 2. It would be interesting to develop a new outcome measure specifically developed for infants and young boys with DMD to early detect the differences in fine and gross motor development compared to TD.

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Early Developmental Outcome in Duchenne Muscular Dystrophy: A Pilot Study

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Duchenne Muscular Dystrophy (DMD) is primarily known for its impact on the motor domain. However, it is also associated with cognitive, language and behavioral deficits. There is compelling evidence, at cellular level and from clinical perspective, for a primary central nervous system involvement in DMD. Subsequently, the period before the age of 5 is often called the 'pre-symptomatic' stage, but first signs and symptoms arise much earlier.

In this descriptive study, we aim to gain better insights into the different developmental domains in infants and young boys with DMD between 0 and 6 years old. We also mapped the mutation types and sites. Motor skills were evaluated by the Peabody Developmental Motor Scales, second edition (PDMS-II) in all boys. For the younger boys (<3.5 years)

the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III) were used to evaluate all domains. In the older boys (>3.5 years) cognition and language were evaluated by the Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI-III) and Clinical Evaluation of Language Fundamentals Preschool, second edition (CELF-preschool-2), respectively. The Vineland screener and Child Behavior Checklist (CBCL) were added to evaluate adaptive behavior. Because of a different mother tongue some boys could not perform cognition and language measures and not all parents were able to fill in the behavioral and social emotional questionnaires.

We compared DMD scores to the reference values and classified them as: 'normal': <1SD below mean; 'at risk': >1SD- <2SD below mean and 'deviant': >2SD below mean.

We evaluated 15 boys with a mean age of 3 years and 8 months (SD: 1y 6mo; range: 11mo- 6y). Eleven boys had a deletion; two a duplication and two a frameshift. The site of mutations ranged from exon 2 to 52. Regarding gross motor skills, lower scores were found compared to the reference populations: 3 boys scored 'deviant' and 9 'at risk'. Fine motor scores were also lower: 6 'deviant'; 4 'at risk'. Difficulties with writing (pencil grasp, visual motor integration) and inhand manipulation were often observed. For cognition, almost all younger boys scored between 1 and 2 SD below mean, whereas all but one of the older boys scored within the normal range. For most boys, no remarkable delays were found for expressive and receptive communication. All boys <3.5 years old scored 'deviant' on adaptive behavior (Bayley-III), whereas only 2 of them scored 'deviant' on the CBCL. Of the older boys only 1 out of 8 boys scored in the 'deviant' zone on the CBCL. Seven boys scored 'deviant' and 1 'at risk' on the Vineland Screener. Social emotional scores (Bayley-III) were 'deviant' for 2 boys and 'at risk' for 1 boy.

Although gross motor problems are expected as primary symptoms in this young group, we also found problems in the other developmental domains. It will be important to monitor young DMD boys starting from the moment of diagnosis to be able to anticipate as soon as possible on these problems as early intervention might be advantageous for the later stage

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Triggers and Risk Factors in Lumbosacral Radiculoplexus Neuropathy

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Objective: To investigate the triggers and risk factors for Lumbosacral Radiculoplexus Neuropathy (LRPN).

Background: Recently, our group found significantly higher frequency of diabetes mellitus (DM) in patients with LRPN compared to age-gender matched controls (66.1% vs 19.8%) from Olmsted County, Minnesota, USA. Within the same population, we found diabetics have odds of 7.91 for developing LRPN compared to non-diabetics. However, triggers and the influence of other comorbidities were not studied.

Materials/Methods: Demographic and clinical data from 59 LRPN patients (62 episodes) and 177 age-gender matched controls were extracted from the Rochester Lumbosacral Radiculoplexus Neuropathy study. Neuropathy triggers were defined as time-related events to the LRPN episode

Results: Triggers for the development of LRPN were found in 21 episodes (34%): new intensive DM treatment in 8 patients, surgery in 6 patients, intensive exercise/health style change in 5, and combination of surgery and intensive DM treatment in 2 patients. Compared to controls, LRPN patients more frequently had: hypertension (64.4% vs 44.6%;p=0.009), stroke/TIA (13.6% vs 4%; p=0.009), obesity (53.6% vs 36%; p=0.02), dementia (6.8% vs 1.1%; p=0.017), dyslipidemia (66.1% vs 40.7%; p=0.0007), and previous diagnosis of an autoimmune disorder (15.3% vs 6.2%; p=0.031). In a multivariate logistic regression model, that included DM, diagnosis of LRPN was associated with DM (OR 8.36; CI 4.01-17.42), BMI (OR 1.07; CI 1.01-1.13), stroke (OR 4.08; CI 1.18-14.17) and other autoimmune disorders (OR 4.58; CI 1.43-14.65).

Conclusions: LRPN episodes may be associated with a trigger (intensive DM treatment, exercise and surgery) in one third of cases. DM is the strongest LRPN risk factor, and most others (hypertension, renal dysfunction, dyslipidemia, obesity and dementia) are likely secondary to DM. A previous diagnosis of an autoimmune disorder is also an independent risk factor for LRPN. Immune dysfunction, rapid

changes in glycemic control and presence of DM are the main inciting factors for the development of LRPN.

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Assessment of Pre-Existing Immune Response to AAV9 in Russian DMD Patients

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Gene therapy is one of the most promising approaches for Duchenne muscular dystrophy (DMD) treatment. One of the potential gene transfer agents is an adeno-associated viral vector (AAV). Some naturally occurring AAV serotypes have good tropism to muscle and heart tissues which are most suffering from DMD. However, due to exposure to wild-type AAV, a large fraction of adult individuals has neutralizing (NAbs) and binding (BAbs) antibodies against at least one AAV serotype. Experience in human and animal trials suggests that NAbs prevent AAV vector transduction and consequently transgene expression thus hampering the success of gene therapy. Moreover, pre-existing immunity to vectors can lead to severe adverse events occurrence in response to AAV infusions. Here we assess pre-existing humoral immunity to AAV serotype 9 among Russian DMD patients. For this purpose we used frozen blood samples stabilized with EDTA collected in Russian Children Neuromuscular Center, Veltischev Clinical Pediatric Research Institute of Pirogov Russian National Research Medical University. Each sample was assessed for total IgG titer (BAbs) using ELISA and NAbs by in vitro AAV9 transduction assay with luciferase and beta-galactosidase reporter genes. Same tests were performed with serum from healthy adult individuals immediately without freezing. In our results majority of DMD patients (85-90%) were naive to the virus. We also found that in some cases NAbs do not correlate with total IgG binding to AAV9. There were no significant differences in Abs titers determined in fresh serum and frozen blood samples. Protocols used for BAbs and NAbs quantification in frozen blood samples allow to pre-select subjects for the study from previously screened patients. Our findings indicate that assessment of pre-existing humoral immunity to AAV vectors is still important especially in systemic administration trials. Neutralizing antibody assays should be used together with binding antibody assays for better prediction of the potential outcome of gene transfer.

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Patients with LAMA2 Mutations in Egypt: Clinical, Whole Body Muscle MRI, Histopathological, and Molecular Findings

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Laminin α2 congenital muscular dystrophy (CMD) is caused by mutations in the LAMA2 gene. It is considered the most common CMD in some communities. We selected patients with CMD from Medical Genetic Center and Neuromuscular Unit, Faculty of Medicine, Ain Shams University, Cairo, Egypt. Patients had neurological assessment, family pedigree study, serum CK level, neurophysiological study, muscle biopsy with histochemistry and immunohistochemistry, whole body muscle MRI and molecular study. We diagnosed 11 families (13 patients, 8 females and 5 males) with LAMA2 mutation. All patients couldn't obtain or lost ambulation very early in life except two sibs with milder disease. Nine patients had whole body muscle MRI which showed, characteristic findings, more involvement of subscapularis, infraspinatus, sparing of deltoids and involved paraspinal and gluteal muscles. All thigh muscles were fatty degenerated, less in sartorius, gracilis, semitendinosus and in the lower legs clearly more in posterior calf muscles. Gene mutation analysis of 13 patients revealed 26 LAMA2 mutations (100%) corresponding to 13 different

mutations of which: 4 have previously been reported and 9 were novels according to the LOVD database. Among these mutations, 65.4% were nonsense, 15.4% were splice-site, 7.7% were missense, 7.7% were deletion of one exon and 3.8% were small duplication. Eleven patients were homozygous, and 2 were compound heterozygous for LAMA2 mutations. Confirmation of the heterozygous state in both unaffected parents was performed in six families. To the best of our knowledge, this is the first comprehensive report of these cases in Egypt.

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Autologous Stem Cell Transplantation May Halt Peripheral Neuropathy Progression and Improve Survival in Al-Amyloid Neuropathy

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Background: Immunoglobulin light chain (AL) amyloid neuropathy is a progressive sensory, motor and autonomic neuropathy with a median survival of 25 to 45 months. Although autologous stem cell transplantation (ASCT) has shown improved survival in AL amyloidosis, little is known about its effects on peripheral neuropathy.
Objective: To study the clinical characteristics of peripheral neuropathy and outcomes in a large cohort of patients with AL amyloid neuropathy who underwent ASCT.
Methods: We included patients with AL amyloid neuropathy who underwent ASCT at our institution from 01/01/1998 to 03/31/2018. Neuropathy was defined by neuropathic symptoms plus signs (per a neurologist) or neuropathic symptoms plus neurophysiologic evidence of neuropathy by nerve conduction studies/electromyography (NCS/EMG) or autonomic reflex screen (ARS). Clinical, neurophysiological and survival data were extracted.
Results: 70 patients with AL amyloid neuropathy were identified. Median age was 60 (range:35-72) years old. At baseline (before ASCT), 45% of patients had muscle weakness, 70% sensory loss, 73% prickling, 69% autonomic symptoms and 43% neuropathic pain requiring medications. Baseline median neuropathy impairment score (NIS) was mild at 9 (0-82), median clinical autonomic severity score (CASS) was moderate at 5 (0-10) and median modified Rankin scale (mRankin) was moderate at 2 (1-3). Baseline median sural sensory nerve action potential (SNAP) amplitude was 4 (0-17) μV and median ulnar motor compound motor action potential (CMAP) amplitude was 8.1 (3-12.9) mV. After transplant the median survival was 78 months. 37 (53%) patients died. The probability of survival at 1-, 5- and 10- years after ASCT was, respectively 87, 62.3 and 31.7%. In univariate cox regression model, mortality was associated with heart involvement (HR: 2.0; CI 1.02-3.88; p=0.0417), number of organs involved (HR: 1.82; CI 1.18-3.16; p=0.005) and severity of autonomic neuropathy by CASS (HR: 1.4; CI 1.09-1.85; p=0.007). Prolonged neurological follow-up was available in 23 patients (32.8 %) who had at least one neurology visit, NCS/EMG or ARS after ASCT. Of those, median NIS (n=15; pre-ASCT 38.5; last f/u 38.25), median mRankin (n=15; pre-ASCT 2; last f/u 2), median Ulnar CMAP amplitude (n=16; baseline 7.95; last f/u 6.95) and median CASS (n=4; baseline 5; last f/u 5.75) remained stable at last follow-up.
Conclusion: AL amyloid neuropathy patients that undergo ASCT have a mild sensorimotor peripheral neuropathy but have more severe (moderate) autonomic impairment. Compared to historical AL amyloid neuropathy studies, our study suggests that ASCT prolongs survival. Mortality risk factors include heart involvement, number of organs affected, and autonomic neuropathy (elevated CASS). ASCT seems to halt progression of AL amyloid neuropathy.

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Vitamin D Serum Levels in Argentinian Myasthenia Gravis Patients - A Hospital Based Study

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Introduction: Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction (NMJ) caused by antibodies, whose production is T cell-dependent. Regulation of autoreactive T cells depends on regulatory T lymphocytes (Treg), which have been shown to be functionally defectives in MG patients. Vitamin D (VitD) has immunomodulatory effects, stimulating Tregs and inhibiting effector T cells. Previous studies have shown that vitamin D levels are low in patients with autoimmune diseases. However, few works have studied levels of vitamin D in autoimmune neuromuscular disorders. The aim of this study was to evaluate serum levels of 25(OH)VitD in patients with MG and healthy controls (hc) and the association of vitamin D levels with clinical severity of the disease.
Methods: 25-OH-VitD serum levels were evaluated in 66 MG patients and 25 age- and sex- matched hc, referred to the Ramos Mejia Hospital in Buenos Aires, Argentina. 25(OH)D levels were measured using chemiluminescence, samples were collected equally distributed throughout the year in both groups. The clinical status and MG severity were determined using ADL (Activities of Daily Living) and MG composite (MGC) scales. Sun exposure and vitamin D dietary intake have been assessed by locally adapted questionnaires based on OPTIFORD projyect.
Results: Of the 66 MG patients, 92.4% were AChR-ab positive MG. 2 had purely ocular MG (3.1%). The mean age of patients at sample collection was 42 years and the mean age at MG onset was 34 years. Patients and controls were not different regarding sun exposure score and mean weekly Vitamin D dietary intake. Mean serum 25(OH)D levels were lower in MG patients (mean, 19.4 ng/mL; range, 5.5–43.7) than in healthy controls (mean, 22.1 ng/mL; range, 5.6– 38.2), but without statistically significant differences between groups. However, vitamin D deficiency (25(OH)D (<25 ng/mL) was observed in 83% of MG patients vs 56% in controls (p=0.007). There was no correlation between 25(OH)D levels and disease severity scores. When we analyzed 25-OH-VitD mean serum levels of subjects and hc grouped according to the season of sampling, we didn't find a statistically significant difference between groups.
Conclusions: We found an association between VitD deficiency and illness, though no correlation with the severity of MG. We were not able to find general differences between VitD levels in MG patients and hc in our population. We aim to increase the number of samples to deepen in the analysis of VitD levels in our local population.

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Arthrogryposis Multiplex Congenita Caused by Mutations in X-Linked Gene ZC4H2: Severe Phenotypes in Females

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Introduction: Arthrogryposis multiplex congenita (AMC) is caused by heterogeneous pathologies. Wieacker-Wolff syndrome, Miles-Carpenter syndrome and recent cases report in females, are now considered to be different expressions of a single condition called ZC4H2—associated rare disorders (ZARD), caused by mutations in X-linked gene ZC4H2, which encodes a zinc-finger protein. This has been suggested to be involved in neural development of interneurons, GABAergic neurons and dendritic spine density. Female patients showed from mild to severe phenotypes.
Material and Methods: Retrospective descriptive study. Clinical, pathological, radiological and genetic characterization of 2 female patients with ZC4H2 mutations.
Clinical cases: Patient 1: Girl 11 years old, healthy non consanguineous parents. She was diagnosed with AMC with prenatal ultrasound. She was born at term by cesarean due to breech presentation. Her anthropometry was normal. Apgar score 9-9. Physical examination at birth demonstrated multiple contractures, talus valgus feet, cleft palate. Respiratory distress, feeding difficulty and severe reflux were observed during neonatal period. She evolved with global development delay and severe intellectual disability, inability to stand, short stature (p -7 SD), multiple contractures, scoliosis, ptosis, ophthalmoplegia, proximal weakness, and hyperreflexia in lower limbs. MRI showed enlarged posterior horn of lateral ventricles, decrease white matter volume, delayed myelination, thin corpus callosum. Electromyogram and serum creatine kinase level were normal. Muscle biopsy: mild myopathic pattern and type one fibers predominance. Molecular finding: heterozygous de novo deletion in the ZC4H2 gene

(c.551delC, p. Pro184Hisfs*3). The X-inactivation pattern in blood was 64:34%. Patient 2: Girl 11 years old, healthy non consanguineous parents. Cesarean delivery at term due to breech presentation. Physical examination at birth showed Apgar score 1-9, height 45.5 cm (p3), multiple contractures and transitory respiratory distress. She developed moderate intellectual disability, strabismus, VI pair palsy, proximal weakness, hyperreflexia in lower limbs. Electromyogram and serum creatine kinase level were normal. Muscle biopsy: reduced COX and SDH stain in some fibers. MRI performed at at 4 months and 5 years old were normal. However, MRI at 11 years old showed microcephaly and reduced volume in corpus callosum and thalamus. Molecular finding: a heterozygous nonsense mutation in the ZC4H2 gene (c.34G>T, p.Glu12*).

Discussion: Clinical phenotypes previously published affected males and females in different degree. Most men had severe phenotypes inherited from carrier mothers. In females the phenotype is broader, from asymptomatic carriers to severe symptoms mostly described in de novo deletions or nonsense mutations, as in our patients. The apparently variable penetrance in female carries was believed to X inactivation, however previous cases and the patient 1 did not show strong correlation. The X inactivation pattern in the nervous system can differ from that seen in the blood, investigation of blood cells might not be suitable for predicting the phenotype.

Conclusion: The severe clinical spectrum and genetic defects in females are similar de novo cases reported with deletions. We agree it is necessary investigate ZC4H2 function protein and inactivation pattern in other tissues to establish genotype-phenotype relation.

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Longer-Term Treatment With Nusinersen: Results in Later-onset Spinal Muscular Atrophy From the SHINE Study

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Background: Several clinical trials have demonstrated a favorable benefit:risk profile for nusinersen and established clinically meaningful efficacy on motor function. Here we report the results from the SHINE open-label extension study (NCT02594124) for participants with later-onset spinal muscular atrophy (SMA).

Methods: Participants from the CHERISH study could enroll in SHINE. Following protocol amendment in SHINE, CHERISH participants transitioned from intrathecal nusinersen 12 mg maintenance dosing every 6 months to every 4 months.

Results: 83 participants from the CHERISH nusinersen and 42 from the sham-procedure group transitioned to SHINE. Using the SHINE 27 August 2019 interim data cut, median time on nusinersen was 4.1 years for participants treated with nusinersen in CHERISH/SHINE and 2.8 years for those who initiated nusinersen in SHINE. The mean (SE) change in Hammersmith Functional Motor Scale-Expanded (HFMSE) total score from baseline (n=84) to Day 1650 (n=20) was 4.6 (2.18) for the nusinersen in CHERISH/SHINE group, and from baseline (n=42) to Day 930 (n=35) was 1.7 (1.15) for those who initiated nusinersen in SHINE. Mean (SE) change in Revised Upper Limb Module (RULM) total score from baseline (n=84) to Day 1650 (n=20) was 6.4 (1.47) for the nusinersen in CHERISH/SHINE group, and from baseline (n=42) to Day 930 (n=36) was 3.4 (0.53) for participants who initiated nusinersen in SHINE. Safety findings were consistent with those previously reported.

Conclusions: HFMSE and RULM scores improved over time with nusinersen, with greater improvements for participants who received nusinersen continuously in CHERISH and SHINE. Continued analysis of SHINE data will increase the information available on the long-term safety/tolerability and efficacy of repeated nusinersen doses in patients with later-onset SMA.

Study Support: Biogen

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Longitudinal Data Collection from Patients with Spinal Muscular Atrophy in a Spanish nationwide registry: CuidAME

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Introduction: Spinal muscular atrophy (SMA) is an autosomal-recessive disorder caused by homozygous deletion in the survival motor neuron (SMN) 1 gene on chromosome 5q13. With an incidence of 1:10,000, SMA is classified as a rare disease. The CuidAME project aims to collect standardized and homogenized longitudinal data from infantile and adult SMA patients. CuidAME is a harmonized structure that guarantees the interoperability with other national and international registries.
Methods: This is a retrospective and prospective multicentre registry in Spain. A steering committee has been set up with national experts in infantile and adult SMA. CuidAME registry colabora the Smartcare project, which has provided an online platform for all SMA health-care providers interested in participating. Inclusion criteria for patients are defined as genetically confirmed 5q-SMA. All patients signed an informed consent form and the approval of the central ethics committee has been obtained. Data collection is performed during routine patient visits and patients follow up is scheduled as follows: untreated patients once or twice a year and patients treated with Nursinersen every four months. Data collected includes demographic data, genetic diagnosis, clinical and motor function status assess by motor measures scales, treatments and biomarkers. Data quality is regularly monitored.
Conclusions: It is expected that the collection of prospective follow-up data of adult patients with SMA will allow a better understanding of the natural history of SMA and the influence of drug treatments. CuidAME platform aims to establish a research network among neuromuscular centres in Spain. The infrastructure database, as well as the dataset, can be used for different research projects.

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Usefulness of Natural History Trajectories in the Interpretation of Nusinersen Treatment Effect in SMA Patients

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Introduction: Spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by mutations in the gene encoding survival motor neuron 1 (SMN1). The condition is characterized by the degeneration of alpha motor neurons, resulting in progressive muscular atrophy and weakness. The approval of the antisense oligonucleotide nusinersen for the treatment of SMA has significantly changed the natural history of this devastating disease. Nusinersen modifies the splicing of the mRNA of the SMN2 gene, thereby increasing the amount of functional SMN protein produced, thus compensating the genetic defect in the SMN1 gene. Here, we review outcomes measures in children with SMA Type I, II and II who were treated with nusinersen and compared these results with their previous history outcomes measures.
Methods: We collected demographic, clinical data and outcome measures in 22 patients with SMA treated with nusinersen between March 2018 and January 2020 in Sant Joan de Déu Hospital. For this analysis, we assessed changes in motor function from 16 months before nusinersen (-16 month), baseline (0-4 months before treatment) to 16 months after treatment (+16 month) using the Hammersmith Functional Motor Scale–Expanded (HFMSE), Revised Upper Limb Module (RULM), and Egen (Classification)Klassifikation 2 scale EK2 in SMA type II and non-ambulant SMA type III; 6-Minute Walk Test (6MWT)in ambulant SMA type III and Hammersmith Infant Neurological Examination (HINE) and the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorder scale (CHOP INTEND) in SMA type I. All evaluations were performed on a single day, every 8 months.
Results: We included 22 SMA patients (12 male/9 female) treated with intrathecal nusinersen, age range from 1,8 to 17 years (mean 10,3) from whom 81% were on stable doses of salbutamol therapy. Seventeen patients were SMA type II or non-ambulant SMA type III, 2 patients SMA type III and 3

SMA type I. Mean score in HFMSE in SMA type II and non-ambulant type III was 14 points at 16 month, 9.67 at baseline and 11.42 at +16 month. Overall, patients with higher initial scores earned fewer points. Patients younger than 6 years showed mild changes in mean HFMSE score from -16 month to baseline (improvement of 0.33 points) and patients older than 6 years had declined in mean HFMSE (worsening of 2.82 points). In contrast, the mean change in HFMSE from baseline assessment to +16 months was significantly higher in patients younger than 6 years (4 points) than in patients aged 6 years or more (0,63 points). Patients younger than 6 years also had a significantly higher mean score in RULM +16 months (+3,75) but they had and improvement in scores from -16month to baseline (+1,5) SMA type I had a mean improvement of 12.3 points in the CHOP INTEND.

Conclusions: Natural history data in the same patient are necessary to make a correct interpretation of the treatment response. Stabilization in motor function can better demonstrate if we have motor function measures before the beginning of treatment with nusinersen.

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Description of Spanish Patients with Myotonic Dystrophy Type I Carrying Interruptions: Mild and Severe Phenotypes

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Myotonic dystrophy type 1 (DM1) patients carrying interruptions in CTG repeats of the myotonic dystrophy protein kinase (DMPK) gene have been associated with heterogeneous phenotypes, mostly mild. Nonetheless, data available on interrupted DM1 patients are scarce.

We studied a cohort of DM1 patients from four Spanish centers. Clinical and genetic information was collected and stored in a secure registry. Clinical phenotype was evaluated in depth including age and onset symptoms, myotonia and muscle strength assessment using the manual Medical Research Council (MRC) scale. The most recent ophthalmological, cardiological and respiratory examinations carried out by the corresponding specialists were also reviewed, as well as blood analyses, electrocardiograms, echocardiograms, and functional respiratory and swallowing tests. Functional status and disability were assessed using the Muscular Impairment Rating Scale (MIRS), the modified Rankin Scale (mRS).

Blood DNA was obtained and analyzed through triplet-primed polymerase chain reaction (PCR), long PCR-Southern blot, small pool PCR, AciI digestion, and sequencing.

Eleven patients, belonging to four families, were found to have CCG interruptions. These CCG interruptions were present in different patterns across and within the families. Seven patients presented interruptions at the 3' end of the CTG expansion and 4 of them, belonging to the same family, at the 5' end of the CTG expansion. Anticipation was observed in one of the five intergenerational transmissions that we assessed. In the other intergenerational transmissions that could be studied, the patients in the next generation were still asymptomatic. Regarding the phenotype, we found some atypical traits, such as very late onset of symptoms (>50 years) in five patients, severe axial and proximal weakness requiring walking assistance and isolated severe dysphagia. They also showed classic DM1 symptoms including cardiac and respiratory dysfunction and myotonia. Five patients (<35 years) diagnosed based on the family history, were asymptomatic upon clinical examination and had no detectable myotonia or cardiac alterations.

This study further contributes to the characterization of DM1 patients carrying interruptions and agrees with previous described patients, meaning, they show a later age of onset and that the most frequent type of interruption found is CCG. Anticipa-

tion is also found in these patients. Despite they also show classic symptoms, a not so mild phenotype is a differential feature compared to those previously reported.

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First Swiss Family with CMD/LGMD-Like Phenotype Caused by CRPPA Mutations

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Dystroglycanopathies represent a clinically and genetically heterogeneous group of recessively inherited muscular dystrophies with phenotype ranging from mild limb-girdle muscular dystrophy (LGMD) to the most severe congenital muscular dystrophy (CMD) with brain and ocular involvement. They are caused by mutations in genes coding for proteins that are involved in glycosylation pathway of α-dystroglycan.

Here we present the first Swiss non-consanguineous family with two affected siblings with dystroglycanopathy caused by compound heterozygous mutations of CRPPA c.685-2delA (new) and c.605C>T/p.(Ser202Leu). The novel c.685-2delA mutation is predicted to affect splicing and co-segregates with disease phenotype. Western blot demonstrated reduced laminin α2 and α-dystroglycan expression in muscle biopsy of the male sibling.

While the brother presented with LGMD-like phenotype without CNS involvement, the sister demonstrated microcephaly, delayed motor and neuropsychological development, myopia and oculomotor apraxia, compatible with intermediate CMD/LGMD-like phenotype. The eye and CNS involvement is not surprising, as both mutations are located in the functionally conserved CDP-ME domain of the CRPPA protein. However, the brother demonstrates isolated LGMD phenotype suggesting that additional factors beyond the type and location of the mutation contribute to the phenotype variability in CRPPA-associated dystroglycanopathies.

Key words: Dystroglycanopathies, CRPPA, CMD, LGMD

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SRCAM (Subsarcolemmal Rims and/or Central Aggregates of Mitochondria) Fibres are Prevalent in Congenital Titinopathies

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With increasing use of massive parallel sequencing over recent years, congenital titinopathies due to recessively inherited truncating and/or splice-site pathogenic variants in TTN (which encodes titin) are emerging as a common cause of congenital myopathy (CM). The clinical phenotype is broad. Muscle biopsies show structural abnormalities including cores, central nuclei (CN) and fibre size disproportion. We report a novel structural abnormality prevalent in muscle biopsies from a cohort of patients with clinical and/or pathological features (cores and/or central nuclei and slow fibre predominance) of CM. Cases were classified genetically as "definite" (2 predicted pathogenic TTN variants), "probable" (1 predicted pathogenic and 1 missense variant) and ''possible'' (1 predicted pathogenic or 2 missense variants) titinopathy. The index case, a male with recessive splice-site TTN variants in trans, presented at birth, with profound hypotonia, respiratory weakness and cardiomegaly. CK was normal. EMG was myopathic. Quadriceps biopsy at 2 months showed mild CN and ill-defined cores. A novel observation concerned a striking sub-population of fibres, often smaller, with circumferential rims with/without central aggregates of oxidative staining. These were designated as myofibres with subsarcolemmal rims and/or central aggregates of mitochondria (SRCAM fibres). We subsequently identified SRCAM fibres in 35.7% of genetically definite or probable/possible

TTN-CM cases (10/28 total; 4/9 definite, 2/3 probable and 4/16 possible). In stark contrast, SRCAM fibres were present in only 3.6% (2/56) of cases with pathogenic variants in other core/CN-CM genes (RYR1, SEPN1, MYH7, MYH2, DNM2, MTM1). They were most frequent in neonates. Analysis of additional cases and ultrastructural characterisation is ongoing. We recommend that patients with a clinicopathological picture compatible with CM and presence of SRCAM fibres in their muscle biopsy should be screened for TTN mutations.

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Utilization of Real-World Observational Data to Study Safety and Effectiveness of Spinal Muscular Atrophy Treatments

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Background: Real-world data (RWD) are essential in providing robust, timely safety and effectiveness data from clinical practice for spinal muscular atrophy (SMA) therapies in the post-approval setting. This approach is preferred following the inception of the European Medicines Agency (EMA) patients' registries initiative in 2015. Biogen supports a disease registry approach for SMA with multiple partners that can address independent, industry, and regulatory-focused objectives. These objectives can include support for filing, launch, and post-approval strategy; understanding the natural history of SMA; and exploring treatment patterns, outcomes, and treatment value.

Methods: Based on guidance from the EMA, collaboration was established with SMA disease registries across the globe to gather robust information on disease outcomes to characterize the natural course of SMA, as well as to increase the understanding of nusinersen and other emerging treatments in a real-world setting. Over the past 5 years, work has been undertaken with registry partners to optimize existing data, align and standardize outcome and safety information collected across registries, support technology, and provide financial support to implement data collection. The data collected include demographics, clinical characteristics, medical history, functional outcomes, hospitalizations, treatments for SMA, and safety data.

Results: Collaboration has been established with multiple global SMA registries and partners. Ongoing collaborations include those with: the International Spinal Muscular Atrophy Registry (ISMAR), composed of three national networks in the United States, Italy, and United Kingdom (UK); the SMArtCARE registry in German-speaking countries; CuidAME in Spain; Spinal Muscular Atrophy Research and Clinical Hub UK (SMA REACH UK); the French Registry of Patients with Spinal Muscular Atrophy; the Canadian Neuromuscular Disease Registry (CNDR); the Polish Registry of SMA Patients; the Swiss Registry for Neuromuscular Disorders; the REaDY HCP registry in the Czech Republic and Slovakia; the Greek SMA registry; the Israeli Registry of SMA Patients; the Australian SMA Disease Registry; the New Zealand SMA Disease Registry; the South Korean SMA registry; the Japan REgistry for Adult subjeCTs with SMA (jREACT-SMA); Translational Research in Europe for the Assessment and Treatment of Neuromuscular Disorders (TREAT-NMD); and the Muscular Dystrophy Association (MDA).

The project involves improving the capacity and capability of registry partners to collect patient-level data aligned to a core minimum data set that are Global Data Protection Regulation-compliant and in accord with FAIR Data Principles (Findable, Accessible, Interoperable, Reusable).

The resulting medical evidence may have application in:

- Medical practice (quality of care/guidelines)
- Regional or local health technology assessment
- Regulatory submissions.

Conclusions: Supporting SMA disease registries across the globe is important to meet the needs of the SMA community, health care providers, researchers, regulators, and payors. Efforts are aimed at bolstering the capabilities of SMA disease registries to fulfill research needs for industry partners and the SMA community and to support post-marketing requirements.

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Different Approaches to Restore Dystrophin Expression on DMDdel8-34 Mice Model

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Duchenne muscular dystrophy can be caused by a myriad of different mutations in DMD gene. However, deletion and duplications of one or more exons is a more common reason of this fatal disease. Big deletion in DMD gene spanning exons from 8 to 34 was identified in one Russian patient. To test exon skipping approach for dystrophin synthesis restoration on this deletion background we created corresponding mice model (DMDdel8-34) using CRISPR/Cas9 gene editing system. Exons 6 and 7 should be simultaneously skipped for DMD reading frame restoration with 230kDa dystrophin shortened form expression. Such therapy in the case of success can help approximately 3% of all DMD patients being most frequent in multiple exons skipping procedure. Here we report the comparison of different approaches tested in vitro on myoblasts derived from the model animals skeletal muscles and in vivo. Among them are classical exon skipping using vivomorpholino antisense oligonucleotides, exon skipping using modified U7snRNAs and gene editing using CRISPR/Cas9 system. Effective sequences and constructs were selected for each approach. Adeno-associated virus (AAV) serotypes DJ and 9 were used for U7snRNA, Cas9 and guide RNA cassettes delivery to myoblasts in vitro and in vivo. We found that DMD reading frame can be restored both affecting mRNA splicing stage and gene editing technique making DMDdel8-34 mice appropriate model for such studies. Functionality of the resulting shortened peptide and amelioration of disease progression will be tested in further experiments.

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Functional Ability, Socio-Demographic, and Physical Activity in People with Limb-Girdle Muscular Dystrophy and Charcot-Marie-Tooth

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Background: Limb-girdle muscular dystrophy (LGMD) and Charcot-Marie-Tooth (CMT) are among the most common hereditary Neuromuscular Disorders (NMD) in Norway. As there is no curative treatment available, physical activity is essential to slow down disease progression and prevent physical deconditioning. Being physically active is recommended by both national and international health organizations, including also people with LGMD and CMT. However, the knowledge about factors which can promote or hinder physical activity in these groups is lacking. In this study, we investigated the associations of variables with physical activity in people with LGMD and CMT.

Method: We did a cross-sectional study with participants from all regions in Norway. We used the Barthel's Activity Daily Living (ADL) index to measure functional ability and categorised it into: normal (score 100), mildly dependent (90-99), and severe-moderately dependent (<90). Physical activity was measured using the International Physical Activity Questionnaire –short form (IPAQ-sf). Based on the IPAQ scoring protocol version 2005, individuals with moderate to high physical activity were classified as physically active. Those with low physical activity were classified as physically inactive.

Results: We included 97 participants with available data for physical activity and functional ability in the analysis: 52 (53.6%) with CMT and 45 (46.4%) with LGMD. We found that participants with LGMD in a severe-moderately dependent group had a higher likelihood of being physically inactive (OR: 26.1; 95% CI 2.9-237.6) compared to the normal ability group. The odds ratio (OR) of being physically inactive for participants with CMT in the severe-moderately dependent group was 7.1 in comparison to the normal ability group. However, this was not statistically significant (95% CI 0.7-75.9). Adjusting for

the variables diagnosis, age, gender, and fatigue, we found that the severe-moderately dependent group had a higher likelihood of being physically inactive (OR: 17.9; 95% CI 3.4-93.0) compared to the normal ability group. The adjusted OR for mildly dependent group was 4.4; 95% CI 1.3-14.6. Participants who had a personal assistant, assistive device, or adapted housing as means of assistance were also less physically active.

Conclusion: In conclusion, we found that functional impairment was associated with physical inactivity. Participants with LGMD seemed to be less physically active in comparison to those with CMT, particularly when the functional ability decreased. Assistive measures were also associated with less physical activity. These findings are important to understand when trying to develop instruments to promote physical activity in people with NMD.

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Multiplex Chromogenic Immunoassay Evaluating Mitochondrial Respiratory Chain Complex I and IV Defects in Muscle Biopsies

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The investigation of clinically suspected mitochondrial disease (mtD) includes performing a skeletal muscle biopsy for biochemical/histochemical assessment of mitochondrial respiratory chain (RC) defects. COX-SDH histochemistry detects RC-complex IV (CIV) defects, but RC-complex I (CI) defects cannot be detected histochemically. CI/CIV defects are common in mtD. Immunohistochemical evaluation of RC complex defects relies on reduced amount of the assembled complex associated with catalytic deficiency, detectable with RC subunit-specific monoclonal antibodies. Our aim was to design a dual chromogenic immunoassay (DCI) for evaluating CI/CIV defects in diagnostic muscle biopsies. In the DCI optimised protocol, primary antibodies (Abcam), TOMM20 (mitochondrial mass), NDUFB8 (CI) and MTCO1 (CIV) were coincubated (TOMM20+CI and TOMM20+CIV), and then TOMM20 developed to yellow and the other marker to teal (Discovery/Ventana Systems) with colocalising antibodies visualising as green. Control sections stained as a mosaic dark green (type I fibres) and light green (type II fibres) pattern. Completely CI/CIV-deficient fibres stained yellow, and partly CI/CIV-deficient fibres stained yellow-green, and were easily detectable due to good visual colour contrast. The DCI and COX-SDH assays were performed in serial frozen sections. 23 biopsies were assessed: 15 with genetically confirmed mtD (mtDNA rearrangements/point mutations/depletion), 4 with high clinical/histological suspicion of mtD, and 4 unaffected controls. % COX and CI/CIV-deficient fibres were counted in two random fascicles, with high concordance amongst % COX-negative and CI/CIV deficient fibres. The DCI detected more CI-deficient fibres in 7/19 cases and more CIV-deficient fibres in 5/19 cases compared to COX-negative fibres (average 6%). Most COX-negative fibres had dual CI+CIV defects with DCI. Segmental and partial CI/CIV defects were detectable. Equivocal COX-SDH stained fibres were often strongly CI/CIV-immunodeficient. In conclusion, our multiplex DCI reliably detects CI/CIV defects comparable in sensitivity to the COX-SDH histochemical assay, is easy to evaluate due to a good visual contrast between CI/CIV positive and negative fibres and can be easily coopted to routine diagnostic work. Studies are underway to optimise the chromogenic technique in formalin-fixed and paraffin-embedded material, as well as combining chromogenic CI/CIV labeling with fluorescent labeling for laminin, allowing for digital evaluation of CI/CIV defects in entire transverse sections of skeletal muscle.

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Genetic and Clinical Spectrum of a Series of Patients with Hereditary Motor Neuropathies

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Introduction: Hereditary motor neuropathies (HMN) are clinically and genetically heterogeneous. To date more than 30 genes have been identified in association with different forms of HMN. Nevertheless, most patients with HMN are not genetically characterized and only a small number of series of patients affected with HMN have been reported.
Objective: To determine the prevalence, the genetic cause and clinical presentation of an extensive series of patients with HMN assessed in the Valencian Region, Spain.
Patients and Methods: We included 125 patients from 79 families with HMN from the Valencian Region who were clinically and genetically studied in a Neuromuscular Disease Unit from 1984 to 2019. Genetic studies were performed by either direct Sanger sequencing or using New Generation Sequencing techniques.
Results: The minimum prevalence of HMN in the Valencian Region (total population of 4,974,475) is 2.33 per 100,000 individuals. The majority of probands were sporadic cases (n= 44/79) and the age of onset in most patients was between 2-10 years (36/125). Among the secondary cases, there were 10 asymptomatic carriers. In the whole series, the causative mutation was identified in 57 out of 125 patients (45.6%) and in 23 out of 79 families (29.11%). In 16 families previously described pathogenic HMN mutations were identified, while in 7 families novel variants in known genes that segregated with the disease and that matched the phenotype were identified. In the rest of families the studies were inconclusive (41/79) or negative (15/79). The most frequent mutations in this series were HSPB1 c.418C>G (five families) and DNAJB2 c.352+1G>A (four families). The GARS c.794C>T change was identified in 13 subjects from one large family. Two families carrying the c.65A>G mutation in SOD1 were also identified. Four families with four different mutations in BICD2 were identified and de novo mutations in the DYNC1H1 gene were found in two probands. The rest of diagnosed patients carried mutations in AAAS, VRK1, IGHMBP2 and FIG4 genes. Some patients carrying mutations in HSPB1, GARS, DNAJB2, FIG4 and IGHMBP2 genes presented subclinical or minor sensory involvement.
Conclusions: The minimum prevalence of HMN in the Valencian Region is 2.33 per 100,000 individuals. The most frequent cause of HMN in our series is the c.418C>G HSPB1 change. Mutations in BICD2, DNAJB2 and GARS are also frequent. The diagnostic rate in our series is similar to other recently published series and highlights the fact that the majority of patients with HMN remain without genetic diagnosis after a comprehensive genetic screening. Our data also emphasizes the clinical and genetic overlap that exist between HMN and axonal Charcot-Marie-Tooth.

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Reliability of Automated Quantitative Analysis of Muscle MRI in Patients with Duchenne Muscular Dystrophy

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Background: Duchenne muscular dystrophy (DMD) is a devastating neuromuscular disorder with an incidence rate of up to 1:5000 males worldwide. The disease leads to progressive muscle weakness, loss of ambulation and early death. In the past years numerous clinical trials have been initiated to develop new treatment strategies. At the same time, the definition of reliable outcome measures has won

increasing interest. Quantitative muscle MRI (qMRI) has been shown to be superior to clinical assessments in detecting changes of disease progression; however, the method has not become part of the clinical routine partly due to the time consuming process of image analysis. More advanced techniques with automated segmentation of the limb pools (i.e muscle, adipose tissue and bones) might simplify the image analysis and contribute to the wider use of qMRI. In this study we present the reliability of an automated machine learning framework of qMRI data and its correlation with clinical assessments and disease progression.

Methods: Baseline and 6-month follow-up data of 41 ambulatory patients (aged 6.5-10 years) with genetically confirmed DMD participating in the "Treatment with L-citrulline and metformin in Duchenne muscular dystrophy"-study were analyzed. qMRI measurement of the thigh muscles at baseline and at 6-month follow-up were analyzed and correlated with the motor function measure and its D1 domain. Statistical analysis was conducted to compare the muscle mean fat fractions at baseline and at follow-up measured by manual and automated image analysis. Further, sample size estimations of the two imaging methods and their correlation to clinical outcomes were completed.

Results: Mean fat fraction of the thigh at baseline and at 6-month follow-up assessed by automated segmentation correlated well with manually analysed data. An increased mean feat fraction at 6-month follow-up could be observed with both techniques. Further, mean fat fraction correlated well with the motor function measure and its D1 domain independently of the image analysis technique. Naive sample size estimation was larger when using the manual analysis method; however, when adjusting for the baseline fat fraction, sample sizes were smaller in this group.

Conclusion: Automated qMRI analysis of mean fat fraction is a less time consuming method and shows good correlation with manual segmentation data and clinical outcome measures. However, automated algorithms are less reliable in cases with a very high muscle fat content or with significant movement artefact, where visual quality control remains necessary. Automated analysis seems to be a useful tool in certain settings, but studies with larger samples size are needed to confirm these results.

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Efficacy of Nusinersen in Type 1-3 Spinal Muscular Atrophy: Real World Data from Hungarian Patients

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Introduction: Spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by a homozygous deletion in the survival motor neuron (SMN) 1 gene. Nusinersen is an antisense oligonucleotide enhancing the production of the SMN protein. Clinical trials have demonstrated its effectiveness in several types of SMA based on which it has received EMA approval in 2017. In Hungary, the first patient received nusinersen treatment in April, 2018. Our aim is to summarize our experience regarding the efficacy, safety and tolerability of nusinersen in our patients.

Methods: We collected data retrospectively in all SMA patients (type 1-3) who started treatment with nusinersen in Hungary between April 2018 and August 2020. The motor functions were evaluated at baseline, at the time of the 4th and at the time of all following injections.

Results: By 31st August, 2020, nursinersen therapy was initiated in 76 patients at one of the Hungarian treatment centres. 45 patients performed the motor evaluation at the 307th day visit. Mean age of these patients at the start of the treatment was 8.1 years (0.4 y-17.9 y, SD 6.0). 9 patients are type 1 (0.4y-1.5y, mean 0.78±0.27), 18 patients are type 2 (1.3 y-12 y mean 4.5±3.3), 18 patients are type 3 (2.9 y-17.9 y mean 10.9±5.2). Fourteen patients had severe scoliosis, four of them underwent spine stabilizing surgery. Approximately 450 injections were administered without any new safety concerns emerging. Motor function has improved in most of the children. By the 307th day visit, on average, a 15.6 point improvement was measured on the CHOP INTEND scale in type 1 patients (p=0.004). All type 1 patients have improved more than four points (7-

23). In case of type 2 patients we have found a 6.7 ((-2) – (+17)) point increase from baseline ($p<0.001$) with Hammersmith Functional Motor Scale Expanded (HFMSE) by the time of 6th injection. The 6 minute's walk test distance also increased by 29.7 meters (min-max (-50) – (+106)) on average, in type 3 patients. The motor function improvement remained stable during the nearly 2 years follow up (median 620 days).

Conclusion: According to our results nusinersen has the same safety and tolerability profile as it was demonstrated in the clinical trials. In a heterogenic patient population of type 1-2 SMA, nusinersen showed similar efficacy as seen in pivotal studies. A clinically and statistically significant improvement of motor functions was also detectable in type 3 patients with heterogenious age distribution.

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Episodic Weakness in a Teenager with a Family History of Hereditary Neuropathy

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A 19 year old female presented with falls and episodic weakness of the lower limbs, starting with pain in the calves and falls at the age of 16 years. There was strong family history of hereditary neuropathy of uncertain type affecting several of her mother's relatives.

Apart from flat feet no abnormality was noted on inspection or gait; neurological examination of power, tone, reflexes and sensation in the limbs were normal. Investigations showed normal nerve conduction studies. Blood tests including creatinine kinase were normal. CT brain showed moderately dilated ventricles and intracranial pressure measurement was normal. Initial clinical impression was that there is 'no neuromuscular cause for her weakness'.

The episodic weakness got gradually worse with an increase in frequency and duration of episodes and daily falls. Weakness was precipitated by prolonged sitting and she also reported stiffness of lower limbs with prolonged sitting or standing. There was no limb weakness between episodes. She was referred for repeat electrophysiology when she was 19 years old. Nerve conduction studies showed mild axonal type sensory motor polyneuropathy in the lower limbs. Long exercise test for periodic paralysis was normal. Genetic testing for CMT2 and CMT X were negative.

There have been reports describing episodic weakness in CMT2 with mitochondrial gene mutation MT-ATP6. She was found to have a mitochondrial MT-ATP6 mutation m.9185T>C confirming a mitochondrial DNA disorder.

It has been reported that episodic weakness improves with acetazolamide but this did not influence attack frequency or severity in this patient and was discontinued when she reported dizziness. Clinical syndromes associated with MT ATP6 mutations include Leigh syndrome; syndrome of neuropathy, ataxia and retinitis pigmentosa (NARP); and spinocerebellar ataxia and CMT like peripheral neuropathy. Although the clinical phenotype may overlap in MT-ATP6 and CMT2, neuropathy associated with MT ATP6 is best classified as a mitochondrial disorder rather than CMT 2. Mitochondrial DNA testing for MTATP6 should be considered in patients with episodic weakness and hereditary axonal neuropathy.

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Immunogenicity in a Phase 3 Facilitated Subcutaneous Immunoglobulin Study in Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

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Background: ADVANCE-CIDP 1 is a placebo-controlled, randomized, double-blind, global phase 3 study evaluating the efficacy, safety, and tolerability of facilitated subcutaneous immunoglobulin (fSCIG; Immune Globulin Infusion [Human] 10% with Recombinant Human Hyaluronidase [rHuPH20]) to prevent relapse in CIDP. The rHuPH20 component of fSCIG facilitates depolymerization of subcutaneous hyaluronan, resulting in increased tissue dispersion and absorption of subcutaneously administered immunoglobulin (IG). fSCIG can be administered at doses and infusion rates that are comparable to intravenous administration. Published data suggest that up to 18% of patients with primary immunodeficiency diseases may develop

clinically non-significant binding antibodies to rHuPH20 which are not associated with any adverse event and decline over time despite continued treatment. A preplanned interim safety analysis was performed to provide data on immunogenicity of fSCIG in subjects with CIDP.
Objective: To provide a preliminary assessment of a potential immune response to rHuPH20 in patients with CIDP (NCT02549170).
Methods: The interim analysis included 96 patients with CIDP who received rHuPH20 with IG 10% or placebo. All patients were monitored for the development of binding and neutralizing anti-rHuPH20 antibodies using a validated anti-rHuPH20 antibody detection assay (ADA, also known as the Screening and Confirmatory Binding Assay). Antibody titers ≥1:160 were considered positive. Statistical analysis was descriptive.
Results: Patients' mean age at baseline was 53.3 (range: 19 to 86) years, 55% were male, and 83% were white. Six (6.3%) patients were found to have positive binding antibody titers (titer range: 1:160 to 1:5120). Four of these patients had positive binding antibody titers at 2 consecutive measurements. No adverse events were related to positive binding antibodies. There were no neutralizing antibodies.
Conclusion: The interim analysis has shown that clinically non-significant, transient, non-neutralizing, binding antibodies to rHuPH20 can occasionally develop in patients with CIDP. These data are in line with previous findings in other patient populations.

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Usefulness of Ultrasound in Detecting Muscle Involvement Pattern In POMPE Disease: Preliminary Results

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Introduction: Pompe disease is a treatable autosomal recessive disorder caused by deficiency of acid alfa-glucosidase. Two classical phenotypes are described: the infantile and the late-onset forms. Among late-onset Pompe disease, most patients present with a limb-girdle weakness pattern, although axial involvement is common. Treatment can modify the course of Pompe disease, and early diagnosis is important. Muscle ultrasound is a useful tool to evaluate clinical and subclinical involvement of muscles, identifying some particular distribution pattern, and acting as adjunct to the physical exam.
Objective: To describe the pattern of muscle involvement by ultrasound, including the tongue, paravertebral and diaphragm muscles in patients with Pompe disease.
Methods: Eight patients with molecular diagnosis of Pompe disease were clinically assessed and underwent muscle ultrasound using the setting for muscle evaluation with a fixed gain (Sonosite Edge, Fujifilm) with a 7-15MHz transducer. The followings segments were assessed: tongue, upper and lower limb (mostly for proximal muscles), abdomen, diaphragm and paravertebral muscles. For the diaphragm we recorded images in the seventh intercostal space in the anterior axillar line, always showing the diaphragm tangent to two ribs, and we measured the thickness during expiration and forced inspiration. All ultrasound images were obtained and scored retrospectively by consensus of two experienced examiners based on Heckmatt's rating scale.
Results: Five from eight patients were male. The mean age was 42 years old, with 10 years of disease duration. Only one patient complaint of dysphagia and five reported dyspnea. The most involved and weakest muscles in clinical evaluation were abdominal (mean MRC 2), gluteus maximus (mean MRC 2) and gluteus medius (mean MRC 3), and adductors (mean MRC 2.5). On ultrasound the most affected muscles were abdomen, vastus intermedius, adductors and lumbar paravertebral muscles, scaled as Heckmatt 3 in virtually all patients. We also observed a pattern of brachialis more involved than biceps brachii, and vastus intermedius more affected than rectus femoris in all patients. Five patients had imaging involvement of the tongue without any complaint of dysphagia. Considering diaphragm examination, seven patients had high echointensity, and all patients with Heckmatt 3 had a thickness ratio (considering inspiration and expiration thickness) lower than 30%, which was considerably lower than in Heckmatt 2 patients (which had a thickness ratio between 30 and 60%). In only one patient we recorded a normal diaphragm (Heckmatt 1) with a thickness ratio of 77%, and this patient was the one with the shortest interval between the symptom onset and diagnosis. **Conclusion:** Muscle ultrasound was able to detect a recurrent pattern of muscle compromise in all patients. Subclinical

involvement of the tongue and diaphragm, even in patients without dysphagia or dyspnea, may help early disease recognition and predict potential respiratory complication.

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Initial Results of the Avalglucosidase alfa Phase 3 COMET Trial in Late-Onset Pompe Disease Patients

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Background: Pompe disease is a rare, autosomal recessive, progressive neuromuscular disorder caused by a deficiency of acid α-glucosidase (GAA), an enzyme that breaks down lysosomal glycogen. Deficient enzymatic activity results in abnormal glycogen accumulation leading to cellular dysfunction; progressive damage to respiratory, cardiac, skeletal, and smooth muscle; and numerous functional disabilities. In patients with late-onset Pompe disease (LOPD), progressive loss of respiratory function resulting from the weakened diaphragm and other respiratory muscles leads to considerable morbidity and early mortality. Avalglucosidase alfa is an investigational, recombinant human acid α-glucosidase (rhGAA) enzyme replacement therapy specifically designed for enhanced receptor targeting and enzyme uptake aiming at increased glycogen clearance and potential improvement of the clinical efficacy achieved with alglucosidase alfa.

Methods: The Phase 3 COMET trial (NCT02782741, sponsored by Sanofi Genzyme) is a double-blind, head-to-head comparison study of avalglucosidase alfa and alglucosidase alfa, at doses of 20 mg/kg, every other week. Patients had to have a diagnosis of Pompe disease confirmed by GAA enzyme deficiency from any tissue source and/or two confirmed GAA gene variants. Treatment-naive LOPD patients ≥3 years of age, without known Pompe-specific cardiomyopathy, able to ambulate ≥40 meters without stopping and without an ambulation-assistance device, and with forced vital capacity percent predicted (%FVC) in the upright position of ≥30% predicted and ≤85% predicted were eligible. Measurement of FVC is widely used to evaluate respiratory function in LOPD and considered a primary endpoint for measurement of Pompe disease progression, and is the primary endpoint in the COMET study. Changes from baseline in %FVC upright were measured. Other outcome measures include changes from baseline in the six-minute walk test (6MWT) scores; maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) in the upright position; hand-held dynamometry measurement; Quick Motor Function Test scores; and the 12-Item Short-Form Health Survey scores. Also monitored was the

number of participants with adverse events (AEs) reported.

Results: Greater improvements in FVC %predicted upright at all timepoints and a 2.43% greater increase in FVC %predicted were seen with avalglucosidase alfa vs. alglucosidase alfa at Week 49. The primary study objective, achieving statistical noninferiority (p=0.0074), was met. Testing for superiority was borderline significant (p=0.0626). Avalglucosidase alfa treatment resulted in greater improvements in the 6MWT (meters and %predicted), with 30.01-meter and 4.71% greater increases, respectively. Similarly, positive results for avalglucosidase alfa were seen for all secondary and other efficacy endpoints. Treatment-emergent AEs were reported in 86.3% of avalglucosidase alfa-treated and 91.8% of alglucosidase alfa-treated participants. Five participants withdrew, four due to AEs, all in the alglucosidase alfa arm. Serious AEs occurred in 8 avalglucosidase alfa-treated and 12 alglucosidase alfa-treated participants. IgG antidrug antibody responses were similar in both groups. High titers and neutralizing antibodies were more common for alglucosidase alfa.

Discussion: Efficacy and safety results of the primary analysis period of the COMET trial demonstrate improvements in clinically meaningful outcome measures and a more favorable safety profile in patients with LOPD treated with avalglucosidase alfa compared to alglucosidase alfa.

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European Postauthorization Safety Study on Long-term Hyaluronidase-facilitated Subcutaneous Immunoglobulin in Primary Immunodeficiency Diseases: Interim Analysis

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Introduction: Recombinant human hyaluronidase (rHuPH20)-facilitated subcutaneous immunoglobulin (fSCIG) 10% is a novel therapy that utilises rHuPH20 to catalyze the hydrolysis of hyaluronan in the extracellular matrix. The resultant increase in subcutaneous tissue permeability enables administering fSCIG at rates, volumes, and frequencies similar to intravenous immunoglobulin. Here, we report fSCIG safety data from the interim analysis of an ongoing observational study in patients with primary immunodeficiency diseases (PID).

Methods: This prospective, non-interventional, open-label, uncontrolled, multicenter study, initiated in July 2014 in Europe, includes patients aged ≥18 years with PID currently receiving fSCIG (EUPAS5812).

Results: This safety analysis includes 103 of 111 enrolled patients who received ≥1 dose of fSCIG as of 10 January 2019; the mean (SD) fSCIG exposure duration was 2.26 (1.19) years. Incidence of treatment-emergent non-serious (non-infectious) adverse events/treatment-emergent serious adverse events was 2.37/0.24 events per person-year; 553/57 events were observed in 83/28 patients. No neutralizing antibodies to rHuPH20 were detected. The median immunoglobulin dose administered was 80.9 (range: 1.3–275.5) mg/kg body weight/week. The proportion of fSCIG administered at home was 91.2% in the first, 93.2% in the second, 93.2% in the third, and 85.2% in the fourth year.

Conclusion: This interim analysis of prospectively collected fSCIG data suggests that fSCIG is well tolerated in a real-world population. The volume advantage of fSCIG makes it an attractive candidate in PID. This advantage becomes even more important in diseases that require higher doses of immunoglobulin, such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). A phase 3 trial of fSCIG in CIDP is ongoing (NCT02549170).

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Intravenous Immunoglobulin May Prevent Prednisone-Induced Exacerbation in Myasthenia Gravis

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Objective: Corticosteroids are recommended as first-line therapy for myasthenia gravis. However, corticosteroids may paradoxically worsen symptoms within the first weeks after treatment initiation.
Hypothesis: Our study is based on the hypothesis that previous infusion of intravenous immunoglobulin may have a protective effect against corticosteroid-induced exacerbations. The main objectives were to determine whether the co-administration of immunoglobulins and glucocorticoids was safe and effective in controlling myasthenia gravis symptoms and to compare the percentage of patients presenting exacerbations with that previously reported.
Methods: We recruited 45 patients between April 2016 and January 2019, all of whom had generalised myasthenia gravis that required the initiation of corticosteroid treatment for the first time. They received intravenous immunoglobulin 7-10 days before starting full doses of prednisone. Close monitoring was carried out over six weeks through validated scales, questionnaires and blood tests.
Results: Only 4.4% of the participants had severe adverse effects to the intravenous immunoglobulin. Among our study participants, 86.7% showed clinical improvement and only 2.2% presented an exacerbation of symptoms during the first weeks after starting prednisone treatment, which was significantly lower than that reported previously.
Interpretation: We can conclude that the adjuvant therapy of intravenous immunoglobulin and prednisone in generalised myasthenia gravis is safe and effective. Our rate of prednisone-induced exacerbation was lower than that reported before, suggesting that intravenous immunoglobulin may have a protective effect against these exacerbations. Future clinical trials should be performed to demonstrate this effect.

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Serum Immunoglobulin G Trough Levels in Response to Intravenous Immunoglobulin, 10% in Multifocal Motor Neuropathy

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Introduction: Intravenous immunoglobulin (IVIG) therapy is widely used as treatment for multifocal motor neuropathy (MMN). Systemic immunoglobulin G (IgG) exposure influences treatment effectiveness; however, the potential correlation between IVIG dose, serum IgG exposure, and treatment effectiveness is not well understood. This retrospective analysis assesses the inter-subject variability of required stable IVIG dose and serum IgG trough level in patients with MMN and the correlation between changes in dose and serum IgG levels.
Methods: Serum IgG trough data obtained from a global pivotal study of IVIG, 10% in patients with MMN (NCT00666263) were analyzed. In the study, adults with MMN were randomized 1:1 to receive double-blind treatment with IVIG followed by placebo (sequence 1) or placebo followed by IVIG (sequence 2) for 12 weeks each. Open-label IVIG was administered for 12 weeks at the beginning and end of the study for clinical stabilization and between double-blinded periods to prevent carryover effects. Switching to open-label IVIG was permitted if symptoms worsened during blinded treatment. The treatment interval ranged from 2 to 5 weeks (+/–3 days). This analysis assessed dose and serum total IgG level changes during the switch from stable IVIG to placebo. Changes in absolute values and percentage changes were calculated relative to baseline values at study entry and the adjacent prior visit.
Results: The median (range) monthly dose of stable IVIG, 10% for the entire study was 1.22 (0.42–3.18) g/kg. During the double-blind switch from stable IVIG to placebo, most patients had an accelerated switch (placebo treatment <12 weeks) back to IVIG (12/22 and 17/21 patients for sequences 1 and 2, respectively); remaining patients successfully completed placebo treatment. For patients with an accelerated switch, total durations on placebo were similar for sequences 1 and 2 (range: 7–43 days),

and monthly IVIG dose received during the scheduled blinded placebo period increased over the previous stable IVIG dose (mean increases of 42.2% and 47.4% for sequences 1 and 2, respectively). Serum IgG trough levels decreased following the switch to placebo. The median (range) serum IgG trough level for stable IVIG periods was 16.40 (9.87–41.0) g/L for the entire study and 12.35 (6.98–18.1) g/L for the placebo periods. Median IgG trough levels were slightly higher in patients with an accelerated switch (17.9 and 15.8 g/L for sequences 1 and 2, respectively) than in patients who completed placebo treatment (13.7 and 13.0 g/L, respectively). Significant correlations were between changes in total dose administered and serum IgG trough levels ($P<0.01$) in both study sequences.

Conclusion: Patients often responded negatively to treatment interruption and required a higher dose of IVIG after the stable IVIG dosing was "interrupted" by placebo. Therefore, it may be important for patients with MMN to maintain stable treatment with IVIG, 10%. Required stable IVIG, 10% dose and serum IgG trough levels were highly variable among patients with MMN. There was a significant correlation between serum IgG trough level changes and total dose changes. These findings provide support for individualizing IVIG treatment regimens and target IgG levels.

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R264Q Mutation in DYNC1H1 Gene Causes Congenital SMA-LED with Epilepsy and Cognitive Impairment

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Introduction: Cytoplasmic dynein heavy chain 1 is encoded by the gene DYNC1H1 and is an essential subunit of the cytoplasmic dynein complex. Mutations in the DYNC1H1 gene are associated with autosomal dominant spinal muscular atrophy with lower limb predominance (SMA-LED), cognitive impairment and malformations of cortical development (MCD).

Objectives: To present an illustrative case of SMA-LED and mental retardation due to a heterozygous missense mutation in DYNC1H1.

Case report: We describe a 19-year-old patient, son of non-consanguineous parents and born at full-term, with no relevant gestational complications, except for reduced fetal movements during the third trimester. Since birth, the patient presented with generalized hypotonia, arthrogryposis and pectus excavatum. He was hospitalized during the first month of life, due to recurrent respiratory tract infections, a femur fracture and failure to thrive associated with severe dysphagia. He required constant ventilatory support and a feeding tube, being subjected to a gastrostomy and a tracheostomy while hospitalized. After hospital discharge, he gradually improved, acquiring delayed motor and cognitive milestones, being able to sit independently by 18 months and acquiring speech by 3 years. He developed seizures when he was 17 years old. On examination, he was wheelchair-bound, with severe muscle weakness and wasting in the lower limbs and mild to moderate weakness and wasting in the upper limbs and trunk. Deep tendon reflexes and plantar responses were absent. He also had pronounced scoliosis and tendon retractions on the hips, knees and ankles. Vibration and pain sensation were normal. He also showed signs of cognitive impairment and child-like behavior. His creatine kinase levels were normal. Electrodiagnostic studies were compatible with a motor neuronopathy. A muscle biopsy in the first year of life showed marked neurogenic changes. An EEG, performed after the onset of seizures, was unremarkable. Genetic testing for 5q spinal muscular atrophy (SMA) was negative. Whole exome sequencing showed a missense mutation in exon 5 of the DYNC1H1 gene (c.791G>A; p.Arg264Gln), in the tail domain, compatible with the clinical diagnosis of SMA-LED.

Discussion: The main features of DYNC1H1 associated SMA-LED are congenital or early onset weakness predominating in the lower limbs, with variable severity and slow progression. Mutations in the tail domain of DYNC1H1 protein are associated with this phenotype, whereas mutations in the motor domain are usually responsible for a clinical picture composed of MCD, epilepsy and cognitive impairment. We present a severe congenital case of SMA-LED caused by a missense mutation in the tail domain with cognitive impairment and seizures, demonstrating that the superposition of both phenotypes exists.

Conclusion: SMA-LED is a rare form of motor neuron disease with a diverse phenotype.

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Autoantibodies Against the Contactin-1/ Caspr1 Complex in Patients with Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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Introduction: Autontibodies directed against the paranodal proteins such as contactin-1 (CNTN1) are useful for diagnosis and treatment selection in a subset of patients with chronic inflammatory demyelinating polyneuropathy (CIDP). Recently, antibodies targeting contactin-associated protein-1 (Caspr1) were reported in one patient with Guillain-Barré syndrome (GBS) and in one CIDP patient with neuropathic pain. Also, our group reported autoantibodies against the paranodal CNTN1/Caspr1 complex (but not CNTN1 alone) in one patient with an aggressive CIDP. Since then, autoantibodies against Caspr1 or against the paranodal CNTN1/Caspr1 complex have been reported in a small proportion of patients from other CIDP cohorts. The aim of the present study was to further characterize the clinical and immunological findings in patients with CIDP and autoantibodies against the CNTN1/Caspr1 complex.

Methods: Through routine clinical testing we identified 15 CIDP patients from 15 different European Centres harbouring autoantibodies against the CNTN1/Caspr1 complex. We collected clinical, neurophysiological, laboratory and treatment response data. Antibodies were detected using cell-based assays (CBAs) and ELISA. Paranodal reactivity was confirmed by teased-nerve fibre immunohistochemistry and the staining pattern in peripheral nerve sections was compared with that of patients with anti-CNTN1 antibodies and a commercial anti-CNTN1 mAb.

Results: All 15 patients (9M, 6F; aged between 40 and 75) fulfilled EFNS/PNS definite diagnostic criteria for CIDP. They presented with an aggressive CIDP; six (40%) had cranial nerve involvement, eight (53%) reported neuropathic pain and 12 (80%) demonstrated ataxia. Seven (47%) patients were initially diagnosed of GBS due to an acute-subacute onset. Neurophysiological studies detected features compatible with acquired demyelination in all patients, but axonal involvement and acute denervation were frequent. Complete response to first line treatments was not observed, while there was a good response to rituximab. In the CBA experiments, all patients' sera showed membrane reactivity when CNTN1 and Caspr1 were co-transfected. When Caspr1 was transfected alone membrane reactivity was seen in 11 patients (73%). Autoantibodies to Caspr1 were also detected in all samples by ELISA, while none of the sera reacted to CNTN1 by ELISA or CBA. Autoantibodies were predominantly of the IgG4 subclass in all but one patient in which the au-

toantibodies were IgG3. All samples showed paranodal reactivity in teased-nerve fibres. IgG from both anti-CNTN1/Caspr1 and anti-CNTN1 positive patients reacted against paranodes, but only IgG from CNTN1 positive patients and CNTN1 mAb reacted strongly against Remak bundles.

Conclusion: Autoantibodies against the CNTN1/Caspr1 complex were present in a subset of patients with aggressive onset CIDP and poor response to first line treatments. Caspr1 ELISA and CBAs with cells co-transfected with CNTN1 and Caspr1 were more sensitive than Caspr1 mono-transfected cells for detecting autoantibodies against the paranodal CNTN1/Caspr1 complex.

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Expanding the Phenotypic Spectrum Associated with SPTLC1 Gene Mutations

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Introduction: Mutations in the SPTLC1 (Serine palmitoyltransferase subunit 1) gene are the most common cause of hereditary sensory neuropathy type 1 (HSN1). However, depending on the mutation, the phenotypes can be varied: motor or sensory-motor neuropathies. Pathophysiologically, SPTLC1 mutations leading to the formation of a neurotoxic deoxysphingolipids (1-deoxySLs). Recently it has been demonstrated that 1-deoxySL formation in humans can be reduced with high doses of oral L-serine, suggesting that the treatment may slow the clinical progression of the disease.

Objectives: To describe the clinical, neurophysiological, and molecular findings in three patients with mutations in SPTLC1.

Patient 1: Female (14 years old): motor delay, progressive weakness and distal muscle wasting, scoliosis, cavus foot and areflexia, sensitivity conserved. Lost ambulation at 12 years old. Neurophysiological studies: Sensitive Neurography was normal. Motor Neurography: velocities conductions in axonal range and EMG characterized by neurogenic pattern. SPTLC1 mutation: c.58G>A p.Ala20Thr (heterozygous).

Patient 2: Male (6 years old): neonatal hypotonia, motor delay, cataracts, pain insensitivity, winged scapula, distal atrophy, autonomous walk. Neurophysiological studies: sensory-motor neuropathy and EMG with a neurogenic pattern. SPTLC1 mutation: c.992G->T; p.S331Y (heterozygous).

Patient 3 (38 years old. Mother of patient 2): clinical manifestations similar to patient 2, progressive weakness, respiratory failure, loss of gait at 20 years of age.

In next months we will start oral treatment with L – Serine in patient 2 and 3.

Comments: According to the mutation, the phenotypic spectrum of SPTLC1 is variable. The treatment with oral L serine should be considered to modify the natural history of the disease.

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Independent Living in Myotonic Dystrophy Type 1 Childhood Phenotype: A Three-Year Follow-Up Exploratory Study

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DM1 is the most frequent inherited neuromuscular disease. It is a multisystemic disease, meaning that in addition to the muscular involvement (myotonia, muscular weakness), there are also impairments in cardiac, respiratory, endocrine, ocular, skeletal and central nervous systems. DM1 is usually classified into five phenotypes. The childhood phenotype involves an earlier and more severe involvement of the central nervous system including intellectual and executive functions impairments. The later in conjunction with motor impairments can further compromise their ability to live independently. Indeed, a more severe clinical profile is observed than the more common adult phenotype. However, research reports result only during the childhood period. It is crucial to inform parents of affected children on their future ability to perform instrumental activities of daily living (IADLs) necessary for independent living. Therefore, an exploratory study was conducted

among 11 individuals in order to document their competence in IADLs (T1). Eight of these participants were also assessed 3 years later (T2).

The Independent Living Scale (ILS) was used as an outcome measure in this study: it requires the participant to do problem solving, to demonstrate knowledge or to perform a task regarding specific IADLs. The ILS is comprised of five subscales: money management, home management & transportation, health & safety activities, memory/orientation and social adjustment. The first three categories are considered IADLs.

Important difficulties were found in all three IADLs at both times. At T1, 8/11 participants were dependent for money management and 6/11 were semi-independent concerning home management & transportation. In regard to health & safety, 5/11 participants were independent, and 5/11 were dependent. At T2, 7/8 participants were dependent in money management, and the last one was semi-independent. Regarding health & safety, 3/8 were dependent and 4/8 were semi-independent. In the total scores, at T1, 5/11 participants were dependent, 4/11 were semi-independent and 2/11 were independent. At T2, half of the participants were dependent and the other half semi-independent. Therefore, when looking at the data overall, the scores seem to decrease between T1 and T2 which indicates a potential decline in IADLs competence.

These results demonstrate the importance of guiding DM1 patients with the childhood phenotype through the continuum of services available from their young age to their adult life. It also exposes a more detailed portrait of the progression of the difficulties caused by the disease and its influence of IADLs. This exploratory study is still ongoing with a larger cohort to further explore and understand difficulties experienced by this population.

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Spanish Family with Scapulo-Peroneal Myopathy Due to HNRNPDL Mutation: The First European Family

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Introduction: LGMD D3 is a rare genetic disease caused by mutations in HNRNPDL. There are only five unrelated families described with this inherited condition: four South American families with European ancestors, and one Chinese family. We describe the first European family with HNRNPDL related muscle dystrophy.
Methods: The index patient was a 70-year-old female with a late-onset scapulo-peroneal weakness and scapular winging. Her 67-years-old paternal cousin had a more severe late-onset scapulo-peroneal and distal weakness predominantly affecting flexor muscles of fingers. They had a family history with an autosomal dominant inheritance. They also had two relatives with cognitive impairment, one of them also affected with myopathy.
Results: CK levels were mildly increased. Electromyography presented myopathic features. Muscle MRI of the index patient showed a involvement of quadriceps, tibialis anterior and medial gastrocnemius with focus of brightness in STIR sequences, while her cousin had a more widespread involvement. Muscle biopsy showed myopathic changes with atrophic angulated fibers and rimmed vacuoles with abundant inclusion bodies. Sanger sequence of VCP and other multisystem proteinopathy genes were normal. A NGS study with a self-custom panel yielded a pathogenic missense mutation in codon 378 of HNRNPDL gene, already described in an Uruguayan family.
Conclusions: We present the first European family with HNRNPDL related muscle dystrophy. Our data support a particular phenotypic profile that differentiate HNRNPDL from others dominant hereditary IBM. Further information will be needed to study association between HNRNPDL mutation and cognitive impairment, as already described in other ribonucleoproteinopathies.

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Intrafamilial Phenotypic Variability and Dysmorphisms in Charcot-Marie-Tooth Disease Type 4F

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Introduction: Charcot-Marie-Tooth disease (CMT) is the most common group of inherited neuropathies.

CMT type 4F is a demyelinating, autosomal recessive form of CMT, caused by biallelic mutations in the PRX gene. This gene codes for periaxin, a protein that is essential for the maintenance of the myelin sheath.

Objectives: To describe the clinical and electrophysiological findings of a Brazilian family affected by CMT type 4F.

Case report: Three patients from the same family were admitted to our clinic with complaints of gait difficulty and foot deformities. Two were siblings of consanguineous parents, a 19-year-old male (Patient V-5) and a 15-year-old girl (patient V-6). The third patient (V-2) was a 13-year-old girl, the youngest daughter of another consanguineous marriage within the same family, and cousin of patients V-5 and V-6. There was no history of pregnancy or neonatal complications. The subjects all showed normal cognitive development but had delayed motor milestones and walked independently by the second year of age. They complained of foot deformities, frequent falls and progressive gait instability. Currently, subjects V-2 and V-5 walk independently but are unable to run and subject V-6 is confined to a wheelchair. Subject V-6 also suffers from dysphagia and has difficulty in writing. On physical examination, all subjects had pes cavus and mild distal muscle wasting. Patient V-5 also showed dysmorphic facial features, with orbital hypertelorism and low-set ears, patient V-6 suffered from scoliosis and brachymetatarsia and patient V-2 had mild cataracts. On neurological examination, all patients showed decreased deep tendon reflexes, mild distal weakness, flexor plantar responses, mild hypoesthesia in distal lower limbs and moderate to severe loss of vibration sense in lower and upper limbs, with sensory ataxia and, in patient V-6, pseudoathetosis in upper limbs. A diagnostic workup for acquired neuropathies, including vitamin B12 levels, was normal in all three patients. Electrodiagnostic studies in all three patients revealed a sensorimotor demyelinating polyneuropathy. Molecular diagnosis (genetic panel for hereditary neuropathies) showed a homozygous point mutation in exon 7 of the PRX gene (c.3198del; p.Phe1066Leufs*61), previously described as pathogenic, in all three patients.

Discussion: Mutations in the PRX gene are associated with CMT type 4F and Dejerine-Sottas syndrome. We describe three patients from the same family with a predominately sensory demyelinating peripheral neuropathy. These findings are compatible with the clinical phenotype of CMT type 4F, in which sensory neuropathy with sensory ataxia predominates over motor symptoms. Another interesting finding is the variability in severity between members of the same family. Furthermore, two individuals presented with dysmorphisms, one with orbital hypertelorism and low-set ears, and the other with brachymetatarsia. To our knowledge, dysmorphisms have not been previously described in CMT type 4F patients and this finding may expand the disease's phenotype.

Conclusion: We described three illustrative cases of CMT type 4F, focusing on the clinical variability and the findings of dysmorphisms related to a mutation in the PRX gene.

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Congenital Hypomyelination Neuropathy: A Case Report

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Introduction: Congenital hypomyelination neuropathy (CHN) is a severe inherited neuropathy with neonatal or early infancy onset, reduced nerve conduction velocity and pathological evidence of hypomyelination. Mutations in several genes encoding for proteins involved in peripheral nerve myelination (MPZ, PMP22, EGR2, MTMR2, SOX10) have been described. De novo mutations in the MPZ gene are the most frequent cause.

Case report: We describe a case of a 5-year old girl, second daughter of healthy non-consanguineous parents, who was born after an uneventful pregnancy. At birth Apgar Score were 10 after 1 and 5 minutes and physical examination was normal. From 6 months of age, she presented with episodes of apnea, hypotonia, sialorrhea and sudden pallor begin, causing multiple hospitalizations complicated by repeated aspiration

pneumonia. It evolved with the need for NIV at night and for long periods during the day. On clinical exam at 6 months she had: cephalic tremor and pendulum horizontal-rotational nystagmus; marked hyperlaxity, poor muscle mass, myotactic areflexia and dorsal dextro-convex scoliosis. Normal studies included: brain MRI, CK, aldolase, aminoacids, organic acids, redox potential and alpha-galactosidase assay. EMG documented very small amplitude responses with long latency delay, abundant fibrillation. The diagnosis of severe congenital hypomyelinating neuropathy was admitted. The initial genetic study of the MPZ and EGR2 genes was considered negative. Subsequently, a panel of hereditary motor-sensory neuropathies genes was requested and revealed, by in silico evaluation, a variant of the MPZ gene (p.G123G), variant of uncertain significance possibly affecting protein splicing (mutation not found in the parents). Clinically, the patient evolved with severe distal predominance of tetraparesis, with distal grade 1 and proximal grade 2 muscle strength. There was a progressive improvement in the respiratory condition, with a reduction in the number of apneas, although maintaining dependence on NIV during sleep.

Conclusions: We report a case of severe hereditary sensitive-motor neuropathy with early onset, whose genetic study of the MPZ gene was initially considered normal. In this case, we emphasize the importance of carrying out the genetic panel in the detection of MPZ mutations and highlight that in patients with hypotonia in the first months that develop a very severe demyelinating neuropathy, the MPZ gene must be taken into account.

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Selection of a Clinical Outcome for Assessing Dysphagia Severity in OPMD

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Introduction: Oculopharyngeal muscular dystrophy (OPMD) is a late-onset muscle disease characterized by ptosis, progressive dysphagia, and limb weakness. Dysphagia is described as the most disabling symptom. Among outcome measures available for dysphagia, the 80 mL-drinking test is a test that have been used in two recent clinical trials related to OPMD. Patient-reported outcome (PRO) measures, such as the Swallowing Quality of Life questionnaire (SWAL-QOL) and the Sydney Swallow Questionnaire (SSQ), have also been used in clinical trials or other interventional study design. Evidence suggests that little attention has been given to the selection of outcomes measures for dysphagia in chronic, progressive muscle disease, such as OPMD. The purpose of this study was to investigate the relationship between PRO questionnaires and the 80 mL-drinking test and their ability to discriminate based on dysphagia severity.

Method: SWAL-QOL, SSQ and the 80 mL-drinking test were administered to 21 participants, stratified by age (50-70 years) and sex. The 80 mL-drinking test was performed twice and we took the mean of two trials. A standard operating procedure (SOP) was developed and validated by an expert panel composed of researchers and clinicians who had worked with OPMD patients. The SWAL-QOL consists of 10 scales that assess dysphagia-related quality of life and a 14-item symptom-frequency scale that assess the frequency of oropharyngeal symptoms. The 10 scales are: food selection, burden, mental health, social functioning, fear, eating duration, eating desire, communication, sleep and fatigue. A total SWAL-QOL score was derived by averaging the 10 scale scores. The Sydney Swallow Questionnaire (SSQ) is a 17-item questionnaire intended to assess the severity of dysphagia. The 80-mL drinking test consists in recording the time to swallow 80 mL of water. Descriptive statistics were used to report the total scores and each score of the 10 SWAL-QOL scales. Spearman correlations were calculated between the scores of the PRO questionnaires and the 80-mL drinking test. The Mann-Whitney test was used to compare groups based on dysphagia severity as assessed by the 80 mL-drinking test; a cut-off score of 8 seconds was used.

Results: Results indicated moderate dysphagia; a lower score was found for eating duration and burden SWAL-QOL scales. The drinking test was correlated with the SSQ (0,54, $p<0,05$) and the eating duration scale (-0,59, $p<0,01$), but not with the SWAL-QOL total score or the symptom-frequency scale (-0,33 and -0,12, non-significant). The SSQ can discriminate between two groups of OPMD individuals known to differ on dysphagia severity ($p<0,05$), as assessed by the 80 mL-drinking test, but not the SWAL-QOL (non-significant).

Conclusion: SSQ is better at discriminating for dysphagia severity than the SWAL-QOL, especially in case of small sample size. Symptom frequency may

not reflect dysphagia severity in OPMD; further research is needed to confirm this hypothesis.

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Long-Term Impact of Inotersen on Neuropathy-Related Quality of Life for Transthyretin Amyloidosis with Polyneuropathy

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Background: A randomized, controlled phase 3 trial (NEURO-TTR) of patients with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN) evaluated the efficacy of inotersen on neuropathic-specific quality of life (QOL), as measured by the Norfolk QOL-Diabetic Neuropathy (DN) survey. At 66 weeks of the trial's randomized phase, patients receiving inotersen experienced statistically significant improvements from baseline, relative to placebo, in total score and several domains of the Norfolk QOL-DN. In the NEURO-TTR open-label extension (OLE) phase, all patients received inotersen. The Norfolk QOL-DN was assessed with data available for two years of OLE.
Objective: To examine changes in Norfolk QOL-DN domain scores for patients with hATTR-PN treated with inotersen for two years in the NEURO-TTR OLE phase.
Methods: The NEURO-TTR OLE phase enrolled 135 (of 139) randomized-phase completers who received inotersen (inotersen-inotersen; n=85) or placebo (placebo-inotersen; n=50) during the randomized phase. In the OLE phase, all patients received 300 mg inotersen once-weekly. The Norfolk QOL-DN, which captures neuropathic-specific QOL on five domains – activities of daily living (ADL; score range: 0 to 20), autonomic neuropathy (0 to 12), large fiber neuropathy/physical functioning (-4 to 56), small fiber neuropathy (0 to 16), and symptoms (0 to 32), with higher scores indicating worse QOL. The Norfolk QOL-DN was administered at OLE baseline and weeks 26, 78, and 104. Descriptive analyses examined observed mean Norfolk QOL-DN domain scores during the OLE phase for inotersen-inotersen and placebo-inotersen subgroups.
Results: For both subgroups, Norfolk QOL-DN domain scores from OLE baseline to week 104 were stable, with relatively small mean changes for inotersen-inotersen and placebo-inotersen subgroups for ADL (mean changes = 2.0, 2.3 points, respectively), autonomic neuropathy (0.3, 0.1), large fiber neuropathy (2.1, 1.5), small fiber neuropathy (0.2, 1.2), and symptoms domains (0.4, -0.5). Further, subgroup differences were similar at OLE baseline and week 104: the mean difference for the inotersen-inotersen and placebo-inotersen subgroups was 2.2 at OLE baseline vs. 2.4 at week 104 for ADL, 0.7 vs. 0.5 for autonomic neuropathy, 7.2 vs. 6.6 for large fiber neuropathy, -0.3 vs. 0.8 for small fiber neuropathy, and 2.5 vs. 1.6 for symptoms, indicating that the gaps between inotersen and placebo arms observed at the end of the randomized phase were sustained even after the placebo-inotersen subgroup received inotersen for two years.
Conclusions: Treatment with inotersen stabilized neuropathic-specific QOL for patients with hATTR-PN over two years, regardless of previous inotersen treatment status. The gaps in QOL between those receiving inotersen versus placebo during the randomized phase did not close over the OLE phase, indicating the importance of early treatment for maintaining QOL in these patients.

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Dysphagia-Related Symptoms in OPMD: A Multimodal Recruitment Strategy to Increase Representativeness

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Introduction: Oculopharyngeal muscular dystrophy is a late-onset muscle disease characterized by ptosis, progressive dysphagia, and limb weakness. Dysphagia is described as the most disabling symptom. The mean age of onset of dysphagia is 50 years. Dysphagia-related symptoms have been partially explored in OPMD by using semi-quantitative measures, patient-reported outcomes, qualitative

interviews and expert consultation. The purpose of this study was to document the presence of those symptoms in relation with dysphagia duration.

Methodology: A mixed sampling recruitment strategy was used to send an online questionnaire to individuals with OPMD. Participants were recruited through the clinical registry of a Neuromuscular Clinic and a Facebook Group. Participants had to be 40 years and older, have a genetic confirmation of OPMD and be able to provide informed consent. They were excluded if they had a second condition that may cause dysphagia. The questionnaire was developed following a qualitative study that was carried out to explore patients' perceptions of their dysphagia-related symptoms. Questions were derived from patients verbatim and submitted to two patients for pilot testing. The final questionnaire included Likert type questions and few open-ended questions about the manifestation of the symptoms, the use of coping strategies, and the impact on mealtime experience. Descriptive statistics were used to summarize the data and a linear-by-linear association test was used to determine the distribution differences between the questionnaire items and dysphagia duration.

Results: 55 participants answered the questionnaire within a 2-weeks period. The representativeness of the sample was extensive, including several states in the U.S. and 6 countries. The most frequent symptoms were: having to swallow again, feeling of food going down slowly, feeling of food that won't go down, sensation of food left in the throat and clearing of the throat. Stress, emotions and distraction make these problems worse. The most common strategies were: chewing thoroughly, taking small bites, cutting food into small pieces, drinking liquid after swallowing and adding sauce or combining foods. Coping strategies were more likely to be linearly associated with dysphagia duration. Strategies varied depending on food type. Impacts on mealtime experience included: to finish eating last, can't talk while eating, meal getting cold, eating smaller servings and avoidance of foods they like; all were linearly associated with dysphagia duration.

Conclusion: Frequency of symptoms is likely to increase with dysphagia duration, but symptoms highly depend on food type and coping strategies, and may change under circumstances. Future studies are needed to document whether swallowing difficulties depending on food type may better reflect the severity of dysphagia than symptom frequency.

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Clinical Characterization of Six Spanish Patients with Congenital Titinopathy

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Introduction: TTN mutations cause a range of skeletal muscle and cardiac diseases, or a combination of both, collectively termed titinopathies. The term "congenital titinopathy" has recently been proposed to designate a continuum of recessive prenatal or infant onset forms of titinopathies that previously were described as different phenotypes (early-onset myopathy with fatal cardiomyopathy, congenital centronuclear myopathy, core myopathy with heart disease, arthrogryposis multiplex congenita with myopathy).

Methods: The study subjects were recruited retrospectively from the database of our neuromuscular clinic. We reviewed the clinical, serological, myopathological, radiological and molecular findings.

Results: We identified six patients, from four unrelated families, with congenital titinopathy, four females and two males.

All patients were homozygous or compound heterozygous in trans for TTN variants. Two patients were compound heterozygous for two truncating mutations. Four patients were compound heterozygous for one truncating mutation and one missense mutation.

The median age was 39.5 years (range 14 - 64 years). The onset was congenital in the six patients. All patients were able to walk. In 3/6 patients, limb weakness was predominantly proximal and affected both upper and lower limbs. 3/6 patients had a scapuloperoneal distribution of weakness. Weakness was symmetrical in all cases. The course was

stable in 5/6 patients, while one patient had a slowly progressive loss of limb strength.

No patient had ophthalmoplegia or ptosis. Facial weakness and high-arched palate were each present in 3/6 patients. Swallowing difficulties affected 2/6 patients, although no one required supplemental nasogastric tube or gastrostomy feeding. Neck flexion weakness was present in all patients. 5/6 patients had axial weakness.

4/6 patients had limb contractures. Scoliosis was present in one patient. One patient had chest wall deformity (pectum carinatum). Joint hypermobility was present in 3/6 patients. 2/6 patients required surgeries related to the disease.

3/6 patients had cardiac pathology: two had dilated cardiomyopathy (one of them fulfilling non-compaction criteria) and one patient had hypokinetic non-dilated cardiomyopathy. All patients with cardiomyopathy were carriers of a truncating mutation in TTN that affects the A-band. 3/6 patients suffered respiratory insufficiency, with nocturnal hypoventilation and required nocturnal mechanical ventilation with BiPAP. Two of them, had frequent respiratory infections.

CK levels were normal in 4/6 patients and mildly elevated (200-400 U/l) in two patients. Lower limb MRI findings were available for the six cases. The most prominent affected muscles were hamstring muscles in thighs, and soleus in legs. Gluteal muscles, gastrocnemius and tibialis anterior were variably involved.

5/6 patients had undergone a muscle biopsy. All of them were abnormal. Increased fiber size variation was found in 3/5, increased internalized nuclei in 3/5, cores in 4/5 (multiminicores were more common than centrally placed cores) and fiber type disproportion in 3/5.

Conclusions: A congenital titinopathy should be suspected in patients with a congenital myopathy, without ophthalmoplegia, in whom the presence of joint contractures, cardiac and respiratory involvement are possible. Muscle biopsies of these patients show mixed histopathological findings, with fiber size variation, cores, internalized nuclei and fiber type disproportion, either alone, or in combination.

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Inotersen Delays Impairments in Functioning and Daily Activities for Three Years in Hereditary Transthyretin Amyloidosis

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Background: A randomized, controlled phase 3 trial (NEURO-TTR) of patients with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN) evaluated efficacy of inotersen on neuropathic-specific quality of life, as measured by the Norfolk QOL-Diabetic Neuropathy (DN) survey. After the 66 week randomized phase, completers could enroll in the NEURO-TTR open-label extension (OLE) phase for continued inotersen treatment. The Norfolk QOL-DN was assessed with data available at Week 104 of the OLE phase, or 170 weeks (3.3 years) after the randomized-phase baseline.

Objective: To examine changes in polyneuropathy symptoms and impairment of daily activities and functioning, as captured by responses to selected items on the Norfolk QOL-DN, for patients with hATTR-PN treated with inotersen for over 3 years during the NEURO-TTR randomized and OLE phases.

Methods: Eighty-five patients with hATTR-PN who received inotersen during the 66-week NEURO-TTR randomized phase were enrolled in the OLE phase, with Norfolk QOL-DN data available at 104 weeks. Patients received 300 mg inotersen once weekly in each phase. Items analyzed were within the following Norfolk QOL-DN domains: activities of daily living (ADL; e.g., 'difficulty dressing', 'difficulty using eating utensils'), autonomic neuropathy (e.g., 'diarrhea', 'fainting/dizziness'), large fiber neuropathy/physical functioning (PF; e.g., 'pain kept you awake at night', 'symptoms prevented usual activities', 'difficulty walking'), and small fiber

neuropathy (e.g., 'unable to feel feet when walking', 'unable to tell hot from cold water [hands/feet]'). Response choices for all items captured 'severe', 'moderate', 'mild', 'very mild', or 'no' problem; 'severe' or 'moderate' were classified as substantial impairment. For each of 18 items, descriptive analysis compared changes in the prevalence of substantial impairment between randomized-phase baseline and Week 104 of the OLE phase (170 weeks total). Positive percentage point changes represented increased prevalence.

Results: Changes in the prevalence of substantial impairments (in percentage points) between randomized-phase baseline and Week 104 of the OLE phase were quite small. The change in prevalence ranged from -1.9% to 11.5% for ADL items, -4.5% to 0.1% for autonomic neuropathy items, -3.3% to 10.1% for large fiber/PF neuropathy items, and -7.1% to 3.7% for small fiber neuropathy items. The prevalence in substantial impairments increased by more than 10 percentage points for only two items: 'symptoms prevented usual activities' (10.1%) and 'difficulty getting on/off the toilet' (11.5%).

Conclusions: Very few patients with hATTR-PN receiving continuous treatment with inotersen developed substantial impairments in any of the 18 assessed daily activities or function items over the course of 3 years. Long-term treatment with inotersen is thus associated with preservation of functioning and ability to carry out activities of daily living.

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Atypical Case of Adult Onset Central Core Myopathy with Potential Novel Mutation in RYR1 Gene

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Myopathies due to mutations in the skeletal muscle ryanodine receptor (RYR1) gene are amongst the most common non-dystrophic neuromuscular disorders and have been associated with both dominant and recessive inheritance. The RYR1 receptor Ca++ release channels are responsible for intracellular Ca++ release from the sarcoplasmic reticulum (SR) initiating muscle contraction. All patients with core myopathies, regardless of mutation, are at high risk for malignant hyperthermia.

We report a 55 year old male who has developed slowly progressive non-fluctuating ptosis in his mid-forties with no diplopia. About 6 years prior, he noticed difficulty with swallowing and difficulty rising on his toes. His father and two sisters also had ptosis at similar age. His three sons have no reported weakness, but two of them who have been examined have hyper-CKemia.

Neurological examination demonstrated significant bilateral ptosis, ophthalmoparesis, nasal speech, and bifacial diplegia with weakness of plantar flexion bilaterally. Serum CK levels have been persistently elevated above 2000 (N < 220 iU/L). EMG showed signs of muscle irritability and myopathic features. Spirometry testing demonstrated a mild restrictive ventilatory defect (FVC = 3.09 L (68% predicted); FEV1 = 2.5 L (73%predicted).

A 91 gene custom next generation sequencing (NGS) panel demonstrated two single nucleotide variants of unknown significance in RYR1 gene (heterozygous, c.10097G>A p.Arg3366His and heterozygous,c.11798A>G p.Tyr3933Cys) expected to be in the cis position based on population data. Deletion and duplication analysis was negative. Muscle biopsy demonstrated clearly demarcated cores devoid of histochemical staining for cytochrome c oxidase and succinate dehydrogenase. Electron microscopy demonstrated central myofibrillar disruption consistent with central core myopathy.

Summary/Conclusion: Recent advances in NGS methods, which include the entire RYR1 coding sequence rather than being restricted to hotspot regions, are contributing to the expansion of the RYR1-related myopathies disease spectrum and allowing for identification of potential novel mutations.

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A Novel Mutation in Mitochondrial Complex IV Causes Ataxia-Neuropathy - Proof of Pathogenicity

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The ataxia-neuropathy spectrum covers a large clinical and pathogenic variety of acquired and hereditary diseases, including the hereditary disorders of

mitochondrial function. These may be caused by mutations in either mitochondrial DNA (mtDNA) or in nuclear genes encoding proteins involved in the replication or maintenance of mtDNA. In mitochondrial diseases, the ataxia usually occurs in combination with other features, including epilepsy, cognitive decline and polyneuropathy. Although mutations in POLG have been recognized as the commonest cause of mitochondrial ataxia-neuropathy, a considerable proportion of patients do not have POLG-deficiency, but harbour mutations in other nuclear genes (TWNK, ARS) or mtDNA genes (MELAS, MERRF, NARP).

A 43-year-old patient developed progressive ataxia, neuropathy, cognitive impairment and sensorineural deafness at the age of 25. Pathogenic mutations in SCA 1,2,3, 6, 17, Cx26, PMP-22, POLG, as well as the common mutations in mtDNA associated with MELAS, MERRF, and NARP were excluded. A muscle biopsy showed some ragged-red and COX-negative fibres despite the absence of clinically evident myopathy. Biochemical measurement of mitochondrial respiratory chain activity was performed in muscle from the patient. Complex-IV activity were reduced by 50% in muscle from the patient, and sequencing of the patient's mtDNA revealed a novel heteroplasmic mutation in MTCOII, a subunit of cytochrome oxidase. Using the established canonical criteria (Mitchell, JMG 2006) for assigning pathogenicity to an mtDNA mutation, the mutation was regarded to be likely pathogenic. The pathogenicityof the mutation was eventually confirmed following the generation of transmitochondrial cybrids, using cultured fibroblasts from the patient.

Only a small number of patients with a mutation in MTCOII have been described, the majority of whom presented in childhood with myopathy. In contrast, our patient did not manifest a myopathy, and presented in adulthood. Regular clinical re-evaluation over several years showed a relentlessly progressive deterioration.

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Human IgG Administration Improves Heart and Muscle Function in a Model of Duchenne Muscular Dystrophy

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Background: Duchenne muscular dystrophy (DMD) is the most common, X-chromosomal inherited muscle disorder in boys, which lead to loss of ambulation, cardiac and respiratory failure and death in young adulthood. The cause of DMD is a mutation in the dystrophin gene with consequent absent or faulty production of the homonymous protein. This results in structural instability of the dystrophin-glycoprotein-complex and muscle degeneration. A newly synthesised dystrophin would cure DMD but the available dystrophin restoring therapies show a high variability in terms of efficiency and clinical benefit. Of note, the dystrophin expression generated an immune response in addition to the existing muscle inflammation for several of these therapies. So far, glucocorticosteroids are used as an anti-inflammatory treatment with the disadvantage of numerous side effects. We hypothesised that human Immunoglobulin G (IgG) is a well-tolerated and effective immunmodulatory alternative over a long-term treatment period in the mouse model of DMD (mdx). This is based on a previous study using mdx mice in the early phase of the disease, in which IgG was clinical effective (Zschüntzsch et al. 2016).
Methods: After a successful weaning phase, mdx mice were block randomized into two groups and placed in individual cages equipped with a running wheel at postnatal day 21. Two days later, IgG at 2g/kg bodyweight or NaCl as control were administered and repeated monthly by intraperitoneal injections over a duration of 18 months. Several clinical outcome measures, i.a. running wheel performance, grip strength and echocardiography were assessed as suggested by TREAT-NMD network. After 18 months, animals were sacrificed. Blood and muscle were sampled for ex vivo muscle contraction tests, quantitative PCR and histological analysis.
Results: In the present study, the continuous recorded voluntary running wheel performance demon-

strated that maximum running speed, number of daily runs, total daily time spent in the running wheel, and total daily running distance detoriated significantly slower during long-term course in the IgG group compared with NaCl controls. IgG better preserved maximum running speed by 0.0003 m/s per day, number of daily runs by 0.2 runs per day, total daily time in the running wheel by 5.2 s per day, and total daily running distance by 1.9 m per day (p values for all parameters were below 0.0001). Cardiac function, assessed three times during the study period, was significantly better under IgG, especially ejection fraction (p=0.027 across all three time-points) and left ventricular fractional area shortening (p=0.012 across all three time-points). In ex vivo contraction tests, diaphragm segments of IgG-treated animals were less susceptible to fatigue (improved ratio to maximum force by 0.086 ± 0.038, p=0.044). The inflammation and myopathic changes in heart, diaphragm and skeletal muscle were also ameliorated.

Conclusion: Our study provided evidence of long-term clinical and paraclinical efficacy of IgG in a mouse model of DMD. Human IgG is well tolerated by humans and may be an immunmodulatory therapeutic partner for dystrophin restoring therapies. A reasonable next step would be a clinical trial of IgG in patients with DMD.

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A Novel Model to Investigate Hereditary Myopathies

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Diseases that cause dysfunctions of nerves or muscles are classified under the umbrella-term neuromuscular diseases. To date, most neuromuscular disease do not have curative treatments and can lead to pain, morbidity, and decreased quality of life. This gives precedence for understanding the underlying biology of the different neuromuscular diseases. Myopathies are a subtype of neuromuscular disease that manifests as muscle weakness due to the abnormal function of muscle fibers. The current models developed to investigate such myopathies are not reliable due to a significant lack in the recapitulation of key features from the human pathology. We will characterize a novel model to investigate the pathology of myopathies by utilizing human fibroblasts that have been reprogrammed to induced pluripotent stem cells (iPSCs). The iPSCs subsequently are differentiated into skeletal muscle cells by a three stage process that mimics standard myogenic progression. For characterization of this model, iPSCs-derived from healthy controls and patients with either alpha-actin (ACTA1)-congenital nemaline myopathy or UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase (GNE) myopathy will be used. These hereditary myopathies both result in severe disabilities as the disease progresses and have no effective treatments. The overarching goal is to establish a model that will reliably recapitulate key features of the human disease and can be applied to many different subtypes of myopathy. It will subsequently be used to elucidate unique molecular signatures that are involved in the manifestation of the diseases and allow for the development of novel therapeutic treatments for improvement of patient quality of life.

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Muscle Fatigue in Adult SMA Patients in Evaluating the Outcome to Treatment

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Primary outcome measures of choice in current clinical trials in SMA are motor function scales (Hammersmith Functional Motor Scale- Expanded, Motor Function Measure, 6 minutes walking test). Fatigability has emerged as an important dimension of physical impairment in patients with SMA. Fatigability is experienced by patients with SMA as the inability to perform prolonged repetitive tasks during activities of daily life. Since outcome measures sensitive to change in fatigability are lacking, their development is a pivotal step in a better understanding

of fatigability in SMA. Here we propose new functional scale divided into several items to evaluate different body areas according to the patient's motor abilities. In particular, for the Upper limb proximal: a) Endurance in keeping up a weight: The patient in a sitting position must keep his arm extended parallel to the floor and holding a weight in his hand for as long as he can up to a maximum of 3 minutes; b) Exhaustible exercise of proximal upper limb with repetitive tasks: Ask the patient to abduct the upper limbs to the maximum of their possibilities and to repeat the exercise as quickly as possible, until the onset of fatigue, in a minute. Calculate the number of times the patient repeats the item and the time elapsed from the beginning to the end of the exercise. For Upper limb distal: c) HandGrip endurance with repetitive maximal isometric contraction: The subject grippes the handle as hard as possible for 2.5 seconds and then rested for 1 second, repeating this sequence for 3 minutes. Both hands will be tested, and a rest of about 3 minutes will be given between tests; e) Repeated nine-hole peg test (r9HPT); f) Open and close hands with the elbows resting on the table as quickly as possible, until fatigue occurs in one minute; g) Digital dexterity repetitive test: number of times the patient must sequentially touch the individual fingers with the thumb of the same hand, back and forth, as fast as possible until fatigue occurs in one minute. For Lower limb proximal: h) TUG test: it measures the time it takes an individual to stand up from a chair, walk 3 meters, turn around, and sit down in the same chair. The test is repeated for five times, with an interval rest period of 30 seconds between each session.

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Liver or Muscle – CK/Transaminase Ratio in a Cohort of Patients with Muscular Dystrophy

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Introduction: Elevation of transaminases is common in patients with muscular dystrophies, and distinguishing the muscular from the hepatic origin can be challenging. Patients can be therefore put through unnesassary tests or the hepatopathy can be missed. Testing of gammaglutamyltransferase (GGT) can be helpful, as this this enzyme is not found in the muscle, but is not always sufficient. Recently there have been effords to explore the correlation between creatinkinase (CK) and „liver" transaminases (ALT, AST), where a linear correlation was found in mouse models of and patients with Duchenne muscular dystrophy and in patients with acute rhabdomyolysis and dermatomyositis.

Aim: To explore the correlation between creatinkinase (CK) and traditional liver enzymes (ALT, AST, GGT) in a cohort of patients with muscular dystrophies with no known liver pathology followed in our neuromuscular centre.

Methods: We retrospectively analysed blood samples from patients with Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD) and symptomatic carriers of BDMD followed in our hospital. All tests were done in the same laboratory and the values of CK, myoglobin, ALT, AST, GGT and bilirubin were recorded and statistically analysed using linear regression analysis. Patients with known hepatic disease, abnormal GGT or bilirubin or those taking hepatotoxic drugs were excluded.

Results: There were 33 paediatric patients with DMD and 19 adult symptomatic carriers of BDMD or patients with BMD analysed. One patient was excluded for history of hepatic steatosis, one for elevation of GGT. There was a positive linear correlation between CK and ALT (F test, $p<0,001$ for both DMD and BMD/carriers) and CK and AST (F test, $p<0,001$ for both groups). There was no correlation between CK and GGT in BMD/carriers group (F test, $p=0,49$), surprisingly there was a negative correlation between CK and GGT in DMD cohort (F test, $p<0,001$). Both CK/ALT and CK/GGT ratios were slightly higher in pedal DMD patients (respective values of median (M) 44,4, interquartile range (IR) 29,2-57,7; and M 2568,0, IR 788,6-3402,4) then in apedal DMD patients (M 25,8, IR 13,4-36,3; and M 130,9, IR 62,6 – 1037,9) and in BMD/carrier group (M 22,8, IR 12,6-25,9; and M 65,05, IR 14,4-116,2).

Conclusion: There was a positive linear correlation CK-ALT and CK-AST in a cohort of patients with muscular dystrophy. There was no linear correlation CK-GGT in BMD/carrier group and a negative linear correlation CK-GGT in DMD.

Discussion: The results suggest that the CK/ALT and CK/AST ratios could be promising tools to help distinguish the hepatic from muscular origin of transaminases in dystrophinopathies. The detected negative correlation CK-GGT in DMD could be

caused by the arteficial elevation of GGT by corticosteroid treatment or possibly by elevation of GGT associated with methabolic syndrom or cardiomyopathy that both tend to apear in later stages of DMD when CK decreases. More research is needed to elucidate this finding.

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Case Presentation- Phenotypical Differences in Two Patients with Novel DYNC1H1 Mutations

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Objective: To present the cases and phenotypical differences of two patients with confirmed heterozygous mutations in the dynein, cytoplasmic 1, heavy chain 1 (DYNC1H1) gene. One patient developed spinal muscular atrophy with lower limb dominance (SMALED) and the other has a phenotype consisting of developmental delay and perisylvian polymicrogyria. Both have mutations in DYNC1H1 not previously described.

Background: DYNC1H1 is located on chromosome 14p32 with 78 exons encoding the heavy chain protein of the cytoplasmic dynein 1 motor protein complex, known to play a key role in retrograde axonal transport in neurons. The phenotypes associated with autosomal dominant mutations include intellectual disabilities, cortical malformations, hereditary spastic paraplegia and autosomal dominant spinal muscular atrophy.

Case One: A 16-year old male presented aged 4 years with gross motor difficulties consisting of frequent falls, motor dyspraxia and intermittent tremor. This followed an uneventful pregnancy and perinatal period, other than mildly reduced foetal movements. Examination at 8 years of age demonstrated weak hip flexion and knee extension with normal deep tendon reflexes. Upper limb examination was normal. Right tibialis anterior and vastus medialis electromyography demonstrated long duration motor unit potentials and reduced interference patterns, more markedly reduced in the proximal muscle, suggesting anterior horn cell disease. There were no fibrillation potentials and normal sensory changes. Initial genetic testing of the SMN1 gene was negative.

Examination of his father revealed absent reflexes in the lower limbs, with electromyography demonstrating proximal muscle pathology with A-waves in the tibialis anterior. Analysis of the DYNC1H1 gene in the patient identified a heterozygous change at c.1687C>G (p.Arg563Gly), not identified in either parent.

Case Two: A term male patient presented at birth with arthrogryposis, left tibial and femoral fractures, unilateral undescended testes and stridor with bilateral vocal cord immobility. He developed dislocation of the hips and on examination at 8 months had weakness (MRC power 2/5), hypotonia, areflexia and contractures in the lower limbs; axial weakness and a high-arched palate. MRI brain revealed bilateral perisylvian polymicrogyria. Electromyography at 13 months showed chronic neurogenic changes in left glossus and left tibialis anterior compatible with a motor neuronopathy.

Given the perisylvian polymicrogyria a cortical brain malformation panel was requested, identifying changes in three genes: LAMA2, WDR62 and DYNC1H1. The heterozygous LAMA2 and heterozygous WDR62 mutations were found in his mother and father respectively and were not thought to be pathogenic. A de novo heterozygous mutation of the DYNC1H1 gene was found at c.3603G>T (p.Arg1201Ser).

Discussion: The clinical phenotypes of DYNC1H1 mutations are known to cause both central and peripheral neurological presentations. We report two different presentations that illustrate the phenotypic heterogeneity seen. One case presented with SMALED, although with normal lower limb reflexes, with a novel heterozygous de novo mutation, which adds to the expanding pathogenic variants known to cause this phenotype. Our second patient had a novel heterozygous mutation presenting with arthrogryposis at birth and was found to have a motor neuronopathy with an associated perisylvian polymicrogyria, reinforcing the association previously described between malformations of cortical development and peripheral neurological disease.

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Clinical Indicators of Hereditary Amyloid Transthyretin Amyloidosis with Polyneuropathy: Now a Treatable Disease

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Background: Hereditary amyloid transthyretin amyloidosis (hATTR) with polyneuropathy (PN) is a progressive and fatal disease caused by the deposition of misfolded transthyretin-derived amyloid fibrils in nerve, heart, and other tissues. Early diagnosis of this disease has become feasible and desirable now that efficacious treatments preventing disease worsening are becoming available. Here we describe neurologic and other clinical features of hATTR PN that should raise suspicion of this diagnosis and thus lead to early diagnosis and treatment.
Methods: Descriptive summary of three neurologists' clinical experience of diagnosing patients with hATTR PN.
Results: Because hATTR PN has become a treatable disease, this diagnosis must be emphasized in the evaluation and differential diagnosis of all cases with neuromuscular disease and especially patients with peripheral neuropathies. hATTR PN is sometimes mistaken for chronic inflammatory demyelinating polyneuropathy because both can exhibit rapid progression with weakness and elevated protein levels in cerebrospinal fluid. Only a high degree of suspicion and performing the necessary tests will lead to improvement in diagnosing hATTR PN and its treatment. From present evidence, we assume that early diagnosis and efficacious treatment will lead to prolongation of life and less severe symptoms and impairments. The following clinical features of neuropathy raise the likelihood of a hATTR PN diagnosis: (1) a family history of neuropathy; (2) neuropathy in genetic ancestry, eg, Japanese, Portuguese, and other ethnicities; (3) symptomatic neuropathic involvement beginning in the third or later decades of life; (4) functional involvement of motor, sensory, and autonomic nerve fibers and of both upper and lower limbs; (5) progressive worsening of symptoms and impairments over months or a few years; (6) bilateral carpal tunnel syndrome; (7) constitutional involvement with weight loss and other systemic symptoms; (8) no diseases such as diabetes mellitus, hypothyroidism, uremia, or other metabolic disease to explain the sensorimotor polyneuropathy; (9) lack of response to immunotherapy; and (10) evidence of cardiomyopathy or other internal organ failure which might be attributable to amyloidosis. Because of the availability of effective treatment, physicians must emphasize early and accurate diagnosis of hATTR PN; therefore, they must go to considerable lengths to make this diagnosis. For some patients, fat, skin, or even nerve biopsy may be justified to make the diagnosis. For some patients, MRI of the heart for amyloid infiltration may also be justified. Increasingly, adult patients with the features listed above should undergo molecular genetic testing to confirm diagnosis of hATTR PN and identify the amyloidogenic mutation.
Conclusions: Because hATTR PN is a rapidly progressive and fatal disease and antisense oligonucleotide treatments can inhibit or slow progression, such intervention ideally should be instituted early before severe impairments have developed. Most cases of PN should undergo a differential diagnosis for hATTR PN; herein, we list features that make the diagnosis more likely. Although clinical judgment should be used as to the need for diagnostic and genetic testing, increasing emphasis should be placed on their use in patients suspected of having hATTR PN because early detection and treatment can prevent worsening and perhaps even death.

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Patients with Mixed Phenotype Hereditary Transthyretin Amyloidosis: Insights from a Genetic Testing Program

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Background: Hereditary transthyretin (hATTR) amyloidosis is a progressive and fatal disease that results from the deposition of misfolded transthyretin (TTR) protein in major organs and systems, leading to multisystem dysfunction, including peripheral neuropathy, autonomic dysfunction, and cardiomyopathy. Patients with hATTR amyloidosis often experience symptoms of both cardiomyopathy (CM) and polyneuropathy (PN); this is referred to as a

mixed phenotype. The hATTR Compass Program offers anonymous, confidential genetic testing and counseling to patients in the United States, Canada, and Puerto Rico suspected of having hATTR amyloidosis with polyneuropathy or with a family history of hATTR amyloidosis. This real-world data analysis from the hATTR Compass Program aimed to determine prevalence and characteristics of patients with a mixed phenotype.

Methods: DNA samples were scanned for TTR mutations associated with hATTR amyloidosis using a single-gene test, a cardiomyopathy gene panel, or a polyneuropathy gene panel. Data from 165 patients with TTR mutations sequentially identified by the hATTR Compass Program were included in this analysis.

Results: Seventy (42.4%) patients with a mutation consistent with hATTR amyloidosis had both PN and CM symptoms. Patients with a mixed phenotype had an average age of 70 years (range, 29–87 years), and the majority were male (57.1%). Most patients with a mixed phenotype were African American (n=54; 77.1%). Ten patients (14.3%) had a known family history of hATTR amyloidosis, 49 (70.0%) had no known family history, and 11 (15.7%) did not know. Most patients with a mixed phenotype had the p.V142I/V122I mutation (n=62; 88.6%), while 4 (5.7%) had p.T80A/T60A, 2 (2.9%) had p.S97F/S77F, 1 (1.4%) had p.V50M/V30M, and 1 (1.4%) had p.H108R/H88R. Patients with mixed phenotype were identified from referrals by cardiologists – 57 patients (81%), cardiovascular clinic teams (physician assistants and nurse practitioners working with an attending physician) - 6 patients (9%), and other (non-cardiology) specialties - 7 (10%) patients. Patients with a mixed phenotype presented with a variety of symptoms including sensory, motor, and autonomic dysfunction, alongside gastrointestinal dysfunction, heart disease, and bilateral carpal tunnel syndrome. Note that symptoms reported may be underrepresented because of limitations of data collection and program participation.

Conclusion: Diagnosis of hATTR amyloidosis is challenging, but recognition of its symptoms and subsequent genetic testing through the hATTR Compass Program can facilitate diagnosis of this debilitating, fatal disease. This study demonstrates that the mixed phenotype is fairly common in patients with hATTR amyloidosis and, regardless of mutation, patients should be assessed for both PN and CM symptoms.

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New International Myositis Society: Guidance and Support for Diagnosis, Interdisciplinary Care and Research in Myositis

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Background: Myositis is a neuromuscular disorder that can affect the skeletal muscle, skin, lung, heart, and other organs. Its pathogenesis is complex, and the diagnosis requires careful workup of muscle inflammation, organ involvement, and auto-antibody testing. Treatment strategies need to consider the individual disease course and extramuscular organ involvement.

The nature of the disease requires a dedicated interdisciplinary work-up and care involving pediatricians, rheumatologists, dermatologists, neurologists, pulmonologists, cardiologists, pathologists and rehabilitation specialists.

Diagnostic delay or insufficient treatment often cause severe disease burden. Main shortcomings relate to different approaches for diagnosis and treatment that vary between specialties or geographic regions. The newly established international myositis society aims to overcome these shortcomings.

Methods: Over the course of three years, major international networks have been contacted, including IMACS, ERN EURO-NMD, ERN ReCONNET, MYOSITIS NETZ, Euromyositis, CARRA, and PRES JDM. All networks agreed on the need for an international myositis society and supported its foundation. A temporary international steering committee was established by a non-exclusive call through the aforementioned networks. A local steering committee drafted bylaws and organized the legal and administrative foundation of the society.

Results: The steering committee selected Germany as home of the society. Members from Germany formed a local steering committee that drafted bylaws in German and English. The bylaws were approved by experienced lawyers and formally accepted by the international steering committee.

The main aims of the international myositis society are to 1) Support the development and harmonization of diagnostic criteria and guidelines of care of myositis and help to implement those in all other international and national societies (e.g. AAN, EULAR, ACR, EAN); 2) Foster the education of myositis specialists and promote interdisciplinary curricula and fellowship programs; 3) Increase international awareness of myositis, promote funding and provide key contacts for funding bodies and other stake holders including NIH, EU, ERN, ESF, FOREUM and others, and liaise with a Journal as home for the society; 4) Provide support for the local organizing committee of the global conference on myositis (GCOM) every two years.

The local steering committee met in person to establish the international myositis society e.V. on 30 Sept. 2019 in Goettingen, Germany. The bylaws were officially approved by German court on 21 Oct 2019 and tax-exempt status was formally granted on 14 Jan 2020. The website and logo development is in progress and will be presented. An international, open call for membership will follow. The society will meet in person during the next GCOM in Prague in 2021 and elect a president and board members. Work of the society will be divided into sub-committees that focus on certain tasks such as imaging, diagnostics, treatment etc.

Conclusion: Foundation of the international myositis society is a major achievement in the field of myositis. It is expected that the society will help to improve future diagnosis and treatment of myositis by implementing interdisciplinary standards of care on a global scale. All standards will be developed in close collaboration with all respective professional societies, including patient representatives and allied health professionals.

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Clinical Trial and Real-World Experience for Managing Thrombocytopenia in Inotersen-Treated Patients with Transthyretin Amyloidosis

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Background: Amyloid transthyretin (ATTR) amyloidosis is a progressive, fatal disease caused by the deposition of misfolded transthyretin-derived amyloid fibrils in various organs and tissues throughout the body. There are 2 types of ATTR amyloidosis: wild-type and hereditary. Wild-type ATTR amyloidosis manifests primarily with signs and symptoms of cardiomyopathy. Hereditary ATTR (hATTR) amyloidosis, a rare disease caused by mutations in the transthyretin gene that are transmitted in an autosomal dominant fashion, may manifest as a predominant cardiomyopathy or polyneuropathy phenotype depending on the mutation; however, mixed phenotypes with both cardiomyopathy and polyneuropathy are not uncommon. Efficacy and safety of inotersen, an antisense oligonucleotide inhibitor of transthyretin protein production, were evaluated in a randomized, placebo-controlled pivotal study (NEURO-TTR) and its open-label extension (OLE). During the NEURO-TTR trial, weekly monitoring of platelet counts was implemented after 3 (3%) cases of grade 4 thrombocytopenia (platelet count <25,000 per microliter) were reported. This analysis

assesses outcomes of enhanced monitoring for thrombocytopenia in patients receiving inotersen in the clinical trial and real-world setting.
Methods: Patients with hATTR amyloidosis received inotersen through NEURO-TTR, OLE, a US expanded access program (EAP), a French compassionate use program (ATU), and an investigator-sponsored trial (IST; includes patients with wild-type ATTR). Data from these 5 studies plus ~3 patient-years of postmarketing exposure were evaluated from 6 July 2018 to 5 January 2019. Data from the US Risk Evaluation and Mitigation Strategy (REMS) were evaluated from 8 October 2018 to 6 August 2019.
Results: As of 5 January 2019, 267 unique patients received inotersen: NEURO-TTR N=112, OLE N=135, EAP N=66, ATU N=2, and IST N=36. Since the implementation of enhanced monitoring in clinical trials, noninterventional studies, and the ongoing REMS program, no cases of grade 4 thrombocytopenia or serious bleeding with severe thrombocytopenia have been reported to date.
Conclusion: With enhanced safety monitoring, events of grade 4 thrombocytopenia or serious bleeding with severe thrombocytopenia have been successfully mitigated across all current clinical studies and treatment programs.

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Examination of Small Nerve Fibers in Patients with CIDP

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Introduction: Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated, chronic disease causing motor and sensory impairment. Diagnosis is based on the typical progression of the disease and additional electrodiagnostic studies. However, there is a lack of well validated markers for the follow-up assessment of CIDP. Due to its ease of use, low effort for the patient and good reproducibility [Petropoulos et al. 2013], corneal confocal microscopy (CCM) is a promising diagnostic tool. This non-invasive method shows the morphology of the subbasal nerve plexus of the cornea. Previous studies applying CCM revealed a reduction in nerve fiber density in CIDP patients [Schneider et al. 2014].

The alteration of small fibers in CIDP patients cannot be displayed using current standard diagnostics, but is sought to be a valuable marker for disease progression. We aimed to evaluate the severity of damage to small nerve fibers using corneal nerve fiber parameters in CIDP patients longitudinally.
Material and methods: In a cohort of 15 CIDP patients presented at the Neurological Clinic of the University Medical Center Göttingen, a cornea scan using a specialized confocal microscope (HRT-RCM II, Heidelberg Engineering GmbH, Heidelberg, Germany) was performed. Acquired images representing the subbasal nerve plexus were evaluated using the software CCMetrics (Rayaz Malik, University of Manchester, Manchester, United Kingdom). The corneal nerve fiber parameters were correlated with the INCAT, MRC and ROD scores, electrodiagnostic studies, walking distance and grip force measurements. In addition, skin biopsies, quantitative sensory testing (QST), sudoscan, heart rate variability measurements and pain questionnaires (painDETECT® questionnaire [Freynhagen et al. 2006], „Questionnaire neuropathic pain“ [Sommer et al. 2011]) were used to estimate the physiological status of small, unmyelinated nerve fibers.
Results: Taken together, our findings revealed damage to small nerve fibers of CIDP patients but no significant difference in corneal nerve fiber parameters in CIDP patients compared to healthy controls have been detected. Nevertheless, our results show an involvement of small nerve fibers in CIDP patients by skin biopsies with reduced intraepithelial nerve fiber density (IENFD), through pathological thresholds in quantitative sensory testing and reduced sudomotor function.
Conclusion: Our study demonstrates small nerve fiber involvement in patients with chronic inflammatory demyelinating polyneuropathy. However, corneal confocal microscopy is not suitable to provide a robust marker of disease progression for all CIDP patients in our cohort. Further studies should be conducted to evaluate the role of small-fiber neuropathy in CIDP.

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Two Novel Molecular Approaches Towards Deciphering Myotonic Dystrophy Type 1

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Myotonic Dystrophy type 1(DM1) is a genetic autosomal dominant disease mainly characterized by myotonia, progressive muscle weakness, accompanied by progressive muscle wasting and several multisystemic features, including cardiac conduction defects, development of cataracts and impaired respiratory and gastrointestinal functions (1-3). DM1 is caused by expansion of CTG trinucleotides repeats in the 3′ untranslated region (UTR) of the DMPK gene (2). The resulting mRNA accumulates as nuclear foci compromising nuclear function. Disease severity and age of onset correlate with the repeat length, and repeat expansions of >1000 often result in a severe congenital form of DM1 (4). Interestingly, muscle diseases, including DM1, comprise a group of diseases characterized by muscle weakness and impaired muscle function; a common feature the mispositioned myonuclei(4). Several nuclear envelope (NE) proteins have been indicated as crucial proteins controlling, not only the nuclear positioning and nuclear movements, but also muscle functions. Among these are, lamin A/C, emerin, LAP1 and SUN proteins all associated with important muscle functions. Regarding DM1, a few studies have reported alterations in the DM1 patient's NE structure and function (2,5), suggesting that in this muscle disease the NE might also have an important role requiring further investigation.

In this work, 2 molecular approaches were employed. Namely, by evaluating the nucleus and NE at a morphological and proteomic level (herein designated NNE profile) and the metabolomic profile of DM1 patients. Thus, control and human patient fibroblasts were used as cellular models of disease. The human patients' fibroblasts have 1000 CTG and 2000 CTG repeats, representing the adult and congenital DM1 types, respectively.

NNE profiling revealed several differences when comparing fibroblasts from control vs DM1 patients. Particularly with regards to lamin A/C, LAP1, emerin and SUN1, in terms of cellular localization and expression levels. For the Fourier Transform Infrared Spectroscopy (FTIR) analyses; differences were observed in the protein and lipid at the molecular structural level. One can deduce that, DM1 fibroblasts' biochemical composition can be distinguished from controls, namely by a larger lipidic stretch and by the presence of protein aggregates. These molecular approaches are promising avenues for novel diagnostic and therapeutic tools for DM1.

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Quantitative Assessment of Brachial Plexus MRI in Diagnosis of Chronic Inflammatory Neuropathies

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Objective: Current practice of qualitative evaluation of brachial plexus MRI for abnormality in chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) is limited by low reliability. Therefore, our study was aimed to develop objective cut-off using an extensive MRI protocol in a large cohort of patients and clinically relevant controls, and determined their diagnostic yield.
Methods: We systematically assessed nerve root diameters (C5-C7, measurements in coronal and sagittal planes) at two sites near the ganglion bilaterally, in a cohort of 123 patients with CIDP, MMN and disease controls. We determined optimal cut-off values for abnormality using logistic regression and ROC analysis. In addition, we evaluated the intra- and inter-rater reliability.
Results: Nerve root sizes were larger in patients with CIDP and MMN compared to disease controls at all predetermined sites ($P<0.001$). We found a moderate to good reliability for nerve diameter assessment (ICC 0.65 – 0.90). AUC was 0.78 (95% CI = 0.69 – 0.87) for measurements just after the ganglion and 0.81 (0.72 – 0.91) 1 cm more distally, with sensitivity exceeding 80% when using 4mm as cut-off value for nerve root diameters. We found no relation between nerve root sizes and any demographic or clinical parameters.
Conclusions: Our study shows that quantitative assessment of cervical nerve root sizes is reliable and that a practical cut-off value of 4mm has good diagnostic performance to identify patients with chronic inflammatory neuropathies.

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Respiratory Involvement in Late Onset POMPE Disease: Description of a Case Series

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Introduction: Late Onset Pompe Disease (LOPD) is a rare, autosomal recessive disorder caused by deficiency of the acid alpha-glucosidase. It causes a progressive respiratory muscular weakness. Without treatment, it can cause death in the second or third decades of life, although the natural history of the disease is heterogeneous. We present the respiratory evolution of ten patients with LOPD, followed for eight consecutive years.
Methods: Observational retrospective study of a series of patients with LOPD, followed in a third level hospital, with respiratory functional tests performed periodically during eight years, including spirometry (FVC), maximum inspiratory and expiratory pressures (MIP – MEP), sniff intranasal pressure (SNIP), cough peakflow (CPF), arterial blood gas test, nocturnal pulse oximeter and capnography, and diaphragmatic ultrasound.
Results: Seven patients were studied, 4 men and 3 women with a median age of 45 years. The first symptom appeared approximately at 6.9 years before the diagnosis. Four patients developed hypoventilation symptoms and three of them had also orthopnea, approximately 8 years after the disease onset, except for one patient whose respiratory symptoms presented at the beginning of the disease. All patients were treated with enzymatic replacement therapy approximately 8 years after the first symptoms appeared. The patients presented a long-term reduction of FVC about 3.5% annually. SNIP also decreased through years but not as evident as FVC, while diaphragmatic thickening fraction seems to stabilize through years.
Conclusion: Respiratory involvement in LOPD is multifactorial. The clinical heterogeneity and the overlapping of signs and symptoms make the respiratory muscle failure diagnosis tends to be late, and traditional methods could not be adequate. We recommend an exhaustive and precocious respiratory evaluation for every patient with diagnosed LOPD.

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Systemic Gene Transfer with rAAVrh74.MHCK7.SGCB Increased β-sarcoglycan Expression in Patients with LGMD Type 2E

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Background: Limb girdle muscular dystrophies (LGMD) usually manifest with progressive hip/shoulder muscle weakness extending to other muscles. LGMD2E (due to β-sarcoglycan [SGCB] deficiency) includes cardiac involvement and elevated creatine kinase (CK). We present initial findings of an ongoing, phase 1 multiple ascending-dose clinical gene transfer trial of ≤9 patients with LGMD2E who received rAAVrh74.MHCK7.SGCB (NCT03652259).

Methods: Participants were patients 4-15 y with confirmed SGCB mutation (both alleles), negative for antibodies against rAAVrh74, and >40%n on 100-meter timed test. Patients received single IV infusion of 5x10^13 vg/kg rAAVrh74.MHCK7.SGCB. Prednisone 1 mg/kg/day was initiated 1 day before gene delivery, tapering after 30 days. Primary endpoints were ≥20% SGCB-positive fibers (Day 60 muscle biopsy) and safety (Day 270). Secondary endpoints were CK decrease and functional endpoints (Day 270).

Results: For the first 3 patients enrolled (age 13, n=2; age 4; n=1), robust SGCB expression was observed by immunohistochemistry (IHC), with a mean of 51% SGCB positive fibers (range 42-63%) expressing a mean 47% intensity (range 38-57%). Co-localization of α-sarcoglycan was observed by IHC. Western blot showed a mean 36.1% SGCB expression vs normal (range 34-39%). Mean CK levels were reduced by 82%, suggesting slowed muscle destruction. Two patients had elevated liver enzymes (1 serious) and 1 had elevated bilirubin following oral steroid taper, which subsequently returned to baseline. Two patients had transient mild nausea, corresponding with increased steroid dosing. No other clinically significant lab findings.

Conclusion: Gene transfer in patients with LGMD2E following an infusion of rAAVrh74.MHCK7.SGCB was positive for the defined endpoints. This is the second gene therapy inducing protein production post transgene delivery with rAAVrh74 vector and MHCK7 promoter, demonstrating potential benefits of a rationally designed delivery system.

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Long-Term Safety/Efficacy of Golodirsen in Male Patients with DMD Amenable to Exon 53 Skipping

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Background: Golodirsen is a synthetic oligomer designed to restore the mRNA reading frame in patients (pts) with DMD gene mutations amenable to exon 53 skipping. We report the safety and efficacy of long-term golodirsen treatment in this first-in-human, phase 1/2, 2-part, multicenter trial.

Methods: 12 pts from part 1 (randomized, 12-week dose-titration phase; golodirsen [n = 8], placebo [n = 4]) plus 13 additional pts with genotypically confirmed DMD amenable to exon 53 skipping therapy were included in part 2 (open label). All 25 pts received continuous open-label treatment with once-weekly golodirsen 30 mg/kg. Safety and measures of pulmonary and functional efficacy were assessed.

Results: Golodirsen-treated pts had a median age of 8 years. Safety data were collected up to 189 weeks, and median golodirsen exposure was 168 wks. All golodirsen-treated pts experienced ≥1 treatment-emergent AE (TEAE), including rhinitis, nasopharyngitis, headache, and proteinuria. Overall, 12 pts (48%) had mild TEAEs, 8 (32%) experienced moderately severe TEAEs and 5 (20%) had severe TEAEs. All severe TEAEs were nonserious and considered unrelated to golodirsen. There were no deaths or discontinuations due to golodirsen. Ambulatory assessments were reported, including 6MWT and NSAA scores relative to baseline. Further, respiratory function was evaluated by percent FVC change from baseline.

Conclusions: Long-term treatment with golodirsen was well tolerated. No patient discontinued because of an AE. These data, and the previously reported encouraging data on dystrophin protein expression at 48 weeks, support further clinical development of golodirsen for the treatment of DMD. Comparisons to well-matched natural history cohorts are underway.

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Open-Label Evaluation of Eteplirsen in Males With DMD Amenable to Exon 51 Skipping: PROMOVI

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Background: Eteplirsen received accelerated FDA approval for treatment of DMD patients with mutations amenable to exon 51 skipping. We report results from a phase 3 open-label study evaluating eteplirsen in boys with DMD amenable to exon 51 skipping therapy.
Methods: Males aged 7 to 16 years inclusive, with confirmed DMD and frame-shift mutations amenable to treatment by exon 51 skipping, received intravenous (IV) eteplirsen 30 mg/kg/wk for 96 wk. An untreated cohort of boys with DMD not amenable to exon 51 skipping was also enrolled. Outcomes included safety, ambulatory function, dystrophin quantification, and pulmonary function.
Results: 78/79 patients received eteplirsen and completed 96 weeks of treatment. Recruitment and retention of patients in the untreated group failed as only 13/30 patients completed the study. Safety was assessed in patients who had received up to 96 weeks of treatment. The most frequently reported adverse events (AEs) were headache, vomiting, and cough. The majority of AEs were mild to moderate and considered unrelated to eteplirsen. There were no treatment discontinuations due to an AE. Eteplirsen-treated patients showed a mean increase in dystrophin over baseline by Western blot. Ambulatory assessments, including loss of ambulation, ability to rise, and NSAA over 96 weeks were reported. Pulmonary function as measured by FVC%p was also evaluated. Comparisons to reported natural history suggest slowing of disease progression with eteplirsen treatment.
Conclusion: Overall, 96 weeks of once-weekly IV eteplirsen appeared to be well tolerated. Dystrophin production and ambulatory and pulmonary measures suggest a positive treatment effect of eteplirsen as seen in previous studies. Comparison with the untreated cohort was confounded by withdrawals and considered inappropriate because of recently demonstrated differences in disease trajectories of the mismatched genotypes included. Comparisons to well-matched natural history cohorts are underway.

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Ophthalmic Findings in a Cohort of Brazilian Patients with Myotonic Dystrophy Type 1

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Introduction: Myotonic dystrophy type 1 (DM1) is a multisystemic disease with several ocular abnormalities as cataract, ptosis, progressive ophthalmoplegia, exposure keratitis, pigmentary retinal changes, and low intraocular pressure (IOP). The purpose of the study was to evaluate the frequency of these abnormalities in a Brazilian cohort and to alert the importance of spectral domain optical coherence tomography (SD-OCT).
Methods: All participants underwent a detailed ophthalmologic examination, including visual acuity assessment, slit-lamp biomicroscopy, ocular motility, IOP, dynamic refraction, fundus examination in addition to spectral domain optical coherence tomography (SD-OCT).
Results: We evaluated 16 patients with DM1 confirmed by genetic analysis, aged 3 to 71 years (mean age 42.7 yrs) being male, 50 % of them. Intraocular pressure (n = 32 eyes) was in average 10.42 mmHg; presence of cataract or the need for cataract surgery in 9 (56.25%); ptosis in 9 (56.25%), myopia (19 eyes, 59.37 %), hyperopia (6 eyes, 18.75 %), exotropia in 3 (18.75 %), ocular motility limitations in 4 patients (25%), blepharitis in 4 (25 %); epiretinal membrane in 6 (37.5 %) and pigmentary retinopathy in 4 patients (25 %). We also observed an irregular-

ity in the choriocapillaris retinal pigment epithelial (RPE) complex in 4 patients (25%) never described previously in the literature.

Conclusions: The OCT is a complementary exam that is fundamental for retinal evaluation, since many of these patients may have low visual acuity unrelated only to the presence of cataracts. Besides, the irregularity in the choriocapillaris RPE complex is analyzed and visualized only by SD-OCT, a condition that implies greater care in the follow-up of these patients since this alteration could lead to retinal dystrophy or even retinal degeneration in the future. We may also highlight an increased prevalence of epiretinal membrane in DM1 in our patient, usually a cause of visual loss, treatable by surgery. Although the cystoid macular edema and reduction of IOP has been described in DM1, we did not observe in our patients. Therefore, the ocular abnormalities found in DM1 patients obliges us to refer patients with DM1 for a careful evaluation with an ophthalmologist since, different ocular changes have different therapies.

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The Use of Ixazomib in MDX Mice

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Background: The dystrophin glycoprotein complex (DGC) is a very important component of skeletal muscle and cardiac membrane, mediating interconnections among the cytoskeleton, membrane, and extracellular matrix. Dystrophin, the protein product of the Duchenne muscular dystrophy, links cytoskeletal and membrane components.

The absence of this protein makes the DGC susceptible to proteolytic degradation by Ubiquitin/Proteasome System. Its inhibition may lead to the rescue of dystrophin. The Ixazomib, a second-generation proteasome inhibitor, used in the treatment of multiple myeloma preferentially binds to subunit β5 of proteasome 20S.We treated mdx mice with this drug.

Method: 16 mdx mice (8 weeks old) were selected; 8 were treated by gavage with 0.2 ml saline and 8 received ixazomib 7.5 mg / kg / week for 12 weeks. The animals were weighed weekly and the strength measurement by the Kondziela's method, was performed 1x /week (weeks 1, 6 and 12). At the end of the study creatinophosphokinase(CK), urea, creatinine, alanine transaminase (ALT), aspartate transaminase (AST) and gamma-glutamyl transpeptidase(GGT) were measured in the blood. Anterior tibialis (TA), long digital extensor (EDL) and diaphragm (DIA) muscle fragments were collected to do quantitative real-time PCR-based analysis of gene expression of osteopontin, myostatin, TNF-α, TGF-β, utrophin and dystrophin. We also, counted the muscle fibers with internalized nuclei.

Results: There was a significant decrease in body mass of the treated group animals compared to controls. There was no significant difference in dosages of CK, urea, creatinine, GGT, AST. However, there was a significant reduction in ALT in animals treated with Ixazomib. In addition, the treated animals showed a significant increase in muscle strength at the end of the experiment (more 7%) while control showed a decreased (less 38%). In the morphometric analysis, there was a significant reduction of fibers with internalized nuclei in the DIA and TA muscles but not in the EDL muscle. The expression of dystrophin, utrophin and TNF-α showed upregulated in DIA muscle (respectively more 98%, 158% and 39%) while TGF-beta and osteopontin showed a significant downregulation (respectively less 29% and 53%).

Conclusion: Ixazomib proved to be beneficial regarding disease progression in the mdx mouse by increasing muscle strength, reducing internal nuclei and increasing dystrophin and utrophin expression and reducing TGF-beta. Proteasome inhibition should be further explored in the treatment of Duchenne muscular dystrophy.

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Intravenous Immunoglobulin G Responsive CIDP with Anti MAG Antibodies and No Monoclonal Gammopathy

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Chronic inflammatory demyelinating neuropathy (CIDP) with IgM monoclonal gammopathy of un-

certain significance (MGUS) and antibodies against myelin-associated glycoprotein (MAG) is rare condition, which presents with a predominantly sensory neuropathy with ataxia and tremor with poor response to immunotherapy. Several case reports or series study showed there are CIDP with anti-MAG antibodies and no monoclonal gammopathy, and those patients could show partial or good response to immunotherapy. We report a case, who is CIDP with anti-MAG antibodies and no monoclonal gammopathy and have good response to intravenous immunoglobulin G (IVIG). A 73-year-old woman visited to our hospital due to gait disturbance for three months. She presented decreased vibration sense of hand and foot, decreased deep tendon reflexes, sensory ataxia, and positive Romberg sign on neurologic examination. Her main problems are postural instability during gait and inability of writing. Nerve conduction study showed distal dominant demyelinating sensorimotor polyneuropathy. Cerebrospinal fluid analysis showed elevated protein with few lymphocytes. Protein electrophoresis and immunofixation study showed no monoclonal gammopathy. The titer of anti-MAG antibodies is 1619 BTU (reference value: <1000.0). Other serum antibodies (paraneoplastic antibody [Hu, Yo, Ri, Amphiphysin, CV2, PNMA2, Recoverin, SOX1, Titin], ANCA, SSA/SSB, ANA, ganglioside [GM1, GD1b, GQ1b]) were negative. She treated with IVIG (0.4g/kg for 5 days). After IVIG treatment, she could walk without assistance and write. We report a case with IVIG responsive CIDP with anti MAG antibodies and no monoclonal gammopathy. So, we suggest test with anti MAG antibody and trial with IVIG in the CIDP patients with distal sensory ataxic involvement.

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Peripheral Neuropathy Revealing Genetic Creutzfeldt-Jakob Disease

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Introduction: Creutzfeldt-Jakob disease (CJD) is a prion disease that is usually sporadic and starts with rapidly progressive cognitive decline, psychiatric disorders and myoclonic movements. There are, however, family forms secondary to mutations in the prion protein gene (PRNP) and forms that start with atypical symptoms such as visual disturbances, hearing loss, hemiparesis, epileptic status or peripheral neuropathy.

Peripheral neuropathy has been reported in isolated patients or small case series of both sporadic and genetic CJD. Usually, patients have walking difficulties related to limb sensory symptoms, such as numbness and tingling, rather than with motor features. The main differential diagnosis is with variant CJD (bovine spongiform encephalopathy), in which dysesthesias and pain in the limbs are often prominent at onset.

Objective: To report a case of sensory neuropathy and dysautonomia secondary to probable genetic CJD (gCJD), diagnosed using cerebrospinal fluid real-time quaking-induced conversion (CSF RT-QuIC) assay.

Case report: A 60-year-old man had progressive numbness of hands and feet, unsteady gait, constipation, weight loss and diminished reflexes. No cognitive or psychiatric problems.He has a family history of two sisters who died with a clinical diagnosis (not mutation, not pathological study) of CJD at 44 and 63 years old, respectively

Blood tests were normal, CSF study was normal and study of onconeuronal and surface antibodies in blood and CSF were negative. An EMG was performed showing a sensory-motor polyneuropathy with predominant axonal pattern, EEG was normal and the MRI showed a restricted diffusion at the level of the head and body of the left caudate nucleus, both thalamic pulvinars and in the left insular cortex. In FLAIR sequence these areas are discreetly hyperintense

We decided to expand CSF study with 14.3.3 protein which is negative. Because the suspicion of CJD was high we decided to perform CSF RT-QuIC assay being positive. Genetic study confirmed the mutation p.Glu200Lys in heterozygous in the PRNP gene (Heterozygosis Met/Val for residue 129 of PrP).

With the results obtained, a gCJD was suspected but, at that time, it didn't meet probable CJD criteria according to the criteria of the Centers for Disease Control and Prevention (CDC) due to the absence of progressive neuropsychiatric symptomatology. However, in the following months, the patient developed visual hallucinations and behavioral disorder

Conclusions: Our case is relevant because it is an unusual clinical presentation of gCJD and we demonstrated the utility of CSF RT-QuIC assay in genetic forms of prion disease.

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Autism Spectrum Disorders in Duchenne Muscular Dystrophy Patients: Not Just a Coincidence

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Introduction: Duchenne muscular dystrophy (DMD) is the most frequent and severe form of the dystrophinopathies. The literature shows that about 30-40% of DMD subjects have intellectual disability. In males with Duchenne muscular dystrophy, neuropsychiatric disorders have also been observed: attention deficit disorder and hyperactivity, autism spectrum disorders, and obsessive-compulsive disorder.
Methods: Retrospective study and review of clinical and biochemical features of 07 Brazilian patients diagnosed with DMD and ASD.
Results: Seven patients had ASD and intellectual disability. Of these 7 patients, 5 had received a formal diagnosis of ASD from their paediatrician or paediatric psychiatrist before the present study; the remaining two had not previously undergone a comprehensive assessment for neurodevelopmental disorders. The association between ASD and the cumulative loss of dystrophin isoforms predicted by mutation locations was then analysed, but there was no association between meeting the ASD criteria and loss of dystrophin isoform even patients showed features of early-onset type (classical DMD presentation). Speech delay was the most commonly reported neurodevelopmental need in our cohort. Speech delay was reported by 100% of parents. 5 out of 7 patients also showed features of obsessive-compulsive disorder. No abnormal findings were seen in brain MRI undertaken in our patients.
Conclusion: The association between Duchenne muscular dystrophy (DMD) and two neuropsychiatric disorders – autism spectrum disorders (ASD) and attention-deficit hyperactivity disorders (ADHD) – has gained growing interest in scientific literature and clinical practice in the recent years. Frequency rates as reported in literature for ASD range from 3% to 32% and for ADHD from 12% to 50%.The mutation in the dystrophin gene, causing a deficiency in the expression of dystrophin in the brain, is believed to be the key etiological factor of this comorbidity, although the function of dystrophin in the brain is less well understood than its function in skeletal muscle. Recently, the term "dystrophin associated neurodevelopmental syndrome" referring to ASD and ADHD in DMD was introduced. Since patients with DMD may have neurodevelopmental delay (particularly speech), as well as autistic-like characteristics in early childhood, this may lead to delayed recognition of muscle symptoms. Given the possibility of specific therapy, early diagnosis becomes essential, making it important that clinicians identify DMD among ASD patients as early as possible, avoiding misdiagnosis and allowing family genetic counselling.

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Spinal Muscular Atrophy with Congenital Bone Fractures 2 (SMABF2): Expanding the Phenotype

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Introduction: Spinal muscular atrophy with congenital bone fractures 2 (SMABF2) is a rare autosomal recessive neuromuscular disorder characterized by prenatal-onset spinal muscular atrophy (SMA), multiple congenital contractures (arthrogryposis multiplex congenita), respiratory distress and congenital bone fractures, with poor prognosis. The most affected patients present with biallelic loss-of-function nucleotide variants in ASCC1 gene, coding a subunit of the transcriptional coactivator ASC-1 complex, although the exact pathogenesis is yet unknown
Methods: Clinical and genetic molecular retrospective chart review of a Brazilian patient with features of SMABF2

Results: Male patient, 12 months, first child to a healthy and non-consanguineous young couple, was referred for evaluation of Spinal Muscular Atrophy type 0. He presented generalized hypotonia, congenital bone fractures, lack of spontaneous movements and poor respiratory effort. Mother referred poor fetal movements during pregnancy period. Karyotyping and screening for several genes related with neuromuscular diseases all tested negative. No deletion or mutations in SMN1 gene were found. Whole-exome sequencing was performed focused on genes known to be related firstly with congenital myopathies, extended to muscle diseases and finally to other neuromuscular disorders. Patient was also found to have a homozygous frameshift variant (c.157dupG, p.Glu53Glyfs*19) in ASCC1, being the first Brazilian reported with such disorder and harboring a previous reported mutation.
Conclusion: Perinatal manifesting neuromuscular diseases include a wide variety of clinical entities such as fetal akinesia/hypokinesia, arthrogryposis multiplex congenita, spinal muscular atrophy (SMA) type I, congenital myopathies and muscular dystrophies, and congenital myasthenic syndromes. ASCC1encodes a subunit of the tetrameric activating signal cointegrator 1 (ASC-1) complex, composed also by TRIP4, ASCC2, and ASCC3 .This complex acts as a transcriptional coactivator with a key role in gene transactivation. Muscle weakness in combination with arthrogryposis and congenital bone fractures is exceedingly rare, and has been reported only in a few cases with severe nemaline myopathy due to ACTA1 or KLHL40 mutations. All reported and new ASCC1 families presented with the same lethal phenotype, nevertheless our patient is one of the patients with longer survival reported so far, expanding the clinical phenotype of this devastating disorder

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Managing a Metabolic Myopathy in Obstetrics: Myopathic VLCAD Deficiency During Pregnancy

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Introduction: Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is an autosomal recessive mitochondrial fatty acid (FA) oxidation disorder that manifests in three clinical forms: (a) severe, (b) milder, and (c) myopathic. Patients with the myopathic form present intermittent muscular symptoms such as myalgia, muscle weakness, and rhabdomyolysis during adolescence or adulthood.
Case Report: A 26-year-old woman, born to a non-consanguineous couple, was referred for evaluation for recurrent, mostly unprovoked, episodes of muscle weakness, chronic myalgia, rhabdomyolysis and elevated plasma creatine kinase (CK) since her twenties . Resting and/or glucose infusion improved her muscular symptoms during these episodes. At 26 years of age, a muscle biopsy was suggestive of lipid metabolic myopathy and, following an abnormal acylcarnitine profie, mutation in ACADVL gene. Before pregnancy, she suffered from muscle weakness and myalgia five or six times per year needing hospitalization most of the times. At 28 years of age, she became pregnant and, although the patient had hyperemesis gravidarum around the first trimester of pregnancy, only mild myalgia was observed. Given the limited literature available on this disorder in pregnancy, an individualized plan of care was established in close collaboration with her team of maternal–fetal medicine and obstetrics. She delivered a healthy young boy after a vaginal delivery, she had increased CK levels but no pain or weakness.
Conclusions: A few reports have stated that the symptoms of women with VLCAD deficiency often improve during pregnancy, probably due to compensation of maternal β-oxidation by the unaffected placenta and fetus. Management of defects in FA oxidation in pregnancy poses a significant challenge in the maternal–fetal medicine. Our case report reinforces that this condition can be safely managed during pregnancy and in the instances of an unaffected fetus, affected mother may benefit from the placental-mediated beta-oxidation

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Study of the Mechanisms Responsible of the Clinical Variability Present in DMD del45-55 Subjects

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The in-frame mega-deletion of exons 45-55 in the DMD gene is a common mutation present in subjects with BMD phenotype, as well as subjects with isolated cardiomyopathy and even in long living asymptomatic ones. Due to its association with milder symptoms, multi-exon skipping of these 10 exons has emerged as a feasible therapeutic approach to 46,9% of DMD patients, which can be achieved with the CRISPR/Cas9 gene editing technology. Our hypothesis is that differences in the location of the intronic breakpoints along these subjects, could contribute to the clinical variability observed among them.

To address this issue, we studied a cohort of subjects with the 45-55 mega-deletion, through a clinical protocol. Intronic breakpoint location was analysed using Next Generation Sequencing (NGS), as well as we studied genetic modifiers of DMD and the presence of other mutation in myopathic-related genes. The cohort is composed by 19 index non-related cases, and we also collected 22 secondary cases. Patients were classified as asymptomatics (65,8%), Becker (14,6%), cardiomyopathic (31,7%) and very late-onset manifestation (19,5%).

The 19 analysed subjects were grouped in only 8 specific deletions. By haplotype analysis we identified that 4 of the deletions were shared by several index cases due to a founder effect, that was region-specific. We couldn't reach any statistical association between the clinical phenotypes and the intronic breakpoints. Three patients had affected the transcription of the brain dystrophin isoform Dp140, and only 1 presented cognitive impairment. No additional mutations in any myopathic-related gene or association between the SNPs in the SPP1 and LTBP4 DMD modifiers genes was found.

As a conclusion, most of the patients we have analysed with the 45-55 mega-deletion have mild or asymptomatic phenotypes, which turns this multi-exon skipping into a possible therapeutic option. However, uncertainties remain over the development of severe manifestations. We couldn't identify factors determining clinical differences among the analysed subjects

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Non-Dystrophic Myotonic Disorders: Patient Insights on Treatment Access

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Background: Non-dystrophic myotonic (NDM) disorders are a heterogenous group of rare, genetic skeletal muscle chloride and sodium channelopathies with altered membrane excitability resulting in prolonged muscle contraction and delayed relaxation. Patients experience stiffness, pain, weakness, impaired mobility, fatigue, disability, falls, and problems with speech, chewing and swallowing. Patients with NDM experience unpredictable frequency and severity of myotonic episodes, associated with life-long symptoms and negative impact on physical functioning and quality of life. Treatment has included products that were previously unlicensed, such as mexiletine. This study sought to evaluate the awareness of, and access to, mexiletine across Europe, and subsequent harm caused by limited treatment access. Following the study, mexiletine gained European marketing authorization and is now available as an anti-myotonic agent to treat symptoms in patients with NDM.

Method: A two-stage study ascertaining the level of access to mexiletine and benefits for those treated with mexiletine was developed and conducted in required languages. Healthcare experts and patient representatives were interviewed, followed by an online survey for patients and caregivers, in 13 countries.

Results: Online questionnaires were completed by 37 patients with NDM, of whom 41% were currently taking mexiletine. Of those not taking mexiletine, 67% had never heard of mexiletine and 25% reported it not being available in their country. Treatment

was required by 67% of patients to allow muscle warming before physical exertion and 50% to improve emotional well-being (Figure), and mexiletine drastically reduced frequency of falling in 44% of patients. Anxiety about future access to mexiletine affected 87% of patients. Disruption in mexiletine treatment harmed 85% of patients.
Conclusion: Mexiletine-treated patients experienced substantial benefits, while access denial resulted in substantial harm.

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Psychometric Validation of Tools to Assess Health Outcomes in SMA From the Patient's Perspective

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Introduction: Although there are scales that evaluate functional aspects of patients with Spinal Muscular Atrophy (SMA), there is a lack of tools that incorporate patient's perspective complementing the evaluation of health outcomes. This study aims to assess tools of this type for the first time in our country.
Objectives: Evaluate the psychometric properties of a set of existing questionnaires and newly created items, to assess the impact of SMA in the physical, psychological and social area of the patient's life.
Methods: Based on the result of focus groups with patients, previously developed by FundAME, a set of areas and items were designed. In addition, a review of the literature was done and identified useful questionnaires to evaluate certain areas (SMAIS, NeuroQOL). An expert committee (neurologists, neuropediatricians, rehabilitating physicians and patient representatives) chose the appropriate questionnaires and new items. A prospective observational study will now be conducted in order to assess the validity, reliability and sensitivity to change of this new set of tools.
Results: The study will be carried out in Spain with around 150 patients older than 12 years and children's caregivers under 12 years of age in collaboration with the Spinal Muscular Atrophy Foundation. Patients will respond to the toolkit twice, separated by at least 6 months, and it will collect a reduced set of sociodemographic and clinical variables: Type of SMA, ambulation status, pharmacological treatment and clinical change between visits.
Conclusions: This study will allow to have a set of tools for assessing health outcomes in SMA, useful in clinical practice, in Spain.

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Neuregulin IsoformsRegulate the Pre and Postsynaptic Organization of C-type Afferent Synapses on Motor Neurons

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C-type cholinergic afferent synapses (C-boutons) on motor neurons (MNs) originate from local interneurons and display a particular postsynaptic ER-related organelle called subsynaptic cystern (SSC). NRG1 immunolabeling was detected close to C-boutons in association with SSCs. NRG1-positive clusters were disrupted in diseased MNs (Gallart-Palau et al., 2014, Salvany et al., 2019). As the antibody used for NRG1 detection (anti-pan-NRG1) is not able to distinguish the different isoforms of NRG1, we took the advantage of transgenic mouse lines to examine NRG1 isoform-specific functions in C-boutons. These studies included transgenic mice that overexpress either full-length NRG1 type I (NRG1type I) (Michailov et al., 2004), or N-terminally HA epitope–tagged full-length NRG1 type III (HA-NRG-1FL) (Velenac et al., 2012). Samples from HA-NRG1FL mice showed highly overlapping immunostaining for the HAtag and the ICD on the surface of MN cell bodies, which was frequently associated with presynaptic VAChT-positive C-bou-

tons. These findings are consistent with the accumulation of unprocessed NRG1 type III in SSCs at postsynaptic sites of C-boutons. Sites enriched in sigma-1 receptor, Kv2.1 potassium channels and M2 muscarinic receptors were notably enlarged, in a similar manner to the expanded distribution of NRG1 type III. Thus, the induction of redundant SSC-like membrane compartments by NRG1 type III overexpression was linked to an increased production and insertion of other C-bouton site-specific partner molecules. However, the number of C-type presynaptic terminals contacting MN somata was not altered. An examination of HA-NRG1FL mouse samples by electron microscopy showed an accumulation of abnormally expanded and reduplicated surface-associated ER membranes, which were arranged like redundant SSCs. All these data indicate that full length NRG1 type III acts as an organizer of ER-membrane contacts, including SSCs, in MNs. To identify possible consequences of enhanced NRG1 type I–mediated paracrine signaling in C-boutons, we next examined NRG1 type I transgenic mice. Immunostaining for the NRC1 intracellular domain with the anti pan-NRG1 antibody ICD showed a strong signal at the MN surface of NRG1typeI mice compared with WT, analogous to that obtained in HA-NRG1 FL mice. However, in stark contrast to HA-NRG1FL mice, VAChT immunostaining revealed a prominent increase in the number and size of C-boutons presynaptic cholinergic terminals innervating the on the MN surface. Ultrastructural examination in NRG1typeI mouse samples confirmed the presence of enlarged presynaptic terminals on the MN soma surface, matching only partially with postsynaptic SSC. Nevertheless, the amplified formation of SSC-like ER-PM contacts in HA-NRG-1FL mice was not observed in NRG1 type I mice. Altogether, these findings suggest that: 1) full-length NRG1 type III acts as a specific organizer of postsynaptic SSC-like membrane compartments without a major impact on the C-bouton presynaptic counterpart; 2) NRG1 type I promotes presynaptic C-bouton synaptogenesis with no influence on biogenesis and molecular architecture of coaligned SSC.

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Overexpression of NRG1-Type III Does Not Ameliorate ALS Clinical Outcome in SOD1G93A Mouse Model

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Amyotrophic Lateral Sclerosis (ALS) is an adult onset disease that affects motorneurons (MNs) in the cerebral cortex, brainstem and spinal cord. Most of ALS cases (~90%) are sporadic, but ~10% of the cases are inherited. In approximately 20% of familial cases, the disease is caused by mutations in the gene encoding Cu/Zn-superoxide-dismutase11 (SOD1). Transgenic rodents overexpressing this mutated gene develop a neuromuscular disorder similar to human ALS2, 3.

Afferent inputs to MNs are crucial in regulating their excitability. Among different types of synaptic afferents, MNs receive prominent cholinergic C-type ("C-bouton") inputs from spinal interneurons. C-boutons modulate MN excitability4 and the synaptic transmission throughout C-boutons is involved in the regulation of MN vulnerability to degeneration.

We have previously observed that neuregulin-1 (NRG1) accumulates in C-boutons, describing C-bouton alterations in a mouse model of ALS5.

Some C-bouton-associated molecules appear to be relevant in ALS: SK channels, the main Riluzole target6; S1R, where mutations cause a juvenile familial form of ALS7 and its pharmacological activation prolongs lifespan of SOD1G93A mice8; the vesicle-associated membrane protein-associated protein B (VAPB), where mutations cause ALS8, and abnormally accumulates in C-boutons9; M2 AChRs, which activity in C-boutons modulates the amount of misfolded and neurotoxic proteins in mutant SOD1 mouse models10; and the NRG1 receptor ErbB4, which mutation causes another type of FALS11.

NRG1 signaling has been directly targeted in SOD1-ALS mice by virus-mediated delivery to the spinal cord, resulting in extended survival time and reduced C-bouton loss12. NRG1-typeI

overexpression confined to the muscle promotes axonal collateral sprouting and muscle reinnervation, but fails to improve the clinical outcome13. Gene therapy based on intrathecal administration of adeno-associated virus to overexpress NRG1-III in SOD1G93A mice is able to preserve neuromuscular function, improve locomotor performance, increase the number of surviving MNs, and reduce glial reactivity in female SOD1G93A mice14.

By cross-breeding SOD1G93A mice and NRG1-typeIII overexpressor mice, we have created a double transgenic mouse line. We have examined changes in body weight, survival and we have performed behavioral and histopathological studies in spinal cord and skeletal muscle tissue showing no improvement either in motor phenotype or lifespan. On the opposite, preliminary results indicate that the endogenous overexpression of NRG1-typeIII in the SOD1G93A mouse model may be detrimental.

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Central and Peripheral Age-Associated Changes in the Neuromuscular System of C57BL/6J Mice

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Data on the potential causative factors of aging sarcopenia are controversial and inconclusive, hampering the intervention strategies aimed at the preservation of skeletal muscle function in the elderly. Here, we performed a detailed characterization of age-associated neuromuscular changes in C57BL/6J mice. Distinct cellular components of the neuromuscular system, including different (slow- and fast-twitch) muscles, were simultaneously analyzed at specific ages. We found that aging was not accompanied by a significant death of spinal motoneurons (MNs), although some of them displayed a "sick" appearance. These MNs were already observed in adult animals suggesting that, with age, some MNs undergo early changes which do not necessarily lead to cell loss. Morphological alterations in motor axons were already observed in adult animals but substantially increased with age. Additionally, aged MNs were depleted of cholinergic and glutamatergic inputs, suggestive of altered MN excitability. Aging was associated with significant reductions in nerve conduction speed and amplitude of the compound muscle action potentials in distal hindlimb muscles. Moreover, aged spinal cord displayed prominent gliosis with increased density of proinflammatory M1 microglia and A1 astroglia. Old muscles exhibited signs of denervation and polyinnervation, changes in fiber type composition, high proportion of fibers showing central nuclei and lipofuscin aggregates, and augmented expression of molecules related to neuromuscular junction development and maintenance, including CGRP, GAP-43, agrin, FGBP1 and TGF-β1. No correlation was found between age-related alterations in muscles and their topography or fiber type composition. Our data provide a coherent global view of aging-associated events with particular focus on neuromuscular system change.

Alba Blasco and Sílvia Gras contributed equally to this work.

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Cholinergic Afferent Synapses on Motoneurons are Selectively Immunolabeled by the Monoclonal Y172 Antibody Against Phospho-c-Jun

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Motoneurons (MNs) receive prominent cholinergic inputs (C-boutons) from spinal interneurons (1). C-boutons exert an important neuromodulatory activity in controlling the excitation state of MNs, which is essential to drive motor behavior (2). Alterations in C-boutons appear to play an important role in MN diseases, particularly in amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) (3,4). During immunocytochemical analysis of the role of c-Jun in healthy MNs with a monoclonal (clone Y172) antibody against phospho (p)-c-Jun (serine [Ser]63), unexpected labeling was identified in the cell body cytoplasm (5). As predicted for c-Jun in adult spinal cord, very few, if any MNs exhibited nuclear immunoreactivity with the Y172 antibody; conversely, virtually all MNs displayed strong Y172 immunostaining in cytoplasmic structures scattered throughout the soma and proximal dendrites. Most of cytoplasmic Y172-positive profiles peripherally located were closely associated with VAChT-positive C-boutons, but not with other types of nerve afferents contacting MNs. Ultrastructural analysis revealed that cytoplasmic Y172 immunostaining was selectively located at the subsurface cistern (SSC) of C-boutons and also in the inner areas of the endoplasmic reticulum. We noticed that MNs from NRG1 type III-overexpressing transgenic mice, which show abnormally expanded SSCs, exhibited increased density and size of peripherally located Y172-positive profiles. A similar immunocytochemical pattern to that of the Y172 antibody in MNs was found for a polyclonal antibody against p-c-Jun (Ser63) but not for another polyclonal antibody that recognizes c-Jun phosphorylated at a different site. The analysis of Y172 immunoreactivity in injured MNs after peripheral nerve transection or in murine models of ALS (SOD1G93A mice) and SMA (Smn2B/- mice) revealed a prominent nuclear-positive labeling and a significant depletion of cytoplasmic immunostaining, which preceded the C-bouton loss occurring in these paradigms. RNA interference experiments to knock down c-Jun in vitro by using different shRNA constructs resulted in a dramatic decrease in nuclear Y172 immunostaining in MNs without any reduction in the density of cytoplasmic Y172-positive profiles, suggesting that the synaptic antigen recognized by the antibody corresponds to a C-bouton-specific protein other than p-c-Jun. Our results lay the foundation for further studies aimed at identifying this protein and determining its role in the context of the development, maintenance, plasticity and pathology of C-boutons.

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Building New Evidence to Improve the Outcomes Assesment in Patients with SMA

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The Spanish SMA patient association, FundAME, is running a project aimed at Building a Registry Module focused on Patient Relevance that will integrate

the National Patient Reported Registry. Up today, the experiences and needs of patients with SMA and their families have not been studied in depth in Spain. The objective of present study is to identify those aspects of the disease that are more relevant or have a higher impact for patients and that should be captured in addition to the functional scales as part of PRO for SMA patients.

This is a qualitative study following focus group methodology. 5 focus groups were conducted by a trained moderator following a semistructured guide that has previously counted on the input of a Scientific and Patient Advisory Board.

Focus groups, organized by FundAME during its annual meeting, were as follows: parents of children non sitters (8 parents); children (10-16 years) with SMA without ambulation (10 children) ; parents of children with SMA without ambulation (10) ; adult SMA patients (7); parents of children with SMA with ambulation (11). All group meetings were recorded and later transcribed. Independent analysis was carried out by two analysts using the software Dedoose.

The main areas that emerged in the meetings were slightly different depending on the group, but common areas were: mobility-independence; fatigue and fatigability; pain; vulnerability; breathing and speaking; feeding; sleep and rest; scoliosis, contractures and hip dislocation; infections and hospitalisations; time spent in care/everyday activities; stigma; and fear of the future. Some of these aspects, such as mobility-independence, were related to activities of daily living such as personal care, washing, toilet, dressing, feeding, transfers from bed/chair/wheelchair or going outdoors alone.

These activities reflect at the same time both the possibility to perform task but also the level of independence and the level of care/assistance needed. Others reflected aspects of endurance, fatigue and fatigability such as the energy needed to go through student/professional day, maintaining position during the day or being able to perform activities / movements repeatedly (taking notes, using mobile phone) on a sustained way throughout the day.

Pain and vulnerability (defined as the state of being exposed to the possibility of dying because of everyday events such as choking when swallowing or getting a serious respiratory infection with minimal social exposure) were two main topics that have not been previously considered as relevant in the assessment of patients with SMA.

The outcome is a list of items of the areas considered to be relevant and important to be systematically measured as part of PRO. These areas were considered critical to be taken into account in the assessment of the impact of SMA on the quality of life of patients and their familiars. This study provides very useful data to incorporate the perspective of the patient and those who are close to him, in the outcome assessment of new treatments for SMA.

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Clinical Diagnosis of Neurological Disorders by NGS: Update After Two Years

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Given the prevalence of hereditary neurological disorders, such as neuropathies (1-5/10.000), spastic paraplegia (1-9/100.000), and neurodegenerative disorders (1-9/100.000), high throughput and cost-effective techniques are primordial in order to offer efficient diagnosis to affected patients. Consequently, Next Generation Sequencing (NGS) has become a valuable tool for clinical diagnosis.

The Institute of Pathology and Genetics (IPG asbl) developed a capture panel (SeqCapEZ choice library from Roche, sequenced on Illumina NextSeq) targeting 117 genes involved in neuropathies (several types of Charcot-Marie-Tooth disease, hereditary sensory and autonomic neuropathies, and ataxias), 63 genes involved in spastic paraplegia, and 36 genes involved in neurodegenerative disorders (ALS, and early-onset and familial Alzheimer's and Parkinson's diseases) for routine diagnosis.

Since April 2018, we analysed more than 500 familial and sporadic cases, with a patient mean age of testing of 55 years old for all neurological indications considered (52 years old for neuropathies, 43 years old for spastic paraplegia, and 56 years old for neurodegenerative disorders). The diagnostic yield (as in at least one clear pathogenic mutation identified), allowing familial, presymptomatic, and prenatal diagnosis, is around 10%.

About 33% of our patients present at least one uncertain clinical significance variant (VUS), which

require extensive literature work and segregation analysis in order to classify them. The negative diagnosis (57%) can be explained either by a genetic cause yet to be identified (multigenic disease, epigenetic variation...), by an effect of the environment (normal aging, diabetes, drug treatments, auto-immune diseases, paraproteinemia...), and/or by technical limitations.

To elucidate those cases, expanded analysis by clinical exome, whole-exome, or whole-genome sequencing, could be offered to young patients presenting a familial form of a neurological disorder. Those investigations will allow us to further develop our panel by the addition of new genes.

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PRE-084, a Sigma-1 Receptor Agonist, Mitigates Glial Reaction and Motoneuron Deafferentation in SMA Mice

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Spinal muscular atrophy (SMA) is a devastating genetic disease characterized by the loss of motoneurons (MNs), skeletal muscle atrophy and paralysis. SMA is caused by deletion or inactivating mutations of the survival motor neuron 1 (SMN1) gene resulting in deficient SMN protein levels. The most promising strategies for therapy are those aiming to enhance SMN expression by using antisense oligonucleotides, and gene therapies to directly replace SMN1 gene. However, SMN-independent, complementary treatments aimed to ameliorate and/or preserve neuromuscular system integrity and function are also necessary. Excitability properties of MNs appear to play a critical role in their degree of vulnerability. MN excitability is modulated by cholinergic inputs mediated by C-type synapses (C-boutons). The Sigma-1 receptor (Sig1R) is a protein highly expressed in MNs, particularly located at C-boutons. Sig1R has a pleiotropic role in MNs and appears to be involved in the modulation of excitability. Previous studies have demonstrated that Sig1R activation prevents MN death, preserves motor activity and prolongs survival in mouse models of amyotrophic lateral sclerosis (ALS). We explored here whether treatment with the Sig1R agonist 2-(4-morpholinethyl)1-phenylcyclohexanecarboxylate (PRE-084) was able to exert beneficial effects in spinal muscular atrophy (SMA). Two murine models of SMA were used: the SMNΔ7 (severe model) and Smn2B/- (intermediate model) mice. We report here that chronic administration of PRE-084 attenuates reactive gliosis and restores the microglial phenotype (M1/M2) balance altered by the disease and, consequently, increases the beneficial antiinflammatory phenotype of these cells. Moreover, the Sig1R agonist partially prevents the loss of afferent inputs on SMA MNs. Nevertheless, PRE-084 does not elicit positive effects on median survival, motor abilities, MN degeneration, and major histopathological changes in SMA mice.

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Autoimmune Comorbidity in Patients with Myasthenia Gravis: Analysis of a Northern Spanish Cohort

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Patients affected by an autoinmune disorder are at a higher risk of developing other ones- specifically myasthenia gravis (MG) patients are known to have a 13-22% risk of developing a second autoinmune disorder, which is higher than the general population.

We evaluated the co-occurrence of autoinmune diseases in a retrospective cohort of patients with myasthenia gravis diagnosed between 2000 and 2017 in Navarra, a northern Spanish region. Our cohort included 256 patients, 136 male and 115 female, of which 207 were AChR positive, 17 were MuSK positive, 2 were Lrp4 positive and 11 had an unknown antibody status. 33 of them had thymoma. 43 were early-onset patients (age at onset < 50 years) and 212 were late-onset patients.

Data about autoinmune comorbidity was available in 251 patients. 53 of them had at least one autoin-

mune disease in association with MG, of which 26 were thyroid diseases, 12 cases of atrophic gastritis of which 5 had pernicious anemia, 3 cases of rheumatoid arthritis and 2 of spondyloarthritis, 4 cases of psoriasis, 3 of vitiligo, 1 lichen, 1 autoimmune ataxic neuropathy, 1 insulin-dependent diabetes mellitus, 1 alopecia areata, 1 undifferenciated connective-tissue disease, 2 cases of primary Raynaud's disease, 2 cases of rheumatic polymyalgia, 1 antiphospholipid syndrome, 1 systemic sarcoidosis, 1 autoimmune Rippling syndrome, 1 celiac disease and 1 case of inflammatory bowel disease. 9 patients had 2 or more autoinmune diseases in association with MG.

Frecuency of autoinmune comorbidity in our sample was 21,1%: 33% among women and 11% among men. 18% among patients with any antibody positivity and 35% among patients without known antibodies; 19% among patients with thymoma and 21% among patients without thymoma; and 19% in early-onset patients versus 21,6% in late-onset patients.

Our results are in line with previous research reporting a high prevalence of autoinmune comorbidity in patients with MG. However, we did not find a greater prevalence in antibody-positive or in early-onset patients, as has been previously reported.

It is important to consider these conditions in our MG patients, as a rapid diagnosis is likely to improve management and prognosis of both illnesses.

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Could Fat-Free Mass Index be a New Follow-Up Tool for Chronic Inflammatory Demyelinating Polyradiculoneuropathy?

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Background: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune demyelinating disease. Muscle mass can be reduced in CIDP. Calculation of FFMI (fat-free mass index) is more reliable parameter for evaluating muscle mass. Electroneuromyography (ENMG) is a golden standard in diagnosis and follow-up of CIDP. The aim of this study is to compare the muscle mass and motor nerve conduction velocity before and after intravenous immune globulin (IVIG) treatment in CIDP.

Methods: Total 23 CIDP patients regularly followed in our clinic enrolled to study. Nerve conduction velocities (NCVs) were provided from ENMG. FFMI was calculated as FFM (fat free mass) (kg) divided by squared (m2) of the subjects' height using parameters provided from TANITA© SC-330 analyzer. Both NCVs and FFMI were compared at the first admission(1st) and 6 months later(2nd).

Results: Mean age was 58±14 (8 male/15 female) years. Peroneal motor NCV-1st and 2nd were 39±8 m/sec, 44±5 m/sec, respectively. Tibial motor NCV-1st and 2nd were 36±11 m/sec, 40±12m/sec, respectively. Motor NCVs-1st and 2nd were found in median nerve (52±6 m/sec, 53±11m/sec) and ulnar nerve (52±6 m/sec, 53±11m/sec), respectively. FFMI 1st and 2nd were 19±1 kg/m2, 22±2 kg/m2 respectively. First and 2nd evaluation of tibial, peroneal motor NCVs and FFMI were found as statistically different indicated that increase of both parameters

Conclusion: Our results suggest that the muscle mass decreases in parallel with the damage to the nerves in CIDP especially in lower extremity. IVIG may be effective for muscle mass loss related to peripheral nerve disorder. Calculating FFMI, which is a non-invasive method, may recommend in the follow-up of CIDP.

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LGMDR1 Modelling Through CRISPR/Cas9 Edited Isogenic iPS Cells

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Autosomal recessive limb-girdle muscular dystrophy-1 (LGMDR1) is caused by mutations in CAPN3

gene, which encodes for calpain 3 enzyme. Despite the genetic basis of the disease is well known, the mechanisms by which these mutations lead to muscular dystrophy is unknown. The evidence suggests that calpain 3 has a multifunctional role maintaining the muscular homeostasis and some studies also suggested that calpain 3 participates in the maintenance of satellite cells and could be implicated in the muscle regeneration (Stuelsatz et al., 2010; Rosales et al., 2013).

To explore the potential role of calpain 3 in the early stages of myogenesis and the maturation of myotubes, we sought to obtain a valid myogenic in vitro model that would not require the scarce and finite primary myoblast derived from patients. 5 patients and 2 control skin biopsies were selected from the available samples at our group to develop iPSC lines with different approaches. 2 of the patient samples were reprogramed at Perlingeiro's lab, where gene corrected isogenic lines were generated with CRISPR/Cas9 for each of the patient lines (Selvaraj et.al, 2019). On the other hand, our group developed iPSC lines from all the samples and isogenic calpain 3 KO lines were generated with CRISPR/Cas9 from one of the controls. To test whether this cellular model reproduces some of the described molecular phenotype in LGMDR1, we used the available isogenic iPSC lines generated from both teams. We also wanted to know if isogenic comparison avoids the variability issues often encountered when working with iPSC lines from different patients.

First of all, a battery of characterization tests was performed in order to assess the pluripotency of the lines, and off-target analysis was performed in the CRISPR/Cas9 edited iPSCs. To study myogenesis, myogenic differentiation was achieved through a transient expression of exogenous PAX7 and an optimized differentiation protocol (Darabi et al., 2012; Selvaraj et.al, 2019). All the lines showed myogenic potential and were able to differentiate into myotubes regardless of the calpain 3 mutations. In one of the patient/corrected isogenic line pairs, MYHC, MYOG, MYOD and PAX7 expression was studied in differentiated cultures, and the myogenic progenitors from the gene corrected isogenic line, showed significantly higher proliferation capacity. Next, we are going to analyze the myogenic gene expression levels at different culture time points at the mRNA and protein levels, measure the fusion index, analyze the described affected pathways on the disease, and evaluate the potential of different molecules to restore the pathological alterations.

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MATR3-Related Distal Myopathy in Patients from the Republic of Bashkortostan

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Background: MATR3-related distal myopathy is a rare autosomal dominant disorder which is also known as vocal cord and pharyngeal distal myopathy (VCPDM). It is caused by a c.254C>G mutation (p. S85C) in the MATR3 gene. VCPDM is clinically characterized by adult onset of muscle weakness in the feet and hand combined with bulbar symptoms.
Methods: This study comprised 21 patients (11 females and 10 males) with genetically confirmed VCPDM from 6 families of Tatar ethnic origin from the Republic of Bashkortostan (population: 4,037,811).
Results: The age of onset ranged between 28 to 65 years (median 41 years). There was no gender difference in age at onset of the disease (p=0,6). Only one male patient had first symptoms of VCPDM under 35 years of age. The disease began with distal muscle weakness (100% of cases) most severely affecting ankle dorsiflexion that resulted in gait disorder (steppage gait). As the disease developed, proximal leg weakness occurred (19 patients). Relevant distal arm weakness was found in 19 patients. 16 patients (76% of cases) also complained of proximal arm weakness. Dysphagia and disphonia were observed in less than 50% of cases and appeared as disease progressed. Serum CK levels ranged from normal to a threefold increase. Needle electromyography (EMG) was performed on 13 patients and showed myopathic changes. Due to the similarity of symptoms and incomplete electrophysiological data, VCPDM was mistaken for hereditary motor sensory neuropathy type 2 (HMSN type 2) and myotonic dystrophy type 1 (MD type 1) that were provisionally diagnosed in 6 and 2 patients respectively.
Conclusion: in the Republic of Bashkortostan MATR3-related distal myopathy occurs more often than expected and might be misdiagnosed as other neuromuscular disorders.

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A Very Peculiar Nerve Conduction Pattern of Matrin 3 Associated Distal Myopathy

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Missense Matrin3 mutations are associated with familial amyotrophic lateral sclerosis (ALS), but a specific Ser85Cys (S85C) substitution on the MATR3 gene produces a distinct phenotype of distal myopathy associated with vocal cord and pharyngeal weakness. Although vocal cord paralysis is a very specific feature, it generally occurs years after limb weakness. We report two cases of patients from the same family.

Patient 1 is a 53-year-old female that begun, at age of 43, with difficulty on walking and hand tasks, like peeling potatoes or wringing a cloth. Her mother, maternal uncle and maternal grandfather had "muscular dystrophy" and one first degree cousin (patient 2) similar complaints. Initial evaluation, showed slight paresis of thumb abduction. CK was on the normal range, nerve conduction unremarkable, and EMG revealed a myopathy pattern and fibrillations. Genetic testing revealed the S85C substitution. Limb weakness progressed and, recently, she complained of occasional choking with water. Examination showed distal tetraparesis more pronounced on thumb abduction and foot dorsiflexion.

Patient 2 is a 48-year-old female and, at 35 years old, started with similar complaints as patient 1. Diagnostic test results were alike her cousin. Recent evaluation showed distal tetraparesis more pronounced on thumb abduction and plantar flexion.

Both patients repeated electroneuromyographic (ENMG) recently due to thenar atrophy and hand dysesthesia (patient1) and hand and wrist pain (patient2). A significant reduction on median motor nerve amplitudes was observed in both patients with normal sensitive potentials of median nerve and ulnar motor and sensitive studies. EMG showed signs of myopathy inclusively in abductor pollicis brevis.

This pattern is not usual to find on an EMG lab. Patients with carpal tunnel syndrome virtually never show prominent changes of median nerve motor fibres before significant sensitive involvement. Very few entities can generate a pattern of significant axonal motor involvement of median nerve without changes on sensitive fibres, namely, motor neuronopathies, like ALS, where this pattern is particularly evident in patients with split hand syndrome. It is also found in post-polio syndrome patients, hereditary motor neuropathies, especially the ones with upper limb predominance and in cases of Hirayama disease, but generally ulnar motor amplitudes are concurrently decreased. A similar median nerve pattern is seen in patients with true neurogenic outlet thoracic syndrome, but a decreased amplitude of ulnar and medial antebrachial cutaneous sensory nerves points the problem to the lower trunk of the brachial plexus. In all those cases, needle evaluation reveals a neurogenic compromise. To our knowledge, patients with myopathies do not present this pattern. We have seen it rarely in patients with severe inflammatory myopathy, but the history is of a subacute progression, and motor amplitudes are globally decreased. This ENMG pattern, to our knowledge, has not been reported in patients with Matrin3 associated myopathy. This work suggests that matrin3 S85C substitution should be suspected and tested in any patient with a clinical and electromyographic picture of distal myopathy and a nerve conduction study revealing a "small" motor and "big" sensory median nerve with preserved motor and sensory ulnar studies.

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Combined Central and Peripheral Demyelination: A Comparative Electrodiagnostic and Sonographic Study

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Background: Demyelinating lesions are usually limited either to the central or to the peripheral nervous system. Rarely, lesions can occur simultaneously or successively resulting in a combined central and peripheral demyelination (CCPD). We performed a comparative nerve conduction and ultrasound in CCPD patients and CIDP (chronic inflammatory demyelinating polyneuropathy) controls.

Methods: We enrolled consecutive patients seen at the neuromuscular outpatient clinic of the UMC Utrecht: 4 CCPD and 10 incident CIDP controls. All

patients underwent standardized nerve conduction studies, and a sonographic protocol assessed nerve size at predetermined sites of brachial plexus and median nerves. In addition, all CCPD patients underwent brain and spinal cord imaging MRI.

Results: Except for stiffness, facial palsies and visual disturbances (central nervous system involvement), we found no differences in term of sensory or motor symptoms between CCPD and CIDP. All CCPD patients showed multiple demyelinating lesions on MRI, meeting the revised Mcdonald criteria for diagnosis of multiple sclerosis (MS). We found patchy electrodiagnostic features of demyelination in all CCPD and CIDP patients, fulfilling the definite criteria of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) for CIDP. Ultrasound revealed a similar pattern of multifocal nerve enlargement along the length of nerves and brachial plexus in both CCPD and CIDP.

Conclusion: This study demonstrates that neuroimaging allows visualization of both peripheral and central nervous system involvement in CCPD. The fact that electrophysiologic and morphological patterns in CCPD and CIDP are similar, indicate shared underlying immune-pathophysiologic mechanisms. At the conference we will present an update of the study cohort, including an additional group of MS patients.

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AKCEA-TTR-LRx, A Follow-On Compound Of Inotersen, Is Being Developed For Hereditary Transthyretin-Mediated Amyloid Polyneuropathy (hATTR-PN)

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Background: Hereditary transthyretin-mediated amyloid polyneuropathy (hATTR-PN) is a progressive and fatal axonal sensorimotor and autonomic neuropathy caused by misfolding/aggregation of transthyretin (TTR), a liver produced protein. Inotersen (Tegsedi™) is an antisense oligonucleotide (ASO) that binds to TTR mRNA to inhibit the production of TTR. In a double-blind placebo-controlled study (NEURO-TTR) inotersen slowed disease progression in patients with hATTR-PN. AKCEA-TTR-LRx is an ASO with the same sequence as inotersen conjugated to triantennary N-acetyl galactosamine (GalNAc3) which targets the asialoglycoprotein receptors expressed abundantly on hepatocytes. The GalNAc conjugation) results in a substantial increase in potency thus allowing a lower and less frequent dosing regimen and an improved safety and tolerability profile. In a phase 1 healthy volunteer study, AKCEA-TTR-LRx given at a 45 mg dose by subcutaneous injection (SC) every four weeks (Q4W) achieved a median reduction in serum TTR of > 85% compared to baseline.

Objective: NEURO-TTRansform (ClinicalTrials.gov number NCT04136184) is a phase 3 global, open-label study that aims to determine if AKCEA-TTR-LRx is effective and safe as compared to historical placebo (placebo arm in the NEURO-TTR trial) for the treatment of hATTR-PN.

Methods: Approximately 140 hATTR-PN patients will be randomized to receive either AKCEA- TTR-LRx (n ~ 120; 45 mg SC Q4W) or inotersen (n ~ 20; 300 mg SC weekly) for 80 weeks. To facilitate the use of the placebo arm from the NEURO-TTR trial as a historical control, entry criteria for the NEURO-TTRansform are almost identical to those in the NEURO-TTR trial. Key inclusion criteria include preserved ambulatory status (Familial Amyloid Polyneuropathy or ATTRv/FAP stage 1 or stage 2), confirmed TTR mutation, and Neuropathy Impairment Score (NIS) between 10 and 130. Key exclusion criteria include estimated glomerular filtration rate < 45 mL/min/1.73 m2, platelets ≤ 125 × 109/L and urine protein/creatinine ratio ≥ 1000 mg/g. Concomitant treatment with tafamidis, inotersen, patisiran, diflunisal, doxycycline and tauroursodeoxycholic acid (TUDCA) are not allowed. If previously treated with tafamidis, diflunisal, doxycycline or TUDCA, patients must have discontinued treatment for at least 2 weeks prior to Study Day 1. Co-primary efficacy endpoints at Week 66 (primary endpoint analysis) are change from baseline in: serum TTR concentration, modified NIS+7 and Norfolk Quality of Life-Diabetic Neuropathy. An interim analysis will be performed

at Week 35. Secondary endpoints include the change from baseline in the Neuropathy Symptom and Change Score, Physical Component Summary score of 36-Item Short Form Survey, Polyneuropathy Disability Score and Modified Body Mass Index.
Results: This trial is currently enrolling patients.
Conclusions: Despite recent advances, there is still a need for effective, well-tolerated and convenient treatments for hATTR-PN. NEURO-TTRansform is a phase 3 trial designed to evaluate the efficacy and safety of AKCEA-TTR-LRx compared to the placebo arm in NEURO- TTR for the treatment of hATTR-PN.

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Calprotectin is elevated in Myasthenia gravis: a potential novel biomarker for diagnosis and disease activity

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Objective: Myasthenia gravis (MG) is the most common autoimmune disease affecting the neuromuscular junction by specific autoantibodies. The etiology of MG and its heterogeneity in clinical courses are poorly understood, although it was recently shown that gut microbial dysbiosis plays a critical role. Since levels of Calprotectin (CLP) seem to correlate with level of dysbiosis, we hypothesize that CLP may serve as potential diagnostic and disease activity biomarker in MG.
Methods: Sera from 251 patients with MG with varying degrees of disease activity, 38 age- and gender matched healthy controls (HC), as well as 13 patients with non- inflammatory neurological diseases (NC) were analyzed for CLP in a cross-sectional design. Prospectively, we tested CLP levels in MG patients for up to 3 years.

Association of CLP levels with socio-demographic parameters, disease activity (MGFA classification system, quantitative myasthenia gravis (QMG) score, myasthenia gravis-specific Activities of Daily Living scale (MG-ADL)), antibody (Abs) status (acetylcholine receptor antibody (AChR-Abs), muscle specific receptor tyrosine kinase antibody (MuSK-Abs), lipoprotein-related protein 4 (LRP4), seronegative), history of myasthenic crisis, treatment regime (pyridostigmine, prednisolone, immunosuppressive therapies), and history of thymectomy were investigated using univariate analysis.
Results: Mean baseline serum levels of CLP were significantly higher in MG patients compared to controls (4.3 µg/ml vs. 2.1 µg/ml; $p < 0.0001$), with an area under the curve (AUC) to discriminate MG patients from controls of 0.77 (CI 0.70-0.83, $p < 0.0001$). Higher levels of CLP were associated with a higher clinical disease severity measured by MGFA classification and QMG score.
Conclusions: Elevated serum CLP levels may serve as promising objective and reliable disease activity biomarker correlating with baseline MGFA and QMG score. In contrast to other biomarkers, CLP is stable at room temperature and measurement is performed rapidly, making it a promising candidate biomarker to support the diagnosis as well as monitoring disease progression in MG. Our study warrants the need for prospective multicenter studies to validate the utility of CLP for decision making in care of MG patients.

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Case report: clinical coexistence of Amyotrophic Lateral Sclerosis and Progressive Supranuclear Palsy

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Objective: A few cases of clinical coexistence of Amyotrophic Lateral Sclerosis (ALS) and Progressive Supranuclear Palsy (PSP) have been previously reported. Frontotemporal lobar degeneration (FTLD) is associated with both ALS and PSP, but with different neuropathologic changes (TDP-43 in ALS and Tau-4R in PSP). We report a case of clinical association of ALS and PSP, with a possible behavioural variant of FTLD (bvFTD)
Methods: We reviewed the patient's medical history and the previously reported cases.
Results: A 70-year-old man, with unremarkable personal or familiar history, started in 2017 with memory loss, irritability, compulsive behavior and dietary changes (preference for sweet foods). An ini-

tial diagnosis of mild cognitive impairment with parkinsonism (symmetric bradikynesia and rigidity) was evoked by a first neurologist. Levodopa therapy was started with poor response. In the next months he suffered a motor decline with freezing of gait and frequent falls. Brain magnetic resonance imaging (MRI) showed a mild global cortical atrophy and DAT-scan SPECT was abnormal (right putaminal hypocaptation). Neuropsychological tests showed deficits in executive functioning.

Throughout 2019 he progressively developed dysphagia and dysarthria. By december/2019 he presented with mild dysarthria, bilateral IV+/V paresis of hip flexors (MRC scale) and generalized hyperreflexia with left Babinski and Hoffman signs. Anti-acetylcholine and anti-MuSK antibodies were negative and the electromyoneurogram found low motor neuron signs in 2 regions. A probable ALS was diagnosed and riluzole was started. Cognitive decline progressed with socially inappropriated behavior and aggressiveness. By August of 2020 the patient required nocturnal non-invasive ventilatory support and was anarthric, tetraparetic (IV/V proximal and III/V distal), with worsening symmetric bradykinesia and rigidity. Supranuclear gaze palsy also appeared. Neither genetic nor anatomopathological testing were performed.

Conclusions: Our patient fulfills both probable PSP MDS-PSP support criteria and probable ALS Awaji-Shima criteria. He can also be diagnosed of possible bvFTD according to the International consensus criteria for bvFTD. Although atrophy pattern in brain MRI was not specific and a perfusión SPECT was not performed, the clinical course is very suggestive.

Recently, the first case of clinicopathological comorbidity of ALS and PSP was published. The authors propose a casual association between ALS –TDP-43 and PSP –Tau 4R pathologies. Co-occurrence of both diseases is possible, so clinicians should be aware of the appearance of new symptoms distinct from those of the original syndrome as, like in our case, the debut of motor paresis and signs of first and second motor neuron damage years after the parkinsonism onset. Another report of 3 cases with clinical ALS and PSP, with only TDP-43 pathology in neuropathological exams, suggested that "PSP-like syndrome" could represent a clinical entity within the spectrum of TDP-43 neurodegeneration.

In conclusion, the clinical association of PSP and ALS symptoms is uncommon but possible. As suggested by previous authors, it could be related either with a casual concurrence of this two proteinopathies in a single patient or with a rare clinical phenotype of an isolated neurodegenerative disorder.

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Evaluation of the muscle imaging profile in a large cohort of patients with LGMD-D2

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Introduction: Muscle dystrophy due to transportin-3 mutation (LGMD-D2) is a rare disease with broad clinical and pathological variability. Thus far muscle imaging studies of LGMD-D2 are limited. Our objective was to gain inside the phenotype of the disease through a study of the imaging profile of a large cohort of patients from the original LGMD-D2 family.

Methods: Cross-sectional and longitudinal study of a cohort of patients with LGMD-D2 evaluated with muscle imaging studies (MRI/CT). Clinical, functional and semi-quantitative muscle imaging data were studied. A whole cumulative Mercuri imaging score (WCS) per patient was calculated as the mean of Mercuri scores for each patient. Hierarchical analysis, graphical representation as a heatmap and correlation between imaging and clinical data by using Bayesian statistic were performed.

Results: 30 patients from the original LGMD-D2 family were evaluated, two of them asymptomatic over the age of 60. 19 patients were females (63%) and 11 were males (37%). The mean time of follow-up of the patients was 11 years (range from 1 to 30 years). Mean age at the onset of the disease was 14 years old, with a range from congenital to 49 years. A specific pattern of muscle involvement could be observed. The most frequent and severely affected muscles were sartorius (97%) and gastrocnemius medialis (90%). The heatmap grouped the patients into four groups according to the severity and spread of muscle involvement in imaging studies. The WCS ranged from 0.44 to 2.78 out of 4, and was significantly associated with Vignos scale. A second MRI was performed in 10 patients, with significant WCS progression at variable rates.

Conclusions: This study describes a specific pattern of fatty muscle infiltration in LGMD-D2 patients.

The involvement of sartorious is an early radiological sign of the disease, even in asymptomatic patients. Muscle imaging studies prove to be a useful tool to better understand the natural history of this complex muscular dystrophy.

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Myelopathy and polyneuropathy due to "laughing gas" inhalation

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Nitrous oxide (N2O - commonly referred to as "laughing gas") is a common medical inhalational anaesthetic. However, recreational use via direct inhalation is becoming increasingly popular amongst the younger population. Abuse or long-term use can cause vitamin-B12 deficiency, and severe neural and psychiatric symptoms. We present 8 patients who developed subacute myelopathy and/or polyneuropathy after nitrous oxide overuse.

Cases: 7 men and 1 woman with ages between 19 and 35 years old. The time from the beginning of the symptoms to the admission at the hospital varied between 1 day and 2 months. All patients referred sensitive symptoms in the legs, 4 also had symptoms in the hands and 3 patients had also hypoesthesia in the thorax and abdomen. All of them had walking difficulties with balance impairment. 5 also had a loss of strength. On examination, 7 patients had distal paresis ranged from 0 to 4+/5. All patients had affected superficial and deep sensibility, and 3 also presented dysmetria. 3 patients had a recent COVID19 infection, indeed, in one of them the polyneuropathy was considered to be due to both causes: COVID and N20 abuse. EMG showed polyneuropathy (PNP) in all the patients with high variability: 2 patients with sensory demyelinating PNP, 2 with sensorimotor axonal and demyelinating PNP, 1 with motor demyelinating PNP, 2 with sensorimotor axonal PNP and 1 with sensorimotor demyelinating. Full-spine MRI showed subacute cervical and thoracic myelopathy located in the posterior columns in 4 patients. Blood test showed decreased vitamin B12 in 4 patients. From the patients within the normal range, 3 had high homocysteine and/or methilmalonic acid. A lumbar puncture was performed in 5 patients. 2 showed lightly increased proteins, and the other 3 were normal.

Patients were treated with intramuscular vitamin B12 when it was low, and pregabalin for the sensory disturbances. One patient was also treated with intravenous immunoglobulins. Only 4 patients had a control visit from 1 to 5 months after admission, and the 4 of them continued to present symptoms and abnormalities in the examination.

Recreational use of N2O has increased worldwide in the past 10 years, potentially due to its easy access (it can be bought in supermarkets and online in "whippets") and the false perception that it is completely innocuous. Inhalation results in immediate euphoria, laughing, and mild hallucinations that last only a few seconds. Due to this rapidly diminishing effect, users usually repeat doses over short periods of time. N2O exerts neurotoxicity though inactivation of cobalamin, leading to demyelination. Both central and peripheral nerve system affectation is increasingly reported. It is mandatory to raise awareness about the potential harm of the drug in order to reduce the number of cases.

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Epidemiology and prognosis of bulbar-onset ALS in a Canary Islands cohort

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Objective: Bulbar-onset is reported to have a worse outcome than spinal-onset amyotrophic lateral sclerosis (ALS). Our objective was to compare the epidemiology and prognosis of our bulbar-onset vs. spinal-onset ALS patients.

Methods: We retrospectively reviewed the medical history of all the patients with ALS followed-up by our neuromuscular diseases unit in the period 1/1/14-30/11/20 and collected clinical data about debut symptoms and disease evolution. Bulbar-onset and spinal-onset ALS groups were compared. We used SPSS Statistics v25 to perform the statistical analysis.

Results: 59 cases of ALS were found: 37 (63%) spinal-onset, 21 (36%) bulbar-onset and 1 respiratory-onset. 67% of bulbar-onset and 49% of spinal-onset patients were females (not statistically significant). Bulbar-onset patients were older at debut (68 vs 58 years, p=0,003). The most frequent bulbar-onset

symptom was dysarthria (13 patients, 62%), followed by dysarthria with dysphagia (5, 24%) and isolated dysphagia (3, 14%). 62% in the bulbar-onset group and 67% in spinal-onset group already died. Mean survival time from debut was 44 months in bulbar-onset and 46 in spinal-onset, without statistically significant differences. Mean diagnosis delay was 13 months in patients with bulbar-onset and 17 in spinal-onset (not statistically significant). At present or before death, 90% of patients with bulbar-onset and 43% of spinal-onset suffered anarthria (p<0,001). Mean time to anarthria was fewer in bulbar-onset group (36 vs 52 months, p=0,007). Requirement of ventilatory support was similar between both groups: 65% in spinal-onset vs 62% in bulbar-onset in a mean time of 34 months in spinal-onset and 41 in bulbar-onset (not statistically significant difference). Almost all patients were treated with non-invasive ventilation (only 1 tracheostomized). Bulbar-onset patients needed food thickeners more frequently (76% vs 32%, p=0,001) and earlier in the disease course (34 vs 44 months, p=0,034). 52% patients with bulbar-onset required gastrostomy, but only 27% of spinal-onset (p=0,05) did. The time from debut until gastrostomy placing was 48 months in bulbar-onset and 62 in spinal-onset (p=0,043).

Conclusions: The most frequent bulbar-onset ALS presentation was isolated dysarthria. Dysphagia was also frequent, suffered by more than one third of bulbar-onset patients. Mean diagnosis delay was 13 months, without significant differences with the spinal-onset group. Although bulbar-onset has been associated to a worse prognosis, our bulbar-onset patients had the same survival time than our spinal-onset ALS patients, even though they were 10 years older at the disease debut. Bulbar-onset was not associated with ventilatory support needing. Two thirds of our bulbar-onset patients were females and the spinal-onset ALS group didn't show sex differences, but we didn't find a definitive association between sex and initial symptomatology. However, patients with bulbar-onset ALS presented a worse evolution of the defining symptoms of the group (dysarthria with dysphagia): anarthria was 2-fold more frequent and appeared earlier in patients with bulbar-onset ALS and bulbar-onset ALS patients required food thickeners or gastrostomy more frequently and earlier. In conclusion, bulbar-onset ALS patients didn't show a worse global or respiratory prognosis than spinal-onset ALS patients, and the main difference was the more serious and early affectation of speech and swallowing.

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A Phase I/Ii Open-Label Gene Replacement Clinical Study for Late Onset Pompe Disease

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Pompe disease, an autosomal recessive neuromuscular disease caused by mutations in the GAA gene leading to functional enzyme acid alpha-glucosidase (GAA) deficiency. Late-onset Pompe disease (LOPD) is characterized by progressive skeletal myopathy with muscle weakness and respiratory insufficiency, leading to full-time ventilator dependence, wheelchair use, and early death. AT845, an AAV-based gene therapy for Pompe disease under development is designed to target muscle tissue. Preclinical studies in GAA KO mice infused with AT845 have resulted in GAA activity ranging from 25% to 500% of wild-type levels in muscle at the clinical starting dose of $3x10^{13}$ vg/kg. Administration of AT845-cyno construct expressing macaque GAA in Macaca fascicularis monkeys resulted in increased expression of GAA in muscle with no detectable immune response or tissue toxicity compared to controls. A one-time infusion of AT845 has the potential for stable, long-term sustained expression of GAA in muscle with therapeutic benefit. FORTIS (NCT04174105), a Phase I/II, multicenter, open-label, ascending-dose clinical study is assessing the safety and preliminary efficacy of AT845 in up to 8 LOPD subjects ≥18 years. Study subjects will receive a single i.v. infusion of AT845 with 1 year of follow-up, monitoring endpoints frequently, including GAA activity and protein level in muscle. Subjects will then be followed for 4 years to determine duration of response and long-term effects. This abstract is an encore and will be presented at 25 Kongress des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) 2021 and American Academy of Neurology (AAN) Meeting 2021.

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Facial Diplegia and paresthesias, an uncommon Guillain Barre Syndrome variant in Honduras

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Background: Guillain Barre Syndrome(GBS) it's the most common and severe acute polyneuropathy, Its incidence in Honduras is 1.89/100,000 habitants, numerous variants of GBS have been described, some of them are uncommon and can be confused with other causes.
Methods: We analyzed consecutive cases GBS with facial diplegia (FD) and paresthesias at the Hospital Escuela at Tegucigalpa, Honduras from 2018 to 2019; we obtained informed consent, clinical data and paraclinical studies.
Results: Case 1: A 23 years old male, with flu-like symptoms two weeks before hospital admission, one day before admission he suffered paresthesias in both legs and bilateral dry eyes, he didn't have systemic commitment, on neurological examination he was alert, with FD other cranial nerves were normal. His muscular strength was normal and the deep tendon reflexes were absent in the four limbs with bilateral flexor plantar response. Laboratory studies(LS) were normal, lumbar puncture(LP) showed proteins of 72 mg/dl and leucocyte count(LC) of 3/mm3. Nerve conduction studies/Electromiography/(NCS/EMG) showed mild facial bilateral axonal loss and prolonged sensory distal latencies (DL) in medial and ulnar nerves, Intravenous immunoglobulin(IVIG) was started for five days without complications at discharge and excellent recovery at three months.
Case 2: A 28 years old male, he referred paresthesias in both hands and difficult for chewing, at admission he has normal vital signs and oxygen saturation and without systemic commitment, the neurological examination was normal except for FD, generalized areflexia and hypoesthesia in both hands and foots. LS to discard other etiologies were in normal range, LP showed protein of 50 mg/dl and LP of 3 /mm3, NCS was made in the 4th day of illness and it showed bilateral latency prolongation in the facial nerves(orbicularis oculi and orbicularis oris) with axonal loss, in the upper limbs DL prolongation in both medial and tibial nerves with normal conduction velocity (CV), conduction block in right medial nerve, F wave were absent in right medial and left ulnar nerves. We started IVIG for 5 days with good recovery one month later.
Case 3: A 63 years old female, 9 days before admission she felt four limbs paresthesias and difficulty closing the eyes, she denied previous travels, immunizations and infectious illness. the neurological examination was normal except for left predominant FD and his tendon reflex that were little decreased on the upper limbs, LS were in normal range, LP showed protein of 51 mg/dl and LC of 3-5/mm3, NCS/EMG showed demyelination and axonal damage over the both facial nerves with denervation signs, with a similar pattern over the median and ulnar nerves, F waves and H reflex were absent in both tibial nerves. We started IVIG for five days without any complications at discharge, two months later she doesn't have any neurological deficit.
Conclusion: This report is the first description of this uncommon SGB variant in Honduras, clinicians must be aware to perform a good neurological examination to suspect this variant and treat it opportunely.

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Genotype-phenotype correlations in Valosing Containing Protein disease: Results of an International Multicentric study

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Introduction: Valosin-containing protein (VCP) disease is an adult autosomal dominant disorder caused by mutations in the VCP gen, which codified for the ubiquitous protein VCP, leading to disabling weakness, osteolytic lesions consistent with Paget Bone Disease and Fronto temporal dementia among other multisystemic clinical features. This disease could be misdiagnosed by other muscle or motor neuron entities.

Objectives: To describe the clinical and genetic features of an international population with mutations in the VCP gen and investigate genotype - phenotype correlations.

Methods: We collected clinical and genetic data from patients with confirmed mutations in the VCP gene in 23 centres from 12 countries.

Results: 128 patients were included (70% males, mean age 55.54, Standard Deviation -SD- 9.6 years). Mean age at symptom onset was 45.42 (SD 10) years and the mean diagnostic delay was 7.74 (SD 6) years. Ninety-eight percent had an heterozygous mutation, being c.464G>A and c.463C>T the most frequent variants. At disease onset, 30% had proximal symmetric lower limbs weakness and 10% asymmetric upper and/or lower limb weakness. Ninety-three percent of the patients had an slow progressive disease onset.

At enrollment, 89% showed proximal lower limb weakness, 58% requiered walking assistance, 56% axial weakness, and 44% respiratory symptoms. Other features found were: dysautonomy (26%), Paget bone disease (22%), cognitive impairment (20%) and upper motor neuron symptoms (9%, UMN). Dysautonomy and UMN signs appeared within the first 2 years of symptoms onset.

Mean age at loss of ambulation was 50,12 (SD 8) years at a mean of 9,14 (SD 5) years from the disease onset. The c.463C>T variant showed an earlier onset and a greater impairment of the upper limb and axial muscles.

Sixteen patients died (main reason respiratory insufficiency) at a mean of 12 (SD 7) years from onset. The age of symptoms onset, ages of developing cognitive impairment, dysphagia and the age at loss of ambulation correlated positively with the age of death.

Conclusion: The main features at presentation resembled a LGMD, however, the early presence of dysautonomy and UMN and the rapid loss of ambulation should raise awareness of VCP. Mutations were mainly located in exons 5 and 3 and the c.463C>T variant had a more severe upper limb and axial weakness.

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Transcriptomic Analysis of Aging Mouse Sciatic Nerve Reveals Early Pathways Leading to Sarcopenia

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Sarcopenia is the age-associated progressive decline in skeletal muscle mass and strength. Based on its symptomatic and histological features, sarcopenia has long been considered a disease of skeletal muscle fibers only. However, accumulating evidence

suggests that sarcopenia could originate from the cellular components controlling muscle strength and hence be defined as a neuromuscular disease. We hypothesized that sarcopenia may be detected first in the efferent nerves of the motor unit and that we would therefore measure changes in gene expression of sciatic nerves preceding signs of sarcopenia in muscle. Our objective was to identify early changes in gene expression related to the development of sarcopenia via transcriptomic profiling of aging peripheral motor nerves in vivo. In this study, we performed RNA sequencing (RNA-seq) of micro-dissected sciatic nerves of 24 C57BL/6J mice at 5, 18, 21, and 24 months old (n=6/group), before clinical manifestation of sarcopenia. We identified differentially expressed genes (DEGs) of aging sciatic nerves based on the model using the negative binomial distribution using the DESeq2 package for R. To investigate the biological characteristics of these DEGs, up- and down-regulated DEGs were explored further via gene ontology (GO) functional enrichment analysis and KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment analysis performed using the database for annotation, visualization and integrated discovery (DAVID). Candidate genes were validated using qRT-PCR. We found that as early as 18 months, we could detect significant differences in expression of genes related to senescence and sarcopenia (e.g. Arntl), signaling pathways controlling skeletal muscle mass, and genes previously associated with sarcopenia in muscle. We also performed qRT-PCR in gastrocnemius muscle to validate previously identified DEGs of sarcopenic muscle and found that some, but not all, were differentially expressed as early as 18 months of age. All DEGs previously reported to define sarcopenic muscles were detected by 24 months of age, in line with previous characterization of sarcopenic muscles in C57BL/6J mice. Altogether, we detected early molecular alterations in efferent motor nerves that could initiate the muscle mass and strength loss programming characterizing sarcopenia. However, since our study is the first to utilize untargeted RNA-seq to investigate the transcriptome of sciatic nerves in the context of sarcopenia, it is difficult to untangle how advanced the changes we detected in the nerves are as compared to those we measured as early as 18 months in the muscles, even if pre-sarcopenic. Future studies will need to investigate both muscle and nerve in parallel at even earlier time points to conclude the tissue origin of sarcopenia but the key molecular events we report here in sciatic nerves shed a new light on mechanisms underlying initiation of sarcopenia pathology.

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Gne Myopathy: Report of the first case in Colombian Population

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Introduction: GNE myopathy (GNEM) is a rare neuromuscular disorder caused by mutations in the GNE gene which encodes the rate-limiting enzyme of sialic acid biosynthesis. There is progressive weakness and muscle atrophy that begins in the distal lower limbs and predominates in the anterior tibialis, producing foot drop. The quadriceps is relatively spared, which is a distinguishing feature of this disease. It has an estimated prevalence of 1 to 9:1,000,000.

The diagnosis is confirmed by the presence of pathogenic (mostly missense) mutations in both alleles of the GNE gene. GNEM prevails in the Jewish community of Persian origin, living in Iran, Israel or in the United States. This condition has also been reported in great number in populations of far-East Asia (Japan and neighboring countries) and Bulgaria. GNEM has not been previously reported in the Colombian population.

Case Description: A 32-yo woman, daughter of non-consanguineous parents, presented with progressive symmetrical weakness in lower limbs of 6 years of evolution, initiated distally and with greater involvement of the anterior tibial muscle, developing foot drop, with subsequent proximal progression with relative preservation of the quadriceps. The marked weakness produced severe gait disturbances and led to the use of a wheelchair. Three years later, she began with weakness in the upper limbs. She did not present facial compromise, ocular motility alterations, dysarthria, dysphagia, dysphonia or cardiac involvement. The CPK was slightly elevated. Sensory and motor neuroconductions were normal. The EMG showed evidence of active myopathy. All metabolic, cardiovascular and gynecological studies were normal. The MRI of the pelvic girdle and thigh

showed marked muscle atrophy and fatty infiltration of the posterior and internal compartments of the thighs, hip adductors and abductors and relative respect of the anterior compartment of the thigh. Genetic studies for myotonic dystrophy were negative. The molecular panel for congenital myopathies showed variants of unknown significance. The panel of mutations for neuromuscular disease (neuropanel-centogene- 1038 genes, Rostock, Germany), detected two heterozygous variants in the GAA gene (GNE gen not included). Pompe disease was excluded.
Targeted sequence analysis of the GNE gene demonstrated the presence of The c.1664C> T (p.Ala555Val) and c.1636G> C (p.Asp546His) sequence changes in the GNE gene. This result confirmed the presence of the pathogenic / likely pathogenic sequence changes in this patient. Her sister was a carrier of the c.1664C> T (p.Ala555Val) sequence change in the GNE gene.
Conclusions: We report the first Colombian case of GNEM. This is a rare and difficult to diagnose myopathy. You must have a high index of suspicion to diagnose it and initiate support measures and genetic counseling in time. In our case, 6 years elapsed between the onset of symptoms and diagnosis. Clinical features, EMG- NCV, muscle MRI findings, and genetic testing are crucial in the diagnosis. It should be taken into account that the genetic study must include the GNE gene.

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Real-world eculizumab use in generalized myasthenia gravis in the US: A pilot retrospective chart-review study

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Objective: To examine real-world experience with eculizumab in patients with generalized myasthenia gravis (gMG) in the United States (US).
Background: Eculizumab was approved in October 2017 for AChR antibody-positive gMG in the US. Published data on real-world use and effectiveness of eculizumab are limited.
Design: A retrospective US chart-review study was conducted. Data were abstracted by physicians from their patients' electronic medical records. Patients with gMG aged ≥18 years who had received eculizumab for ≥6 months were included. Patient outcomes for two consecutive 6-month periods – before and during eculizumab treatment – were analyzed, including myasthenia gravis (MG) crisis, exacerbation, and related hospitalization. Descriptive statistical analyses for each period are presented.
Results: In 84 patients with gMG, mean (standard deviation) age was 46.3 (19.2) years, 55% were female, 74% White, and 16% Black/African American. At eculizumab initiation, the median MG Activities of Daily Living score was 8. The majority of patients were clinically categorized as Myasthenia Gravis Foundation of America Class II–III (71%), 10% Class I, and 14% Class IV (5% unknown). MG crisis occurred in 25% of patients in the 6 months before initiating eculizumab and in 1% of patients during the following 6-month period in which they received eculizumab. MG exacerbations were experienced by 38% and 10% of patients, respectively. The proportion of patients hospitalized due to MG crisis was 21% in the 6 months before eculizumab initiation and 1% during 6 months of eculizumab treatment; for MG exacerbation, the proportions were 14% and 4%, respectively.
Conclusions: Results from this pilot study suggest that real-world eculizumab treatment is associated with substantial reductions in MG crises/exacerbations and related hospitalizations in patients with gMG, consistent with outcomes of the Phase 3 REGAIN study and its open-label extension. A larger real-world study of longer duration is underway to confirm these findings.

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Longitudinal evaluation of gait features in growing boys with Duchenne muscular dystrophy

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Introduction: Prolonged ambulation is considered an important treatment goal in children with Duchenne muscular dystrophy (DMD). Therefore, three-dimensional gait analysis (3DGA) could provide sensitive outcome measures to evaluate the successes of clinical trials. However, quantitative descriptions of the natural history of gait deviations are first required. Sutherland et al. described the gait deterioration based on three stages. These stages were only partially confirmed by later cross-sectional studies, which highlight a strong need for longitudinal assessments of gait deviations in the same cohort of growing children with DMD.
Research question: How do gait deviations evolve with increasing age in children with DMD?
Methods: 3DGA was collected in 25 boys with DMD, ranging in age between 4.6 and 15.9 years at the time of enrollment, and was repeated at multiple points, one to four times, with an interval of six months, resulting in a data set of 77 3DGA-sessions. A database of 87 typical developing (TD) children between 4 and 18 years old was used as a reference to calculate the gait profile score (GPS). The spatio-temporal parameters were converted into non-dimensional values. Ten kinematic and three kinetic trials were averaged per 3DGA-session. From the averaged waveforms, discrete parameters (e.g. maxima and minima) were extracted. Linear mixed effect models were used to investigate the effect of age on these gait parameters (α-level=0.05). Random effects were included to correct for the correlation among repeated measurements within subjects. The best fitted regression model after inclusion of random intercepts and slopes was determined. All analyses were performed in MATLAB (R2017A).
Results: The results of the linear mixed effect models are shown in table 1.
Discussion: Children with DMD deviated 0.50° per year from TD children, indicating the GPS to be a promising, sensitive parameter for longitudinal follow-up. In addition, our results confirmed the three stages previously described by Sutherland et al., because equinus gait, anterior pelvic tilt, hip flexion and internal foot progression angles increased, whereas cadence decreased with age. Furthermore, the pelvic motion increased with age, which could be a compensation for the reduced hip flexion/extension motion. Hip abduction increased with age, which is probably related to the increased step width. Previously, decreased internal hip extension moments were reported in children with DMD. We confirmed the longitudinal increase of this compensation mechanism for weak hip extensors. Unexpectedly, internal knee flexion moments decreased with age. Due to increasing knee flexion contractures, the compensation mechanism for weak knee extensors may decrease with increasing age. Therefore, gait parameters may constitute promising markers to evaluate the efficacy of treatments. Studies with longer follow-up, allowing more complex mixed effect models, are required to determine the sensitive parameters that could predict loss of ambulation.

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Clues in the differential diagnosis of Demyelinating neuropathies: which electrophysiological parameters are useful

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Background: Demyelinating neuropathies can be hereditary or acquired. Most often, clinical signs, onset and progression help to distinguish between this two etiologies. However, in some patients, especially those with mild symptoms it can be challenging to determine whether it is an acquired or hereditary condition. Although electrophysiology shows demyelination in both disorders, particular features may be more indicative of one of other etiology. Our aim was to evaluate clinical and electrophysiological features to identify those that may help us to distinguish between the two diseases.
Methods: A search of patients was carried out in our databases. A retrospective review of each of the stories from 2008 to the present was carried out. Patients with hereditary demyelinating neuropathy with a confirmed molecular diagnosis were included. In the other arm, patients with inflammatory neuropathy fulfilling criteria for CIDP were included. Clinical and electrophysiological data were gathered. Analysis of the data was performed using The Statistical Package for Social Sciences (SPSS). Quantitative variables were summarized with means

and standard deviations (SD). For qualitative variables, we calculated frequencies and percentages. The association between qualitative variables was performed using the Chi-squared test, or Monte Carlo method. Comparison of quantitative variables between groups defined by a dichotomous categorical variable was performed by Student's t-test for independent samples or Mann-Whitney test. The ROC curve was calculated for those electrophysiological parameters that were significant.

Results: Thirty-five (40,7%) patients with CIDP and fifty-one (59,3%) with hereditary demyelinating neuropathy were included. As expected, clinical signs like pes cavus are more common among patients with hereditary neuropathy (See table). Overall, we found that nerve conduction velocities are slower among patients with hereditary neuropathies. Ulnar motor conduction velocity ≥27,65 m/s and Peroneal conduction velocity ≥31,65 m/s are associated with inflammatory origin with 82% sensitivity and 76% specificity and 95% sensitivity and 82% specificity respectively. Distal latency ≥4,87 ms in ulnar motor and latency ≥5,27 ms in Peroneal are associated with hereditary origin with 71% sensitivity and 79% specificity and 92% sensitivity and 87% specificity respectively.

Conclusion: Electrophysiological parameters may be useful to differentiate between inflammatory and hereditary demyelinating neuropathy. An almost twofold reduction in conduction velocity and a 1.5-fold increase in latency value are found in patients with hereditary neuropathies compared to CIDP.

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Man in the barrel syndrome due to Motoneuron Disease Confined to the cervical spinal cord

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Introduction: The man in the barrel syndrome (MIBS) refers to the presence of diplegia of the upper limbs, with preserved mobility of the head and lower limbs (as if the patient were restricted to a barrel around the trunk), without sensory deficits. Several causes of MIBS (also called brachial amyotrophic diplegia/ BAD) have been identified, including bifrontal lesions (original description), brainstem lesions, spinal cord (anterior horn cells), peripheral nerve (anterior cervical roots, brachial plexus or peripheral nerves) and neuromuscular junction lesions.

The main differential for MIBS in the absence of other clinical or diagnostic abnormalities is regional presentation of classic ALS confined to the cervical spinal cord region. We present a case of MIBS due to motor neuron disease confined to the cervical spinal cord.

Case Description: We report the case of a 76-year-old woman with progressive brachial diplegia of 4 years of evolution. On neuroexamination, plegia was observed in the proximal muscle groups of both upper limbs with force 0 / V and severe distal paresis GI/V. Distal paretic tremor was evident. In the craniofacial, cervical and lower limbs the muscle examination was normal. Sensory examination was normal and muscle stretch reflexes were absent in upper limbs. Fat infiltration and edema were observed in both upper limbs. The biochemical studies, the immunoreumatological profile, the CPK levels, the pulmonary function tests, the cardiovascular studies and the CSF studies were normal. GM1 antibodies were absent. The neurophysiological study showed signs of active denervation in all the muscles evaluated in the upper limbs and, in the muscles in which some degree of contraction could be obtained, a clearly neuropathic pattern was observed. The motor nerves of the upper limbs showed predominantly axonal changes secondary to distal wallerian degeneration. Motor NCVs were normal in lower limbs. Sensory NCVs were normal.

Cranial and cervical MRIs did not show lesions that explain the clinical abnormalities. The MRI of the cervical roots and brachial plexuses showed a decrease in thickness without changes in the intensity of the signal in the lower cervical roots and brachial plexuses, symmetrically. CT of the chest and abdominopelvic region did not show relevant findings.

Discussion: The presence of brachial diplegia without cervical or craniofacial involvement and without sensory abnormalities is compatible with the diagnosis of man-in-the-barrel syndrome in this case. The absence of intracranial, cervical cord, spinal nerve root and brachial plexuses lesions, as well as the absence of primary lesions of the peripheral nerves and the neuromuscular junction, with normal

CSF and GM1 antibodies absent, with an electrophysiological evaluation showing evidence of active denervation and a clearly neuropathic pattern, suggest as a cause a regional presentation of classic ALS confined to the cervical spinal cord region.

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Predictive Factors of Nusinersen Treatment Response in Infantile-onset SMA: Results from the ENDEAR/SHINE Studies

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Background: Identification of reliable predictors of response to disease modifying therapies in spinal muscular atrophy (SMA) is important to support and improve patient management.
Objectives: To identify predictive factors of nusinersen treatment response in infantile-onset SMA using data from the ENDEAR/SHINE studies.
Methods: Participants with infantile-onset SMA (symptom onset ≤ 6 months of age, 2 SMN2 copies) who completed the Phase 3 ENDEAR study (NCT02193074) were eligible to receive nusinersen in the open-label extension, SHINE (NCT02594124). Data from the 27 August 2019 interim data cut were used in this analysis. Multiple baseline patient and clinical characteristics were considered, including age at treatment initiation, weight-by-age percentile, disease duration (time from SMA symptom onset), ventilatory and nutritional support, compound motor action potential, and motor function measured by CHOP INTEND. The primary outcome evaluated in these analyses was achievement of independent sitting during the study, as defined by HINE-2 and WHO motor milestones. Firth's bias-reduced logistic regression and LASSO regularized regression were used to determine significant predictors of treatment response.
Results: Of the 80 patients originally randomized to and who received nusinersen in ENDEAR (median age at first dose: 5.4 [range: 1.7-8.0] months), 41 (51%) patients achieved independent sitting (median follow-up time at last visit: 3.6 [range: 0-5.0] years). At baseline, 21 (26%) patients were at <5% weight-by-age percentile and median (range) CHOP INTEND score was 27.5 (8.0-48.5). Median (range) disease duration at treatment initiation was 3.0 (0.0-6.0) months. Based on the August 27, 2019 data cut, initial results from the multivariable model identified weight-by-age percentile (≥5% vs <5%), disease duration, and baseline CHOP-INTEND score as significant predictors of achieving independent sitting. Those with a higher weight-by-age percentile had a 4.6-fold increased odds of independent sitting (p=0.03) and each 1-point increase in CHOP INTEND was associated with a 1.1-fold increased odds of independent sitting (p=0.02). Conversely, each additional month of disease duration at treatment initiation was associated with a 50% reduction of the odds of independent sitting (p=0.02).
Conclusions: Results underscore the prognostic importance of disease duration, baseline motor function and growth parameters while reinforcing the importance of earlier treatment initiation. These observations apply to recently diagnosed, symptomatic patients with 2 SMN2 copies. Additional clinical characteristics and potential biomarkers, such as neurofilament, will be considered in further modeling and results for time to treatment response will also be presented.
Study Support: Biogen

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Global Newborn Screening for Spinal Muscular Atrophy: Progress Overview

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Background: In spinal muscular atrophy (SMA), irreversible motor neuron damage occurs before the onset of symptoms and loss of motor neurons is irreversible. However, treatment has a clinical benefit

on the disease course and NURTURE and SPR1NT study data show that it is more effective to treat early when patients are presymptomatic or soon after symptom onset. Newborn screening (NBS) is the practice of testing infants for serious genetic disorders shortly after birth, thus identifying underlying illness and allowing early initiation of treatment. Several pilot programs have demonstrated that NBS for SMA is simple, accurate, and feasible in the real-world setting, and subsequently SMA NBS has been recommended or implemented in many countries, along with treatment and reimbursement guidelines. Our objective is to assist with the inclusion of SMA NBS panels worldwide by collecting information on current initiatives and decision-making processes, how NBS impacts patients and their families, and how the rare disease community can support the advocacy of NBS.

Methods: We conducted a survey of colleagues from medical, patient advocacy, and public policy and government affairs groups to collect information on SMA NBS initiatives worldwide. Information included the status (planned and on track, delayed, ongoing) and data reported for both established and pilot SMA NBS programs at the national and regional level.

Results: Of the 95 countries surveyed, 70 provided information about SMA NBS programs. Of these 70, 22 countries had some form of SMA NBS program at the national or regional level, including both established and pilot programs with varying statuses (planned and on track, delayed, ongoing). Data from SMA NBS programs from 8 countries (Australia, Belgium, Canada, Germany, Japan, Netherlands, Taiwan, and United States) have been reported to date. Patient advocacy groups support SMA NBS and have played a critical role in its adoption in some countries. We will provide an updated overview and data on worldwide efforts to implement SMA NBS at the national and regional levels to be shared with and used by the SMA community, healthcare systems, researchers, regulators, policy makers, and payors.

Conclusions: Pilot programs have demonstrated the need to implement established SMA NBS programs to accelerate the identification of infants with SMA. Raising awareness of the status of SMA NBS implementation efforts worldwide may help support wider adoption of NBS, leading to earlier diagnosis, and better long-term treatment outcomes for infants with SMA.

Supported by: Biogen

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Konectom™ Smartphone-based Digital Outcome Assessments for Adults Living with Spinal Muscular Atrophy: A Conceptual Framework

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Objective: To develop a conceptual framework supporting the Konectom™ smartphone-based digital solution that enables adults living with spinal muscular atrophy (SMA) to quantitatively self-assess motor function in the real-world environment.

Background: SMA is a progressive neuromuscular disorder characterized by impaired motor function. While the most prevalent SMA types have symptom onset occurring in infancy to childhood, adult onset also occurs. The size of the population of adults living with SMA may grow over time due to rapid advances in disease-modifying therapies for SMA. Decreased mortality may increase the heterogeneity in the adult phenotype. There are unmet needs for improved multidisciplinary care and suitable motor function assessments for adults with SMA. To meet the increasing demand for clinical care for adults living with SMA, it is necessary to develop performance outcome assessments of motor function that are sensitive to disease progression and relevant to real-world abilities.

Design/Methods: We developed a conceptual framework capable of capturing the heterogenous symptomatology in three functionally distinct groups of adults living with SMA (walkers, sitters, and non-sitters). Development comprised: A) A targeted literature search focused on neuromuscular disorders and further refined for SMA to identify

common neurological domains evaluated in this disorder; B) Creation of an adult SMA conceptual framework covering signs and symptoms (nineteen signs and symptoms grouped into four domains); and C) Eight semi-structured interviews conducted with adult SMA experts (six physicians and two physiotherapists).
Results: Experts endorsed the completeness of the conceptual framework for describing the three SMA functional profiles. Fatigability in motor tasks and smartphone typing skills are considered useful to monitor disease progression for all functional profiles. Upper limb function and speech/voice are expected to provide more information about disease progression and impacts on quality of life for sitters and non-sitters, while lower limb function is more relevant to walkers.
Conclusions: We have developed a comprehensive conceptual framework that will enable us to design and develop digital outcome assessments capable of quantifying functional abilities related to daily living, and other non-motor signs that are clinically meaningful for a heterogeneous group of adults living with SMA.
Supported by: Biogen

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Preserved Swallowing Function in Infants Who Initiated Nusinersen Treatment With Presymptomatic SMA: NURTURE Study Results

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Background: Patients with spinal muscular atrophy (SMA) Types I or II experience deterioration of swallowing function and high levels of bulbar comorbidities such as risk of aspiration pneumonia, choking, and failure to thrive. Without treatment, tube feeding is often needed. Nusinersen has shown significant and clinically meaningful efficacy on motor function and survival endpoints across a broad spectrum of SMA subtypes, with limited data reported to date on bulbar function.
Objectives: To assess swallowing function in NURTURE study participants.
Methods: NURTURE (NCT02386553) is an ongoing, Phase 2, open-label study evaluating nusinersen in infants who initiated treatment prior to the onset of clinical SMA symptoms. Twenty-five participants (n=15 with 2 SMN2 copies, n=10 with 3 SMN2 copies) aged ≤6 weeks at first dose were enrolled and were treated with intrathecal nusinersen 12 mg. Swallowing function was assessed using the Parent Assessment of Swallowing Ability (PASA) questionnaire. The PASA includes 33 questions relating to general feeding, liquid swallowing, solid swallowing, and swallowing concerns over the previous 7 days, and was administered at multiple timepoints after treatment initiation.
Results: As of the February 19, 2020 interim data cut, participants had a median age at last visit of 3.8 (range, 2.8-4.8) years. At the last available assessment (Day 778), 84% were not tube fed (11/15 with 2 SMN2 copies, all with 3 SMN2 copies); of the 4 tube fed participants, 2 participant's parents answered "always" and 2 answered "often" to being tube fed in the previous 7 days. Ninety-one percent of participants never gagged or choked on liquid food, 87% never gagged or choked on solid food. Eighty-eight percent (21/24) and 96% (23/24) of parents disagreed/strongly disagreed with being concerned over their child choking and aspirating on their food while eating, respectively.
Conclusion: Swallowing ability was maintained in 13/15 participants with 2 SMN2 copies and in 10/10 participants with 3 SMN2 copies who initiated nusinersen treatment. Only 2 participants with 2 SMN2 copies required full-time tube feeding, in contrast to the expectation of nearly universal bulbar insufficiency in this population. Swallowing function continues to be monitored in NURTURE to better understand the efficacy of nusinersen.
Supported by: Biogen

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Phenotypic clusters in proximal myotonic myopathy

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Background: The most common phenotype of the myotonic dystrophy type 2 (DM2) is the proximal myotonic myopathy (PROMM). PROMM is a heterogeneous disease, but there have not been literature data if certain symptoms can be grouped in sub-phenotypes.
Aim: To perform cluster analysis of clinical symptoms in PROMM patients from the Serbian DM registry.
Method: 124 genetically confirmed PROMM patients from the Serbian DM registry were included. Hierarchical cluster analysis included patients' sociodemographic and clinical data.
Results: Two major PROMM clusters appeared after statistical analysis. Patients in cluster B had a later onset (approximate cut of was 40 years of age) and shorter duration of the disease compared to cluster A. However, patients of cluster B had milder disease regarding muscle weakness, presence of cataracts, gastrointestinal symptoms, cardiac problems, and glucose metabolism impairments. On the other hand, patients in cluster B had worse achievement on the revised Addenbrooke's Cognitive Examination test.
Conclusion: Patients with PROMM may be divided into two major different phenotypes based on the age at onset of the disease (before and after the age of 40). Patients with younger-onset generally had a more severe phenotype, except for cognitive decline that was more pronounced in the late-onset PROMM.
Keywords: myotonic dystrophy type 2, proximal myotonic myopathy, phenotype analysis, muscle weakness, cognitive impairment

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Functional and Survival Benefit of Sodium Phenylbutyrate–Taurursodiol in Amyotrophic Lateral Sclerosis

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Background: An oral, fixed-dose sodium phenylbutyrate and taurursodiol coformulation (PB-TURSO) was designed to reduce neuronal death by mitigating endoplasmic reticulum and mitochondrial dysfunction.
Objective: To report efficacy and safety results from a randomized, controlled trial (CENTAUR) and open-label extension (OLE) of PB-TURSO in amyotrophic lateral sclerosis (ALS).
Methods: Adults with definite ALS (revised El Escorial criteria) and ≤18 months from symptom onset were randomized 2:1 to PB-TURSO or placebo for 6 months. Participants completing the randomized phase were eligible to enroll in the OLE and receive PB-TURSO for ≤30 months. The primary efficacy outcome in CENTAUR was rate of decline in Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) total score through 6 months. Analyses of key events including all-cause death, permanent assisted ventilation (PAV; >22 hours/day for >7 days), and first hospitalization were performed at a cutoff date of July 2020 (longest follow-up, 35 months after randomization). The all-cause death analysis included all participants randomized in CENTAUR, including those who discontinued, were lost to follow-up, or did not enroll in the OLE; vital status was determined for all randomized participants via public records search. Other key events were recorded prospectively in clinic reports, with censoring at last follow-up for those without reported events. PB-TURSO safety was assessed in the randomized and open-label phases.
Results: Of 137 randomized participants (PB-TURSO, n=89; placebo, n=48), 98 were eligible for OLE

enrollment and 90 (PB-TURSO, n=56; placebo, n=34) enrolled. Mean rate of ALSFRS-R total score decline over the randomized phase was slower with PB-TURSO versus placebo (difference, 0.42 points/mo; 95% CI, 0.03–0.81; P=0.03). The mean hazard of death was 44% lower in the group originally randomized to PB-TURSO versus placebo (hazard ratio [HR], 0.56; 95% CI, 0.34–0.92; P=0.023); median survival durations were 25.0 (95% CI, 19.0–33.6) and 18.5 (95% CI, 13.5–23.2) months. The mean hazard of death or PAV was 42% lower in those originally randomized to PB-TURSO versus placebo (HR, 0.58; 95% CI, 0.36–0.93; P=0.025), with median times to event of 23.8 (95% CI, 18.2–29.1) and 18.5 (95% CI, 13.5–21.7) months (Figure). The mean hazard of first hospitalization was 44% lower in those originally randomized to PB-TURSO versus placebo (HR, 0.56; 95% CI, 0.32–0.96; P=0.034); median time to event was not reached (NR) (95% CI, 14.8–NR) for original PB-TURSO and was 14.4 (95% CI, 6.8–NR) months for original placebo. Similar rates of adverse events (AEs) were recorded in the PB-TURSO and placebo groups during the 24-week randomized trial. Early gastrointestinal AEs were more frequent with PB-TURSO in the randomized phase and in participants originally randomized to placebo who initiated PB-TURSO upon OLE entry. Additional OLE analyses are ongoing.

Discussion: Administration of PB-TURSO resulted in statistically significant retention of function and longer overall survival in people with ALS. Long-term risk of death or PAV and risk of first hospitalization was also significantly lower in participants originally randomized to PB-TURSO. Updated data from analyses of the OLE will be shared during ICNMD 2021.

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NEO1/NEO-EXT Studies: Muscle MRI Results in Patients with Pompe Disease After Long-Term Avalglucosidase Alfa Treatment

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Long-term safety and efficacy of avalglucosidase alfa is being assessed in adult participants with late-onset Pompe disease (LOPD) in the NEO-EXT study (NCT02032524), an ongoing extension of the NEO1 study (NCT01898364). NEO1 participants were either treatment-naïve (n=10) or had received alglucosidase alfa for ≥9 months (n=14). Twenty-one participants completed NEO1 and 19 entered NEO-EXT. Qualitative and quantitative muscle magnetic resonance imaging (MRI) was used to measure disease burden at study enrollment and the impact of avalglucosidase alfa on different components of muscle pathology. At NEO1 enrollment, the degree of disease burden, as measured by muscle glycogen content, Mercuri grading, and 3-point Dix-

on fat fraction, was evaluated in the context of a clinical evaluation and was found to be consistent with the previous natural history data for Pompe disease. During NEO-EXT, quadriceps and hamstring 3-point Dixon fat fraction, water T2 (with/without B1 heterogeneity correction) as well as muscle mass index were generally stable for up to 4.5 years of avalglucosidase alfa in most participants (change/year in % fat fraction from baseline: quadriceps: treatment-naïve 0.3, treatment-experienced –0.02; hamstring: treatment-naïve 1.2, treatment-experienced –1.8). Few muscle biopsies were performed in NEO-EXT, since they were only required if glycogen content was ≥5% or a participant showed significant clinical decline. The results are consistent with stabilization of disease by avalglucosidase alfa in this population of previously treatment-naïve and treatment-experienced participants with LOPD. The data suggests that avalglucosidase alfa contributes to muscle preservation, in contrast with worsening fatty replacement seen in untreated patients with LOPD and in some recipients of alglucosidase alfa. These data further support a link between quantitative MRI indications of disease activity and disease burden as assessed by muscle glycogen content and clinical endpoints of motor function. Fat fraction along with muscle function tests can be considered good measures for stratification and longitudinal follow-up in clinical trials in participants with LOPD.

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The European Lambert-Eaton myasthenic syndrome registry: Long-term outcomes following symptomatic treatment

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Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder characterized by autoantibodies against presynaptic voltage-gated calcium channels at the neuromuscular junction causing proximal muscle weakness and autonomic changes. Symptomatic treatment with potassium channel blockers aims to improve neurotransmission by prolonging presynaptic depolarization, enhancing calcium transport into the nerve ending. Thirty centers across four countries participated in the non-interventional European LEMS registry as part of the post-approval monitoring program for the potassium channel blocker 3,4-diaminopyridine phosphate (3,4-DAPP). Any patient diagnosed with LEMS not participating in a clinical study of 3,4-DAPP was eligible to participate. Participants were assessed at enrollment, then annually or bi-annually thereafter. Assessments included quantitative myasthenia gravis (QMG) questionnaire, reflexes, muscle strength, ataxia, autonomic nervous system (ANS), daily functioning and EQ-5D health status. Recruitment began in May 2010 and the last participant was enrolled in August 2016. The study was completed in August 2019. Overall, 105 participants were enrolled; 96 (91.4%) were evaluable. Mean (standard deviation) age at diagnosis was 55.9 (13.9) years. Duration of participation ranged from 0.7–105.8 months. In total, 36 (37.5%) participants discontinued prematurely, 15 (15.6%) died and 18 (18.8%) were lost to follow-up. Mean participant age was 60.0 years at enrollment, 49 (51.0%) were male, and the majority were Caucasian (n=69; 71.9%). At enrollment, 50 (52.1%) participants were being treated with 3,4-DAPP; 74 participants (77.1%) were exposed to 3,4-DAPP at any time during the study. 3,4-diaminopyridine (3,4-DAP) was being administered to 21 (21.9%) participants at baseline. Other treatments were administered at baseline to 25 (26.0%) participants. Frequently administered concomitant medications included pyridostigmine (n=52; 54.2%), corticosteroids (n=49), immunoglobulins (n=31; 32.3%), and azathioprine (n=26; 27.1%). No difference in total QMG scores were observed between treatment groups (Table). The majority of participants had reduced reflex tone. Muscle strength at baseline was generally good and maintained during follow-up, although duration of follow-up was substantially longer for patients treated with 3,4-DAPP (up to 78 months versus 54 months for 3,4-DAP and 18 months for other treatments). Ataxia line walk tests were positive for 12/47 (25.5%) participants at baseline and performance was generally maintained during follow-up. Dry mouth was the predominant ANS symptom and no notable ANS changes were observed during the

study. The majority of subjects had reduced/limited functioning at baseline, but sustained or improved functioning was observed in participants administered 3,4-DAPP (Table). Inconsistent and sporadic occurrences of functional improvement and regression were observed with 3,4-DAP and other treatments. Participants administered 3,4-DAPP had improvements in mean EQ-5D visual analogue scores at three consecutive follow-up assessment periods versus baseline. EQ-5D assessments were limited by sample size with 3,4-DAP and other treatments, but deterioration was more common than improvement. Overall, 55 treatment-related adverse events (AEs) were reported by 32 (33.3%) participants and no new safety signals were identified for any treatment. Nine treatment-related serious AEs were reported by eight (8.3%) participants. These data provide further information on the natural history of LEMS and further support the risk-benefit balance previously determined for 3,4-DAPP in the symptomatic treatment of patients with LEMS.

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FIREFISH Parts 1 and 2: 24-Month Safety and Efficacy of Risdiplam in Type 1 SMA

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Objective: To determine the efficacy and safety of risdiplam in infants with Type 1 spinal muscular atrophy (SMA) treated for 24 months during Parts 1 and 2 of the FIREFISH study (NCT02913482).

Background: SMA is a severe, progressive neuromuscular disease caused by reduced levels of survival of motor neuron (SMN) protein due to deletions and/or mutations of the SMN1 gene. A second gene, SMN2, produces only low levels of functional SMN protein. Risdiplam is a centrally and peripherally distributed, oral SMN2 pre-mRNA splicing modifier that increases the levels of functional SMN protein. Risdiplam (EVRYSDI™) has been approved by the FDA for the treatment of patients with SMA, aged 2 months and older.

Design/Methods: FIREFISH is a multicenter, open-label, two-part study of risdiplam in infants with Type 1 SMA and two SMN2 gene copies (inclusion criteria 1–7 months old at enrollment). Part 1 assesses the safety, tolerability and pharmacokinetics/pharmacodynamics of different risdiplam dose levels (low-dose cohort, n=4; high-dose cohort, n=17). The pivotal Part 2 (N=41) assesses the efficacy and safety of risdiplam at the dose selected from Part 1. Parts 1 and 2 had the same inclusion/exclusion criteria.

Results: The primary endpoint of Part 2 at Month 12 was met (data-cut: 14th November 2019): 29% (12/41) of infants were able to sit without support for ≥5 seconds, as measured by the Gross Motor Scale

of the Bayley Scales of Infant and Toddler Development, Third Edition (item 22; P<0.0001, performance criterion=5%). Previously we presented pooled safety and efficacy data from 58 infants in FIREFISH Part 1 (high-dose cohort, n=17) and Part 2 (N=41) who had received treatment with risdiplam for a minimum of 12 months (data-cut: 14th November 2019). At Month 12, 88% (51/58) of infants were alive and did not require permanent ventilation. Infants showed improvement in motor function, with 57% (33/58) scoring ≥40 on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. Infants also achieved motor milestones such as sitting without support, standing with support and bouncing (as assessed by the Hammersmith Infant Neurological Examination, Module 2) that are not observed in the natural history of Type 1 SMA. After 12 months of treatment, there were no treatment-related adverse events leading to withdrawal.

For the first time, we will present pooled safety and efficacy data from 58 infants in FIREFISH Part 1 (high-dose cohort, n=17) and Part 2 (n=41) who received risdiplam treatment for a minimum of 24 months.

Conclusions: The safety and efficacy of risdiplam are consistent between FIREFISH Parts 1 and 2, incorporating a large population of infants from study sites that span a broad geographic area worldwide. Parts 1 and 2 are ongoing globally and will provide further data on the long-term efficacy and safety of risdiplam in infants with Type 1 SMA.

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Clinical outcomes on spinal muscular amyotrophy adult cohort treated with Nusinersen : a prospective study

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Approved since December 2018 in Quebec, Canada, Nusinersen is the first treatment available for spinal muscular atrophy (SMA). Several studies demonstrate the obvious efficacy in the infantile population but there are still few published studies in adult cohorts. It is therefore important to monitor adult cohorts to evaluate the functional outcomes and to determine the most relevant tests for the follow up. The evaluations are scheduled prior the introduction of the injection and at 6, 12, 18, 24 months and then annually. Patients are divided into three groups: ambulatory (A), sitter (Sit) and non-sitter (N-Sit). Group A is assessed for pulmonary function tests (PFTs), Spinal Muscular Atrophy Functional Rating Scale (SMA-FRS), Hammersmith Functional Rating Scale Extended (HFMSE), Revised Upper Limb Module (RULM), manual muscle testing with dynamometer (MMT), Time Up and Go (TUG), Timed up and down stairs test (TUDS) and 6 Minutes Walk Test (6MWT). Group Sit and N-Sit are assessed for PFTs, SMA-FRS, HFMSE, RULM, MMT and CHOP ATEND. Responses to yes/no questions on improvement are collected on specific categories: strength, energy/endurance, tonus, respiratory aspects, deglutition, mastication, mouth opening and change of voice. Subjective gains for patients and caregivers are also collected.

Twelve adult patients (21-55 years old) are currently being treated with Nusinersen in our facility. One patient is at 3 years follow up, seven patients at 18 months and four patients at 6 months. Preliminary data after 18 months follow up shows improvements (1) of the SMA-FRS and HFMSE in all cohort; (2) of the distal strength (MMT) principally in ambulatory group and (3) of the RULM and CHOP ATEND in the Sit and N-Sit groups. Ambulatory patients improved at the 6MWT in the first months and one maintained his gain even at 3 years. Stabilization in PFT (peek cough flow and vital capacity) in all the groups was observed. At the yes/no questions, the majority reported amelioration in strength (n=8/8), energy/endurance (n=7/8) and tonus (n=6/8). In the other yes/no specific categories, patients reporting deficiencies prior to the injection described gains.

Subjectively, participants and their caregivers noted an improvement in the endurance, recovery time and tonus that leaded to better transfers, more autonomy and capacity to train and even gains on motor achievement.

These results tend to demonstrate the favorable effects of Nusinersen in the adult population. However, some of the beneficial effects like strength, mastication, deglutition, change of voice and recovery time were not well objectify by the current used tests. Furthermore, quality of life scales and bulbar functions tools specific for SMA need to be define. Also, tests should be chosen according to the mobility level of the patient (ambulatory vs non-ambulatory).

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Shoulder pain in amyotrophic lateral sclerosis: experience of our hospital

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Introduction: Pain can appear at every stage of amyotrophic lateral sclerosis (ALS) evolution and it impacts highly in patients' quality of life. Although it is an often underestimated symptom, its frequency can range from 15% to 85%. Different types of pain might arise from distinct underlying mechanisms (nociceptive, neuropathic and possible central sensitization). Shoulder pain is especially frequent in ALS due to the progressive atrophy, weakness and immobility of the periscapular muscles.
Objective: The objective of this study was to determine the frequency of shoulder pain in our patients with ALS and to analyze its possible association with their clinical characteristics, diagnostic delay or survival. We also describe the pharmacological treatments prescribed for pain.
Materials and Methods: We retrospectively reviewed the medical history of all the patients with ALS diagnosis in follow-up by our Neuromuscular diseases Unit between 1/1/14 - 1/12/20. We collected ALS subtype (spinal or bulbar onset), frequency of shoulder pain and pharmacological treatments. We used the R Studio v4.0.3 to perform the statistical analysis.
Results: 67 cases of ALS were found, 36 patients were females and the mean age at diagnosis was 61.4 years (33-85). The most frequent onset of ALS was spinal (66%) vs bulbar (31%). 73% of the patients reported having pain at some point during their clinical course. Likewise, 42% of all ALS patients specified shoulder pain during follow-up. Of these, 10 were affected with bulbar-ALS and 18 with spinal-ALS. 100% of the patients with shoulder pain had weakness in the affected arm. We found a statistically significant correlation between the existence of upper extremity weakness in the first evaluation and the appearance of shoulder pain during their clinical course ($p<00.2$). However, there was no correlation between shoulder pain and the ALS phenotype (bulbar/spinal), age, sex, diagnostic delay or survival. As for the pharmacological treatments employed, 75% of patients received oral medication: 29% nonsteroidal anti-inflammatory drugs (NSAIDS), 11% paracetamol and 25% paracetamol with tramadol. 11% took opioids (fentanyl). In addition, 12% required intra-articular injections of anesthetics and/or corticosteroids. Many of our patients were also taking drugs for spasticity, cramps and/or generalized neuropathic pain (gabapentin, baclofen, tizanidine, tricyclic antidepressants...) that could also have some adjuvant effect on shoulder pain relief.
Discussion: Our study confirms the high prevalence of pain in ALS, especially shoulder pain, as well as its direct relationship with early weakness of upper extremities. However, we did not find a lower incidence in patients with bulbar-onset vs. spinal-onset. Suspecting a nociceptive origin of the pain, NSAIDs, opioids and/or intra-articular injections were the most prescribed treatments for the shoulder pain in our patients. Therefore, we must bear in mind that pain is a relatively frequent and disabling symptom, that has been insufficiently studied in ALS. There are no guidelines at the moment about its specific treatment, so its management is based on clinical experience.

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Case report: early-onset ALS with unusual MRI signs

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Introduction: We herein report a case of an early onset ALS patient who presented to The first university clinic of Tbilisi State Medical University, complaining of muscle weakness and wasting during the last 7 months, with unusual MRI signs.
Case report: A 21-year-old male on neurological examination demonstrated reduction of overall muscle bulk, Triceps, and Biceps -left-hand predominant involvement observed. A weakness of limbs observed, It is safe to say, No signs of UMN involvement were seen, pathological reflexes absent, no bulbar involvement, sensation intact, autonomic nervous system -Norm, No cognitive changes. The patient underwent an MRI of the spine and head, nerve

conduction studies, CSF analysis. MRI of the spine demonstrated spinal cord atrophy on the level of 4-6 cervical segments, with hyperintensity of predominantly grey matter, MRI of the head showed no abnormalities. Overall lab tests were within normal values. On nerve conduction studies significant Neurogenic changes in Left arm and wrist muscles, acute denervation in biceps muscle in form of fasciculations and fibrillations. Based on the above mentioned, the Patient went on Rilutek and awaits a clinical trial.

Discussion: Our Patient fulfilled only suspected ALS criteria based on El Escorial- Revised criteria, however considering the progressive spread of symptoms and signs, without any laboratory changes, no evidence of other diseases we concluded working diagnosis, which is progressive muscular atrophy(leaning on Gold coast Criteria), a recognized variant of ALS. We strongly believe based on the available literature, that we are dealing with FUS mutation associated with early-onset ALS case with specific neuroimaging patterns on the Spinal cord. Genetic testing was performed on our patient and results will be available soon, therefore atypical Presentation and unusual neuroimaging patterns, shouldn't delay a prompt diagnosis for the patient to be involved in a clinical trial for future therapies to be successful.

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Timing and localization of myasthenia gravis-related gene expression

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Autoantibodies against or mutations in many of the proteins involved in organizing and maintaining neuromuscular signalling cause skeletal muscle weakness (autoimmune or congenital myasthenia gravis (MG) respectively). Several reports suggest that these autoantibodies might also affect the central nervous system (CNS). Furthermore, new therapeutic strategies targeting these proteins/genes are immerging. A comprehensive overview of the timing and localization of the expression of MG-related antigens and genes in other organs is currently lacking. To assess which tissues are at risk for non-motor symptoms or off-target effects, we used in silico tools to interrogate public expression databases. Acetylcholine esterase, nicotinic AChR 1 subunit, agrin, collagen Q, Dok7, Lrp4, MuSK and rapsyn were included as MG-related genes because of their well-known involvement in either congenital or autoimmune MG. Expression of MG-related genes was investigated in all human tissues using GTEx data, and in specific brain regions, neurodevelopmental stages, and specific CNS cell types using datasets from the Allen Institute for Brain Sciences. We found MG-related genes are widely expressed throughout the human body, with notable co-expression in the brain and reproductive tissues. MG-related genes furthermore show heterogenous spatio-temporal expression patterns within the CNS. Interestingly, AGRN, LRP4 and MUSK are prominently expressed outside a synaptic context in non-neuronal cell types. For each of the investigated genes several (new) tissues, brain areas and cortical cell types with (relatively) high expression were identified suggesting a potential role for these genes outside skeletal muscle. The possible presence of MG-related antigens in other tissues suggests that autoimmune MG, congenital MG or treatments targeting the same proteins may affect MG-related protein function in these organs.

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Association Between Statin Use and Survival in patients with ALS: A Propensity Score-Matched Analysis

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Introduction: Statins are one of the most commonly used drugs in adults. There remains clinical equipoise for healthcare providers managing ALS patients on statin therapy given the unclear association between statin therapy and survival based on prior studies.

Objective: To evaluate the association between statin use and survival in adult (> 18 years old) patients with ALS included in the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database.

Methods: We performed a retrospective study of patients with a diagnosis of ALS that were included in the multi-centre registry of prior clinical trials in

patients with ALS, known as the PRO-ACT database. We matched patients with prior use of statin to those without prior statin use using propensity score methods, accounting for age, sex, ethnicity, baseline ALS-Functional Rating Scale score, Riluzole use, and bulbar onset of disease. We followed patients from start date (time of entry in the database) to 36 months after and recorded death and loss to follow-up readily available in the database. We compared survival in the matched pairs using Kaplan Meier curves, and calculated hazard ratio (HR) of death using Cox proportional hazard models, accounting for the matched nature of the cohort. Given the non-proportional effects of statin use on mortality, we employed piecewise regression models to report mortality associated with statin use in two time-frames: from 0-12 months and from 13-36 months.
Results: From a total of 3439 people, we identified 131 people with prior statin use, and matched them to 131 controls from the non-users. We ensured that the matching process was adequate. There was no difference in survival at 3 years based on Kaplan Meier curves (stratified log rank test, P = 0.68). The HR of 3-year mortality was 0.83 (95% confidence interval, 0.53-1.32) after accounting for propensity-matching. Statin use was not associated with mortality in the first 12 months (HR 0.66; 0.39-1.11), nor between 13 to 36 months (HR 2.70; 0.77-9.53).
Conclusion: Our findings suggest that statin use is not associated with survival in adult patients with ALS. Healthcare providers should exercise caution when discontinuing or replacing statins in patients with ALS, especially if statins are otherwise clinically indicated.

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The Impact of non-dystrophic Myotonia on PAtients and Caregivers' qualiTy of life (IMPACT) survey results

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Background: Non-dystrophic myotonias (NDM) predominantly manifest as delayed muscle relaxation leading to muscle stiffness that, in some forms of NDM, tends to diminish with repeated contraction. Symptoms of NDM can also include transient weakness/paralysis, pain, cramps, muscle hypertrophy, and fatigue, and can vary by NDM subtype. Although the impact of these symptoms on patients' quality of life has been described previously, NDM has historically been viewed as a disease that has a minor impact on patients. In this survey, we aimed to unveil the patients' perspective on how their symptoms impact their daily life as well as how people caring for patients with NDM are affected.
Method: Patients and caregivers of individuals diagnosed with NDM were asked to participate in two separate anonymous online surveys. Each survey was run for three months using an online survey tool. Details of diagnosis, treatments, and relationship of caregiver to a patient were those reported by the participant and were not confirmed by health care providers.
Results: The patient survey was completed by 181 people with NDM from 27 countries and 59 caregivers taking care of patients with NDM. Chloride channelopathies were most represented (n=116) versus sodium (n=43). 64% of NDM patients reported their symptoms to appear more than 10 years prior to receiving a diagnosis and many others at least 2 and up to 10 years (27%). Symptoms and patients' abilities are described in Table 1. Although 59% of respondents have used symptomatic drug treatment with predominant use of mexiletine (41%), many patients indicated that they fear side effects (20%), or have never received a prescription (12%), or they don't want to take any pharmaceutical treatment (11%). Although regularly seeing different specialists, 33% reporting only moderate satisfaction and a third (34%) saying they were not satisfied with clinical management of their disease.

It is the first survey examining disease burden on NDM caregivers demonstrating that almost half (45%) of caregivers are spending at least 5 hours a

week on care, with 29% spending at least 10 hours a week. The symptoms caregivers most likely wanted to improve in NDM patients were muscle stiffness, pain, emotions (embarrassment due to inabilities caused by NDM), reduction in falling and fatigue. The symptoms patients most wanted to be improved were muscle stiffness, mobility problems, pain and tiredness. There appeared to be a correlation between a) symptoms/abilities experienced more often and those improved with drug treatment and b) symptoms that appeared more often and those patients or caregivers desired to improve most.

Conclusion: Our data confirm that the lack of appreciation of the burden of the disease on patients' quality of life, as well as a lack of awareness of the impact of NDM symptoms contribute to delaying confirmation of diagnosis. Caregivers play an important role in NDM and the burden on caregivers can be significant in some cases. These outcomes should guide clinicians to better address myotonia symptoms to improve clinical management of this patient group and keep the well-being of caregivers in mind.

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A novel quantitative platform for utrophin evaluation in cell culture

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Introduction: Utrophin is a dystrophin paralog which expression is increased in DMD patients' muscle as well as in the mdx murine model. Utrophin overexpression has been proposed as a natural mechanism to compensate for the lack of dystrophin and consequently a promising therapeutic approach for the treatment of patients with Duchenne and Becker muscular dystrophies (DMD/BMD). In the evaluation of potential therapies aiming to overexpress utrophin, western blotting and quantitative PCR are methods commonly used, but a variety of non-standardised protocols and lack of good positive controls difficult the in vitro assessment of new drugs. Novel techniques, such as myoblot assays (1), droplet digital PCR and CRISPR/Cas9 gene edition have provided the neuromuscular community with tools that could contribute in accurately quantifying utrophin expression in cell culture.

Objectives: To establish a method for utrophin quantification in vitro combining accurate measurements of gene and protein expression with a reliable positive utrophin over-expression control (2). This platform should facilitate the evaluation of new therapies in early stages of development and eventually accelerate the transit of these treatments to the clinic.

Methods: Myoblot protocols were optimised to quantify utrophin protein in microplates and droplet digital PCR (ddPCR) protocols were optimised to obtain absolute utrophin gene expression quantification. An immortalised DMD cell cultured was edited by CRISPR/Cas9 methods to generate a culture that endogenously overexpresses utrophin, useful as a positive control in both techniques. The original DMD cell cultures (negative control) and the edited culture (positive controls) were used to assess utrophin expression after treatment of the DMD cultures with different utrophin modulators.

Results: We have characterised our newly generated cell cultures and have optimised the cell culture protocol to implement a workflow for utrophin quantification that includes accurate protein and gene expression evaluation, combining myoblot and ddPCR techniques. Using this combo, we can perform screening assays of utrophin overexpression drugs with higher sensitivity and reproducibility than the standard methods.

Conclusion: The combination of myoblots and ddPCR procedures with a reliable utrophin overexpression control offers many advantages and facilitates a detailed evaluation of potential treatments aiming to overexpress utrophin protein.

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Myotubular myopathy associated with Klippel-Feil Syndrome

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Introduction: X-linked myotubular myopathy (XLMTM; OMIM #310400) is a rare congenital disease characterized by severe hypotonia and respiratory failure at birth in affected males. It has a lethal course in the first year of life, but some individuals may show improvement in respiratory and motor function. It is caused by mutations in the MTM1 gene, which encodes myotubularin, a key enzyme for skeletal muscle maturation.

Case report: a 1-year-old boy presented with muscle weakness and hypotonia, complaining of dysphagia and respiratory weakness, requiring invasive ventilation. After a few months, he recovered his respiratory function, depending on ventilatory assistance only during the night. He started to develop motor milestones, such as cephalic sustenance, sedestation and walking with orthosis support. There was no parental consanguinity or similar cases in the family. Clinically, he presented hypotonia, an elongated face, V-shaped mouth, proximal limb weakness, cleft palate, pectus carinatum, short neck, scoliosis, dolichocephaly, limited cervical movement, ophthalmoparesis, facial weakness, cryptorchidism and low posterior hairline.

Results: CK level was 105IU/L (reference: <168IU/L); electromyography showed a myopathic pattern. Exome sequencing revealed a pathogenic variant in the GDF3 gene (c.796C>T,p.(Arg-266Cys)). Muscle biopsy showed atrophic rounded fibers, nuclear centralization and necklace fibers; an ATPase stain showed optically empty spaces, which stained intensely blue in NADH, pathologically consistent with myotubular myopathy. A Microarray study detected loss of genetic material on the X chromosome (Xq28) equivalent to 268kb. Such deletion represented a pathogenic copy number variation covering MTM1 and MAMLD1 genes.

Discussion: approximately 90% of XLMTM cases result from point mutations in the MTM1 gene, while 10% are due to deletions/duplications in Xq28; in the latter, severe phenotype is expected, with death within the first year of life. In large deletions, the concurrent involvement of the MAMLD1 gene is described, associated with genital abnormalities. In the case reported, there were no genital abnormalities, except cryptorchidism. It is noteworthy that the good evolution of this case is unexpected for such deletion. The exome study did not detected point mutations in the MTM1 gene, but identified a pathogenic variant in the GDF3 gene which causes Klippel-Feil syndrome (OMIM #613702). This syndrome had not yet been associated with myotubular myopathy. It is characterized by a clinical triad: short neck, low posterior hairline, and limited neck movement, present simultaneously in less than 50% of patients. This case presents all of these characteristics, allowing us to describe the first association of Klippel-Feil syndrome and myotubular myopathy. Another important aspect to be highlighted is the insistence on a molecular diagnosis even when an exome does not show pathogenic variants in MTM1. This is because in 10% of cases diagnosis will be by microarray or MLPA test.

Conclusion: the relationship between the genotype and clinical evolution of this case contrasts with that reported in literature. Pathologic findings reinforce the importance of muscle biopsy when a complete exome shows no pathogenic variants, allowing the choice of a more appropriate molecular methodology. This appears to be the first case of Klippel-Feil syndrome associated with XLMTM described in the literature.

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Diffusion Weighted MR Spectroscopy of the brain in Duchenne Muscular Dystrophy

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Introduction: The neuromuscular disorder Duchenne muscular dystrophy (DMD) presents with a wide range of neurocognitive deficits in approximately 30% of patients. These difficulties can be of great impact on the family. Therefore, a better understanding of these brain comorbidities and their origin is important. Diffusion-weighted MRI studies of the brain have demonstrated structural white matter differences between patients with DMD and controls. However, it is unclear how these water diffusion results are associated with specific alterations in tissue microstructure. With diffusion weighted spectroscopy (DWS), the diffusion properties of intracellular metabolites, such as N-acetylaspartate (NAA), creatine and total choline can be measured. The apparent diffusion coefficient (ADC), illustrating the average movement of a metabolite in space during the observed diffusion time, gives insight into these diffusion properties and could be linked to compartment and cell type specific pathology. Here, we aimed to assess potential changes in metabolite ADC in DMD patients compared to controls in a brain region where increased ADC of water was reported.

Materials and Methods: Scans were acquired in a two-center study (LUMC (NL) and Newcastle University (UK)) at 3 Tesla (Philips Achieva, Best, The Netherlands) using an 8-channel head coil. A 3D T1-weighted scan (TE/TR, 4.6/9.8 ms; spatial resolution 1.17x0.92x1.17 mm; 4:55 min) was obtained for anatomical reference. DWS data were acquired using an ECG triggered PRESS sequence from a volume of interest (VOI) located in the white matter (figure 1)(TE=125 ms, TR=2 cardiac cycles, VOI 30x20x15mm, 24 signal averages, acq. time 3:20 min, b=0 and b=3765 mm/s2, three diffusion directions). Inclusion criteria for analyses were a signal-to-noise ratio >6; a Full-Width-Half-Maximum for NAA of <0.030 ppm and a Cramer-Rao Lower Bound of <6% for NAA and <10% for choline and creatine. Covariates were age, genetic mutation, study center and volume fractions. Volume fractions of CSF, white matter and grey matter in the VOI were determined using FSL FAST tissue segmentation and MATlab calculations. Metabolite ADCs were compared between patients with DMD and healthy controls using a multivariate general linear model in SPSS and considered significant at $p<0.05$.

Results: DWS data from 20 DMD patients and 11 age matched controls were included in the analysis. Tissue fractions, genetic mutation, study center and age did not significantly correlate with the ADC of the three metabolites. No differences in mean ADCs were found between DMD patients and healthy controls (mean ± SD: NAA 0.16±0.02 vs 0.17±0.02; creatine 0.17±0.02 vs 0.17±0.02 and choline 0.16±0.04 vs 0.14±0.03)

Discussion/Conclusion: Average diffusivities of NAA, creatine and choline did not differ between DMD patients and healthy controls, in a region where previously water ADC was shown to be increased in DMD. This may indicate a lack of cell-type specificity. With respect to metabolite concentrations; higher NAA, and both higher, lower and equal concentrations of choline have been reported. Further analyses will be performed to determine the water ADC and metabolite concentrations in this cohort in the same VOI to assess the relationship between the metabolite ADC, water ADC and metabolite concentration.

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The UK FSHD Patient Registry: Linking Patients to National and International Research Projects

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Background: The UK Facioscapulohumeral Muscular Dystrophy (FSHD) Patient Registry is a patient self-enrolling online database collecting clinical and genetic information about FSHD type 1 (FSHD1) and type 2 (FSHD2). The registry was established in May 2013 with support from Muscular

Dystrophy UK, assisted by the TREAT-NMD Alliance and is coordinated by Newcastle University. The registry aims to; facilitate academic and clinical research, better characterise and understand FSHD, and disseminate information relating to upcoming studies and research advancements.

Method: The registry is used to capture longitudinal, self-reported data through an online portal available to patients and clinicians. Where specialised clinical or genetic information is required, the neuromuscular specialist involved in the patient's care can be invited to provide some additional information and the patient can select them from a pre-populated list at the registration stage. The registry has adopted the TREAT-NMD core dataset (https://treat-nmd.org/downloads/file/registries_toolkit/FSH_core_dataset_May2011.pdf). This includes but is not limited to patient-reported items such as symptoms (including weakness), ventilation status and current best motor function as well as clinician-reported items such as genetic confirmation of FSHD.

Results: Between May 2013 and February 2021, 1,026 participants registered with the UK FSHD Patient Registry. On average, 9 new participants register each month.

For those who have a clinical diagnosis, 96% have FSHD or FSHD1, and 4% have FSHD2. Overall, 48% have genetic confirmation of their condition and the most commonly reported weakness was shoulder (92%), followed by hip (71%), facial (70%), then ankle (67%). The average age of shoulder weakness onset was 24 ± 15 years, with 50% of all shoulder weakness onset reported between the years of 0 – 19. For pain, patients rated shoulder and lower back pain the highest compared to arm, hand, hip, leg and foot pain on a universal pain assessment tool. As this was developed specifically for the registry it requires further validation. Twenty six percent of patients who provided information on pain medication (175/603) collectively reported using 37 different pain medications. Excluding over the counter pain medications; ibuprofen (81%), paracetamol (63%) and co-codamol (44%), the most common pain medications used were tramadol (19%), amitriptyline (18%), naproxen (14%) and diclofenac (11%).

The registry has previously supported approximately 27 registry enquiries including; the ACT-MuS clinical trial, where the UK FSHD Patient Registry helped recruit more participants than any other referral route, and a natural history study of infantile onset FSHD, where 42% of patients were recruited from registry. In the past 12 months, the registry has facilitated 12 enquiries including, three COVID-19 surveys, and various surveys capturing information on dysphagia, pregnancy, sleep and the patient/caregiver experience.

Conclusion: The registry is currently one of the largest national FSHD patient registries and is an example of a versatile, cost-effective research tool that can help facilitate and advance a wide range of FSHD research. Additional work continues to be done to improve reporting of genetic information on the registry and there are future data linkage plans between the registry and the Newcastle Research Biobank for Rare and Neuromuscular Diseases.

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The UK Myotonic Dystrophy Patient Registry: Linking Patients to National and International Research Projects

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Background: The UK Myotonic Dystrophy Patient Registry is a patient self-enrolling online database collecting clinical and genetic information about myotonic dystrophy type 1 (DM1) and type 2 (DM2). The registry was established in May 2012 with support from Muscular Dystrophy UK and the

Myotonic Dystrophy Support Group, assisted by the TREAT-NMD Alliance and is coordinated Newcastle University. The registry aims to; facilitate academic and clinical research, better characterise and understand DM, and disseminate information relating to upcoming studies and research advancements.
Method: The registry is used to capture longitudinal, self-reported data through an online portal available to patients and clinicians. Where specialised clinical or genetic information is required, the neuromuscular specialist involved in the patient's care can be invited to provide some additional information and the patient can select them from a pre-populated list at the registration stage.

The dataset collected within the registry includes all mandatory and highly encouraged items agreed at the 2009 TREAT-NMD and Marigold Foundation workshop held in Naarden (https://treat-nmd.org/downloads/file/registries_toolkit/DM1_core_dataset_August2009.pdf). This includes, but is not limited to, patient-reported items such as myotonia (including medication), fatigue/day-time sleepiness (including medication) and current best motor function, as well as clinician-reported items such as genetic confirmation of DM, heart condition and ventilation.
Results: Between May 2012 and February 2021, there have been 796 patient registrations. Patients have an average age of 44 years, and there are approximately 5 new registrations per month.

For those who have reported a clinical diagnosis, 96% have DM1 (of which 12% have a diagnosis of congenital DM) and 4% have DM2. Overall, 42% have genetic confirmation of their condition and the most commonly reported symptoms are day-time sleepiness/fatigue (75%) and myotonia (72%).

Twenty one percent of patients report medication use for day-time sleepiness/fatigue, and 11% percent report medication use for myotonia. The most common medication used for day-time sleepiness/fatigue was modafinil (86%) and for myotonia this was mexiletine (33%). For those who have a heart condition, 20% of patients report medication use for this.

The registry has previously supported approximately 28 research enquiries to date, including; the OPTIMISTIC clinical trial where more than 50% of UK participants were recruited via the registry, PHENO-DM1 where 40% of participants were recruited via the registry, and the AMO Pharma phase II clinical trial of tideglusib, where the registry helped recruit 35% of participants. In 2020, the registry has facilitated 11 enquiries including an industry enquiry, three COVID-19 surveys, and various surveys capturing information on dysphagia, pregnancy, patient preferences for future treatments and the patient/caregiver experience.
Conclusion: The registry continues to be a versatile, cost-effective research tool, helping facilitate and advance a range of DM research. Additional work continues to be done to improve reporting of genetic information on the registry and there are future data linkage plans between the registry and the Newcastle Research Biobank for Rare and Neuromuscular Diseases.

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Elbow flexor MRI fat fraction predicts loss of hand-to-mouth movement in Duchenne muscular dystrophy

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Objective: To study the potential of quantitative MRI (qMRI) fat fraction (FF) as biomarker in non-ambulant Duchenne muscular dystrophy (DMD) patients, we assessed the additive predictive value of elbow flexor FF to age on loss of hand-to-mouth movement.
Methods: Non-ambulant DMD patients (≥8 years) were included. 4-point Dixon MRI scans of the right upper arm were performed at baseline and at 12, 18 or 24 months follow-up (Figure 1A). Elbow flexor FFs were determined from five central slices. Performance of the Upper Limb (PUL) 2.0 was assessed for the right arm at all visits. Loss of hand-to-mouth movement (LoHM) was defined as the inability to move a filled glass independently to the mouth using the right hand and allowing support of the elbow on a table, similar to the PUL hand-to-mouth item where

a 200gram weight is used. LoHM was determined at study visits and by phone-calls every four months. FFs were fitted to a sigmoidal curve using a mixed model with random slope to predict individual trajectories. The added predictive value of elbow flexor FF to age on loss of hand-to-mouth movement was calculated from a Cox model with the predicted FF as a time varying covariate, yielding a hazard ratio.

Results: Forty-eight MRIs of 20 DMD patients were included. Median decline in PUL total score over 12 months was 3 points (n=15; range -1 to 8). Median decline in PUL elbow domain score was 2 points (range 0 to 4; Figure 1B). Acquired and predicted FF data are shown in Figure 1C. The hazard ratio of a percent-point increase in elbow flexor FF for the time to loss of hand-to-mouth movement was 1.12 (95%-confidence interval 1.04-1.21; p=0.002). This corresponded to a 3.13-fold increase of the instantaneous risk of loss of hand-to-mouth movement in patients with a 10% higher elbow flexor FF at any age. FF trajectories had steeper slopes in patients who lost hand-to-mouth movement at an earlier age (rho=-0.82, p=0.003, Figure 1D).

Conclusion: In this prospective study, elbow flexor FF predicted loss of hand-to-mouth movement independent of age. qMRI measured elbow flexor FF can be used as surrogate endpoint or stratification tool for clinical trials in non-ambulant DMD patients.

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Early detection of cardiovascular functional disorders with CMRI in Greek adoloscents with Duchenne muscular dystrophy

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Introduction: Duchenne muscular dystrophy (DMD) - associated dilated cardiomyopathy (DMD-CM) is a major complication and leading cause of death in DMD patients. It is characterized by left ventricular (LV) systolic dysfunction leading to end-stage heart failure along with associated supraventricular and ventricular arrhythmias. Early detection and management are associated with delayed progression of LV dysfunction and improvement in outcome.

Purpose: The aim of our study was to identify early cardiovascular functional disorders with cMRI in Greek adolescents with DMD.

Material and Methods: Ten consecutive male DMD patients, aged 12.8+1.8 years old were examined. Three patients were still ambulatory. All patients received treatment with corticosteroids, ACE inhibitors, beta-blocker and spironolactone. All patients were investigated by ECG, transthoracic echocardiography (TTE) and cMRI. Function assessment of LV with ejection fraction (LVEF), Fractional Shortening (FS) and wall motion abnormalities were evaluated with both methods. Presence of late gadolinium enhancement (LGE) was assessed by cMRI and graded by distribution: 0= no LGE or LGE in basal inferolateral wall only vs 1 = LGE involving a more diffuse area.

Results: None of the patients had clinical symptoms or significant arrhythmia. All patients had normal LV systolic function (LVEF ≥65% and FS>35%), confirmed by TTE and cMRI with normal regional wall motion. Seven out of ten patients had a characteristic pattern of non-ischemic LGE detected in the subepicardium of the lateral/inferolateral wall (0), while three had more extensive (10-18%) LGE in the lateral and posterior wall (1). Those with extensive LGE had normal LVEF and FS. These findings suggest that LGE in DMD patients with normal LVEF and FS, indicates that myocardial fibrosis occurs prior to the onset of decreased systolic function. The genetic profile of the three patients with impaired cardiac profile in cMRI had mutations in exons 50, 48-50 and point mutation in intron 70 respectively. LGE cMRI detects the initiation of cardiac abnormalities earlier than TTE alone and the need of early initiation of cardioprotective treatment. No correlation was found between the prior initiation of corticosteroid treatment and the neurological state of the patients with the cardiovascular impairment (p=NS).

Conclusions: cMRI should be performed routinely and early in adoloscents with DMD, not only for LV function estimation, but mainly for LGE imaging assessment. Unmasking subclinical cardiomyopathy in adolescents is the main benefit of this technique which may lead in early initiation of cardioprotective therapy.

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Hypertrophic Cardiomyopathy as the first manifestation of Friedreich Ataxia in the first decade of life

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Introduction: We present a case series of children with Friedreich ataxia (FA) and first manifestation from the cardiovascular system without neurologic symptoms in the first decade of life.
Purpose: The occurrence of cardiomyopathy as first manifestation of FA in children is rare and usually occurs in 2nd or 3rd decade of life after the onset of neurologic symptoms.
Material and Methods: Three children, one boy and two girls, 9 to 10 years old, underwent pre-athletic screening test by electrocardiography (ECG) and echocardiography. Because of ECG and echocardiography findings, ambulatory ECG was performed, troponin levels were measured and cardiovascular magnetic resonance (CMR) was done. Neurological evaluation and genetic tests followed.
Results: All children presented with hypertrophic pattern in ECG (Sokolow-Lyon index: SV1+RV6 > 3.5mV) and T wave inversion in leads II, III, AVF, V4-V6. Evaluation of 2D and Doppler echocardiogram showed moderate concentric cardiac hypertrophy (intraventricular septum thickness / lateral wall thickness, IVS / LA: 12.66±0,57mm / 12,5±0.7mm) without obstruction of outflow truck and normal systolic LV function. Hs-cTn Troponin levels were elevated in all patients versus controls ($p<0.005$). One child had mild isolated premature atrial and ventricular contractions in ambulatory ECG without the need of specific treatment. The CMR (in all three patients) evaluated evidence of oedema and fibrosis and also revealed the presence of Late Gadolinium Enhancement (LGE) > 5% of LV mass, indicative of severe fibrosis. Therefore, the FA patients were re-categorized as having severe FA Cardiomyopathy, with normal LV ejection fraction. Due to a slightly peculiar walking, neurological assessment was requested. After a detailed neurological examination, mild instability in walking in a straight line was observed, absent tendon reflexes, lack of impairment in the deep sensory pathways and absent pyramidal signs. The patients underwent genetic test: homozygosity was found related to the frataxin gene. Children were referred to a Neuromuscular Unit. In all children spironolactone was given for its cardioprotective effects in myocardial fibrosis, as well as Carvedilol. After three years follow up there was no deterioration in cardiac findings and no progress of the cardiomyopathy. Neurological clinical follow up showed mild impairment of neurological signs, especially instability.
Conclusion: Concentric cardiac hypertrophy as first symptom in FA without neurological symptoms is very rare, especially in the first decade of life. Close follow up, clinical suspicion for unmasking the disease and early treatment may help for better outcome in the future.

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Ultrasound and MR imaging in new onset myositis at diagnosis and after IVIG treatment

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Background: Muscle imaging has become an increasingly important tool in the diagnostic work-up and follow-up of idiopathic inflammatory myopathies (IIMs). The objective was to compare US and whole-body Magnetic Resonance Imaging (MRI) for detection of muscle changes compatible with IIM at diagnosis and over time after treatment.
Methods: Newly diagnosed patients with IIM underwent US of 14 muscles and MRI of 36 muscles at diagnosis and after nine weeks monotherapy with intravenous immunoglobulin. In separate analyses, muscle changes were classified as compatible with IIM when quantitative US showed an echo-intensity

z-score ≥1.5, semi-quantitative US Heckmatt score was ≥2, qualitative US was abnormal, and MRI showed oedema on T2-weighted two-point Dixon scans. Patients were classified as abnormal in case of changes in ≥3 muscles.

Results: Eighteen patients with IIM were analysed of whom 50% had dermatomyositis. At diagnosis, US examination of in total 252 muscles revealed changes compatible with IIM in 36 (14%) with quantitative analysis, in 153 muscles (61%) with semi-quantitative analysis and in 168 muscles (67%) with qualitative analysis. MRI examination of in total 623 muscles showed oedema in 476 (76%). At diagnosis, abnormal classification of patients was reached in 5 (28%) with quantitative US, in 16 (89%) with both semi-quantitative and qualitative US and in all with MRI. Follow-up of 12 patients did not show changes over time with quantitative US, but showed a decrease in abnormalities as assessed with semi-quantitative US (p=0.009), qualitative US (p=0.014), and a tendency to decrease with MRI (p=0.084).

Conclusion: At diagnosis MRI is more sensitive than semi-quantitative and qualitative US to detect muscle changes compatible with IIM. Semi-quantitative US and qualitative US showed slightly more sensitivity to change over time.

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Multimodality screening for cardiac involvement in newly diagnosed idiopathic inflammatory myopathies: a cross-sectional study

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Background: Cardiac involvement in patients with an idiopathic inflammatory myopathy (IIM, commonly referred to as "myositis") causes IIM-related mortality in approximately 4%, yet standardized screening strategies are lacking. Therefore, we explored different diagnostic modalities to screen for cardiac involvement in patients with newly diagnosed IIM.

Methods: We prospectively included adult patients with muscle biopsy-proven IIM from February 2017 to February 2020 at a single center. All patients underwent cardiac evaluation for IIM-related cardiac involvement using the 2019 consensus criteria for myocarditis, which is based on the presence of a symptomatology, laboratory biomarkers, electrocardiography (ECG), echocardiography, and cardiac magnetic resonance imaging (CMR).

Results: We included 48 patients, of whom 24 (50%) had dermatomyositis. Twenty-six patients (54%) had symptoms of possible cardiac origin at time of diagnosis. We found six definite (13%) and two probable (4%) diagnoses of (peri)myocarditis. Of these, all but one had elevated cardiac troponin T (cTnT) levels. One patient with a diagnosis of probable or definite (peri)myocarditis had conduction abnormalities for which a pacemaker implantation was required. We found left ventricular diastolic dysfunction in five patients (10%), and pulmonary hypertension in one patient (2%). CMR detected cardiac involvement in 25% and 43% of asymptomatic patients and patients with both unremarkable ECG and echocardiography, respectively.

Conclusion: Routine multimodality screening for cardiac involvement in IIM at time of diagnosis yields a considerable number of (probable or definite) (peri)myocarditis diagnoses. We propose a standardized screening strategy in patients with newly diagnosed IIM based on CMR in those with elevated cTnT.

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A Randomized, Double-Blind, Placebo-Controlled, Gene-Delivery Clinical Trial of rAAVrh74.MHCK7.micro-dystrophin for Duchenne Muscular Dystrophy

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Background: Adeno-associated virus (AAV)-mediated gene transfer therapy has shown early signs of potential to treat Duchenne Muscular Dystrophy (DMD). The intent of rAAVrh74.MHCK7.micro-dystrophin (SRP-9001) is to safely express a functional micro-dystrophin protein in skeletal and cardiac muscle. Preclinical studies and Phase 1b/2 clinical trial findings warrant further investigation of gene transfer therapy in DMD.

We designed an AAV vector (rAAVrh74) containing a codon-optimized human micro-dystrophin transgene driven by a muscle-specific promoter with a cardiac enhancer, MHCK7, to be tested in a 3-part Phase 2 clinical trial that included two 48-week randomized, double-blind, placebo-controlled periods (Part 1 and 2) and an up-to-212-week open-label follow-up period (Part 3). Key eligibility criteria included ambulatory boys aged ≥4 to <8 years with a confirmed DMD gene mutation (exons 18–58), an established clinical diagnosis and stable steroid dosing (≥12 weeks). A single-dose ($2x10^{1}$ vg/kg) SRP-9001 intravenous (IV) infusion treatment arm was compared with a placebo IV infusion arm. Safety endpoints included incidence of serious adverse events and treatment-emergent adverse events (up to Week 260). Primary efficacy endpoints included change in micro-dystrophin expression (baseline to Week 12) and change in functional outcomes by North Star Ambulatory Assessment (baseline to Week 48). Secondary endpoints included Time to Rise, 4-Stair Climb, and 10-Meter and 100-Meter Timed Tests (baseline to Week 48).

Objectives: The purpose of this study is to evaluate the safety and efficacy of IV SRP-9001 in people with DMD by measuring biological and clinical endpoints in a Phase 2 multicenter, randomized, double-blind, placebo-controlled trial (NCT03769116).

Results: Results from the 41 patients that have been randomized and dosed (SRP-9001 or placebo) in Part 1 will be presented.

Conclusions: Initial safety and efficacy findings from this study suggest the potential of SRP-9001 therapy for clinically meaningful functional improvements in people with DMD.

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A placebo-controlled study to evaluate the efficacy and safety of pegcetacoplan in amyotrophic lateral sclerosis

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Background/Intro: Inflammation is a key feature underlying the pathogenesis of numerous neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS). In ALS, the complement system has been implicated in the neuropathology and progression of disease. Pegcetacoplan is a subcutaneously administered C3 complement inhibitor that is being investigated in hematology, nephrology, and neurology. The current clinical study (NCT04579666) is investigating whether attenuating C3 activity can improve survival and function in people diagnosed with apparent sporadic ALS.

Objective: Determine the efficacy and safety of pegcetacoplan compared to placebo among people diagnosed with ALS in a global, multicenter, randomized, double-blind, placebo-controlled, Phase 2 study.

Patients & Study Design: Approximately 228 patients diagnosed with apparent sporadic ALS, ≥18 years of age and with an ALS Functional Rating Scale-Revised (ALSFRS-R) score ≥30, slow vital capacity (SVC) ≥60% of the predicted value at screening, and with symptom onset within 72 weeks prior to screening, are eligible for enrolment. Following screening, patients will be randomized 2:1 to treatment groups receiving either subcutaneous pegcetacoplan (1080 mg) or placebo twice weekly for a duration of 52 weeks. The primary efficacy endpoint is the difference in the Combined Assessment of Function and Survival (CAFS) ranked score at 52 weeks after treatment initiation. Additional, secondary functional efficacy (ALSFRS-R, percent SVC, muscle strength, quality of life, and caregiver

burden) and safety endpoints will be analyzed at 52 weeks. Following the placebo-controlled period, all patients will have the option to receive pegcetacoplan in an open label period for an additional 52 weeks.

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Patient-reported symptom state in a Swedish nationwide prevalent Myasthenia gravis cohort

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Background: Management of Myasthenia gravis (MG) has evolved considerably in the past century. However, MG still causes significant morbidity and has a considerable impact on patients' quality of life. Patient reported outcome measures are gaining increasing attention for MG, both in research and in clinical practice. Here, we aimed to describe Myasthenia Gravis-Activities of Daily Living (MG-ADL) in relation to clinical characteristics in a large Swedish nationwide cohort.

Methods: In a cross-sectional prevalent cohort study, the Genes and Environment in Myasthenia Gravis study (GEMG), performed November 2018 - August 2019, Myasthenia gravis (MG) patients were invited to submit an extensive 106-item life environment questionnaire, including the MG-ADL score. Subjects were identified via the national MG-registry, from 12 collaborating neurology clinics, including all Swedish university hospitals, and through the patient organization. Patients were classified as early onset MG (EOMG, <50 years), late onset MG (LOMG, ≥50 years) or thymoma-associated MG (TAMG). Comparisons of disease-specific characteristics were made between subgroups, sex and different MG-ADL scores.

Results: A total of 1077 patients were included, yielding a 74% response rate. Of these, 505 (47%) were classified as EOMG, 520 (48%) LOMG and 45 (4%) TAMG. Mean age at inclusion was 64.3 years (SD 15.7) and mean disease duration was 14.6 years (SD 14.0). Complete MG-ADL scores (n=1035) ranged from 0-18p, where 26% reported a score of 0p, i.e. no MG-related impact on the MG-ADL scale. In a multivariate regression model higher MG-ADL scores were associated with female sex, obesity and diagnostic delay (ORadj=1.8, 1.9 and 2.0, P<0.01) and inversely correlated with high educational attainment and coffee consumption (both ORadj=0.6, P<0.05), but not with age at inclusion, disease subtype nor disease duration. Almost half the population (47%) reported MG-ADL ≥3p, corresponding to an unacceptable symptom state based on a previously estimated cutoff for patient acceptable symptom state (PASS) score in MG.

Conclusions: In this nationwide study, comprising 42% of the prevalent MG population in Sweden, we observe that almost half of patients report current disease symptoms associated to an unacceptable symptom state, indicating the need for improved treatment options.

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Efgartigimod In AChR-Ab-Seronegative Generalized Myasthenia Gravis Patients: Subgroup Analysis Of The Phase 3 Adapt Study

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Introduction: Efgartigimod is a human IgG1 antibody Fc-fragment which blocks neonatal Fc receptor (FcRn), decreasing recycling of IgG thereby reducing pathogenic IgG autoantibody levels. Efgartigimod demonstrated efficacy and was well tolerated in ADAPT, a phase 3 study in patients with generalized myasthenia gravis (gMG). Acetylcholine receptor antibody seronegative (AChR-Ab-) patients account for 15-20% of the gMG population, have unmet clinical needs, and have historically been excluded from clinical trials. In ADAPT, the response to efgartigimod in AChR-Ab- gMG patients was also explored.

Methods: ADAPT was a 26 week, global multicenter phase 3, randomized, double-blind, placebo controlled trial that evaluated the safety and efficacy of efgartigimod in patients with gMG. Inclusion criteria included MG-ADL ≥ 5 (≥50% non-ocular symptoms), MGFA class II-IV, and a stable dose of at least one gMG treatment. Patients were randomized 1:1 to receive four weekly infusions of efgartigimod (10 mg/kg) or matched placebo, with subsequent treatment cycles initiated according to clinical need as defined by MG-ADL score. The primary endpoint was percentage of acetylcholine receptor antibody positive (AChR-Ab+) patients who were MG-ADL responders (≥2 points improvement sustained for ≥4 weeks) after the first treatment cycle. Although not a specific measure of efficacy in the AChR-Ab- population, a secondary endpoint also explored responder status in the gMG population as a whole.

Results: 167 (129 AChR-Ab+ and 38 AChR-Ab-) patients were randomized. AChR-Ab- patients, including 6 MUSK-Ab+, were evenly distributed between treatment groups. Baseline characteristics were well balanced across both the AChR-Ab- and AChR-Ab+ patients. Baseline mean (SD) MG-ADL scores for AChR-Ab- patients were 9.7 (3.1) and 9.8 (2.5) for the efgartigimod and placebo treated groups respectively. Significantly more AChR-Ab+ patients treated with efgartigimod compared to placebo met the primary endpoint of MG-ADL responder status (67.7% vs 29.7%). Responder status in the overall population, a key secondary endpoint, showed that significantly more efgartigimod treated patients achieved MG-ADL responder status compared to placebo (67.9% vs 37.3%; $p < 0.0001$). In the AChR-Ab- population, 13/19 (68.4%) efgartigimod treated patients and 12/19 (63.2%) patients in the placebo group achieved MG-ADL responder status. In contrast, more stringent criteria showed a numerically larger proportion of patients achieving QMG response criteria in 10/19 (52%) efgartigimod vs. 7/19 (36.8%) placebo patients. 9/19 (47.4%) AChR-Ab- efgartigimod vs. 4/19 (21.1%) placebo patients were both MG-ADL and QMG responders with 6/19 (32%) efgartigimod vs 3/19 (16%) placebo meeting criteria for minimal symptom expression (MSE; MG-ADL 0 or 1) after the first treatment cycle. Adverse events were mostly mild to moderate and consistent with AChR-Ab+ population.

Conclusions: Although ADAPT was not designed to measure the significance of treatment in AChR-Ab- patients, efgartigimod demonstrated a favorable benefit risk profile in treating AChR-Ab- MG patients. In seronegative gMG patients yet to be identified autoantibodies may play a central role in the pathogenesis.

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Interim Analysis of Post-Marketing Surveillance of Eculizumab in Patients with Generalized Myasthenia Gravis in Japan

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Introduction: Eculizumab, a humanised monoclonal antibody targeted to terminal complement protein C5, is approved in Japan for treatment of patients with anti-acetylcholine receptor antibody-positive (AChR+) generalised myasthenia gravis (gMG) whose symptoms are difficult to control with high-dose intravenous immunoglobulin (IVIg) or plasmapheresis. In Japan, all patients with gMG receiving eculizumab undergo post-marketing surveillance. We report the third interim analysis from the surveillance.
Methods: This interim analysis assessed safety and effectiveness through 26 weeks of eculizumab treatment (data cut-off, October 2020). Eight patients were excluded from the effectiveness analysis due to previous participation in the open-label extension phase of the Phase 3, randomized, double-blind, placebo-controlled REGAIN study.
Results: Data are available for 96 adult patients in Japan (female, 60.4%; mean age at eculizumab initiation, 51.5 years). Twenty-one patients discontinued eculizumab during the 26-week follow-up. Three deaths were recorded. One patient died following a fungal infection, and one patient with type 2 diabetes and hypertension died 10 days after the first eculizumab infusion due to atrial fibrillation and acute myocardial infarction (both deaths deemed to be related to treatment with eculizumab). A third death occurred 45 days after the patient's last dose of eculizumab and was considered unrelated to treatment. Adverse drug reactions were reported by 32 patients (most frequently headache [n=8]). No meningococcal infections were reported by the time of data cut-off. Mean (standard deviation) changes from baseline in MG-Activities of Daily Living and Quantitative MG scores were -4.1 (3.6) (n=67) and -5.2 (5.4) (n=60), respectively, at 12 weeks, and -4.8 (3.9) (n=63) and -6.2 (5.5) (n=58), respectively, at 26 weeks. The proportion of patients receiving at least one IVIg treatment/plasmapheresis decreased from 62.5%/30.7%, respectively, in the 6 months before eculizumab initiation to 17.0%/11.4%, respectively, during the 6 months after initiation. Frequency of IVIg use also decreased following eculizumab initiation (Figure 1).
Conclusion: This third interim analysis confirms that eculizumab was effective and well tolerated for treatment of AChR+ gMG in a real-world setting in adult Japanese patients whose symptoms were difficult to control with high-dose IVIg therapy or plasmapheresis. These results are consistent with what was observed in the Phase 3 REGAIN study and its open-label extension.

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Enhancing Delivery of Acid Alpha-Glucosidase to Skeletal Muscle in Pompe Disease: Challenges and AT-GAA Attributes

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Background: Pompe disease (PD) is a rare neuromuscular disorder caused by deficiency of acid alpha-glucosidase (GAA), a lysosomal glycogen-catabolizing enzyme. Despite availability of a recombinant human GAA enzyme replacement therapy (rhGAA ERT), clinical unmet needs remain, including suboptimal response in skeletal muscles caused in part by several key challenges: instability of ERT in circulation and inefficient uptake via the cation-independent mannose 6-phosphate receptor (CI-MPR) at low interstitial concentrations. Once inside cells, GAA requires processing to attain maximal activity for glycogen degradation; however, the relative contributions of proteolytic and N-glycan processing are poorly understood. AT-GAA—an investigational 2-component therapy comprising cipaglucosidase alfa (a next-generation rhGAA enriched with bis-phosphorylated N-glycans for improved uptake) administered with miglustat (a small molecule stabilizer of cipaglucosidase alfa)—has been

demonstrated to significantly improve the PD pathogenic cascade (eg glycogen reduction, and reversal of autophagic dysfunction and muscle pathology) compared to alglucosidase alfa in Gaa knockout (KO) mice. We demonstrate that N-glycan processing is required for enzyme activation and further describe the relative impact of the 2 components of AT-GAA on observed efficacy in Gaa KO mice.

Objectives: To evaluate rhGAA and modified rhGAAs resistant to N-glycan trimming for processing and enzyme activation. To further characterize the relative effect of each of the individual components of AT-GAA (cipaglucosidase alfa and miglustat) on observed efficacy in Gaa KO mice.

Results: Modified rhGAAs resistant to N-glycan trimming demonstrated lower activity. Cipaglucosidase alfa was fully processed, and indistinguishable from mature, endogenous human GAA. In Gaa KO mice, miglustat stabilized cipaglucosidase alfa and preserved its activity in the unfavorable physiological pH of blood.

Conclusion: Results highlight the importance of improving both rhGAA ERT uptake and preserving intracellular processing to maximize glycogen degradation. In Gaa KO mice, the impact of miglustat on cipaglucosidase alfa stability and activity is demonstrated, which has relevance toward developing an effective treatment for PD.

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MyoScreen™, a Platform for Rapid Identification of Candidate Therapies Targeting Myotonic Dystrophy Skeletal Muscle

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DM1 (Myotonic Dystrophy type 1) is an autosomal dominant disorder characterized by myotonia and progressive muscle weakness and wasting. Caused by a CTG triplet repeat expansion in the DMPK (dystrophia myotonica protein kinase) gene, this leads to abnormal DMPK mRNA accumulation into nuclei foci, sequestering of various RNA binding proteins, such as MBNL1 (Muscleblind Like Splicing Regulator 1), and mis-splicing of multiple genes.

No treatment exists for DM1 but several therapeutic strategies are under investigation. In the absence of appropriate animal models for DM1, a predictive in vitro model for deciphering the mechanisms involved in DM1 and accelerating the identification of new therapeutic targets and therapies remains a crucial unmet need.

Our objective was to provide such an in vitro DM1 model capitalizing on the use of MyoScreen™: a well-established high-content analysis and high-throughput screening platform integrated with human primary skeletal myotubes that demonstrate mature sarcomeric organization and expected responses to chemical/electrical stimulation and pharmacologically-relevant drugs[1].

Primary myoblasts from three DM1 patients with blood-determined CTG repeats ranging from 300-1300 and one Healthy donor were sourced and amplified. With minimum optimization of the basic MyoScreen culturing protocol, DM1 and Healthy myoblast donors differentiated into aligned myotubes. Main hallmarks of the disease, such as DMPK foci colocalizing with MBNL1 were present in the DM1 myotubes. High-content analysis was used to compare between the DM1 donor myotubes with quantification of metrics such as mean number of foci per cell, foci number per nucleus distribution, DMPK and MBNL1 colocalization and fluorescent intensity levels. No direct relationship between the CTG expansion size and foci number was noted.

The splicing profile of several genes involved in the Excitation-Contraction (EC) coupling machinery are altered in DM1 myotubes. Thus, calcium flux upon chemical induction of EC coupling was also investigated in DM1 and Healthy donors on the MyoScreen platform. Defects in calcium transients were detected in two DM1 donors, again without apparent correlation to the number of CTG repeats.

To further characterize alterations of MBNL1 within DM1 myotubes, Cell Profiling was applied to extract over 300 MBNL1 expression and localization features from the generated images. We found this to be a powerful method to discriminate between DM1 and Healthy myotube populations. A corresponding machine learning model was then built to measure the efficacy of a (CAG)7 ASO (antisense oligonucleotide) to rescue the disease-associated alterations identified in the DM1 MyoScreen myotubes. A dose-dependent rescue was observed in all three DM1 donors with MBNL1 expression features restored by up to 60%, along with decreased foci count.

Overall, the DM1 MyoScreen platform will be useful for predictive preclinical testing to rapidly identify new therapeutic targets as well as selection of candidate therapeutics targeting skeletal muscle including ASO conjugates, compounds, siRNAs and AAVs (adenovirus associated vectors) producing antisense RNAs and proteins.

[1]MyoScreen, a High-Throughput Phenotypic Screening Platform Enabling Muscle Drug Discovery (2018) SLAS Discov.

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Efficacy and safety of cipaglucosidase alfa/miglustat versus alglucosidase alfa/placebo in late-onset Pompe disease: PROPEL study

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Background: Pompe disease is a rare autosomal recessive disorder characterized by progressive loss of muscle and respiratory function due to acid α-glucosidase (GAA) deficiency. The approved treatment is enzyme-replacement therapy (ERT) with recombinant human GAA (rhGAA) alglucosidase alfa. AT-GAA is an investigational, 2-component therapy comprising cipaglucosidase alfa, a novel rhGAA with enhanced glycosylation for improved uptake and processing, and miglustat, an enzyme stabilizer.
Objectives: Comparison of AT-GAA versus alglucosidase alfa/placebo in a double-blind, parallel-group study (NCT03729362) of adults (aged ≥18 years) with late-onset Pompe disease (LOPD). ERT-experienced and -naive patients were randomized 2:1 to co-administration of intravenous cipaglucosidase (20 mg/kg)/miglustat or alglucosidase alfa (20 mg/kg)/placebo every 2 weeks. The primary and first key secondary endpoints were mean change from baseline to week 52 in 6-minute walk distance (6MWD) and % predicted forced vital capacity (FVC; sitting), respectively. Other key secondary endpoints included lower extremities manual muscle test (MMT), GSGC (gait, stairs, Gower, chair), PROMIS-physical function, and PROMIS-fatigue.
Results: 123 patients were randomized in 62 sites across 24 countries; AT-GAA, n=85; alglucosidase alpha, n=38 (intention-to-treat population). Baseline characteristics were similar between arms. At week 52, 6MWD showed clinical improvement with AT-GAA versus approved therapy but did not reach statistical superiority (mean [SE]: +20.8 [4.6] versus +7.2 [6.6] meters; P=0.072). AT-GAA demonstrated a nominally statistically significant and clinically meaningful improvement in FVC for superiority over approved therapy (-0.9 [0.7] versus -4.0 [0.8]; P=0.023). A clinically significant improvement in GSGC and numerical trends in favor of AT-GAA versus approved therapy in lower MMT, PROMIS-physical function, and fatigue were also observed. Biomarkers showed significant improvements with AT-GAA versus approved therapy (creatine kinase: -22.4% versus +15.6%, P<0.05; urine hexose tetrasaccharide: -31.5% versus +11.0%, P<0.001). Additional endpoints including % predicted 6MWD, GSGC component scores, MIP, MEP, total and upper MMT will be presented. The safety profile was similar between arms.
Conclusion: In this study population, AT-GAA showed positive trends or clinically meaningful improvements on motor and respiratory functions and biomarkers, compared with approved ERT.
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Integrated Analysis of Annualized Incidence of Serious Adverse Events in Infantile-onset SMA Treated with Nusinersen

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Background: Results from the nusinersen clinical trials have shown significant and clinically meaningful efficacy on motor function and survival endpoints across a broad population of individuals with spinal muscular atrophy (SMA). Nusinersen demonstrated a favorable benefit-risk profile in a previous integrated safety analysis of two investigational trials (CS3A, ENDEAR) in infantile-onset SMA with a median follow up of 0.84 (0.2-3.9) years.
Methods: SHINE is an ongoing, open-label extension study for participants who previously participated in nusinersen investigational trials. Safety data as of the 27 August 2019 SHINE data cut were evaluated in participants with infantile-onset SMA grouped according to age at screening (≤7 mo and >7 mo). Safety over time was analyzed in approximate annual (360-day) intervals from nusinersen initiation and were limited to participants with complete follow-up for each yearly interval.
Results: The median time on study was 3.7 (range:0.02-6.3) years for participants with infantile-onset SMA ≤7 mo of age at screening (n=100) and 3.0 (0.2-4.0) years in those >7 mo of age at screening (n=37). Among individuals with infantile-onset SMA ≤7 mo and >7 mo of age at screening, SAEs were documented in 91% (91/100) and 84% (31/37) of participants, respectively. No SAEs were considered related to treatment. Twenty-three percent (23/100) and 8% (3/37) of participants died in the ≤7 mo and >7 mo age at screening groups, respectively, with most events classified by MedDRA System Organ Class and Preferred Term as respiratory, thoracic, and mediastinal disorders. Of the 38 (38% [38/100]) participants in the ≤7 mo age group followed through Year 4, the incidence of SAEs was 79% (30/38), 63% (24/38), 42% (16/38), and 53% (20/38) in Years 1 to 4, respectively. Of the 23 (62% [23/37]) participants followed through Year 3, the incidence of SAEs in the >7 mo of age group was 52% (12/23), 57% (13/23), and 52% (12/23) in Years 1 to 3, respectively. The most frequent SAEs, as measured by total incidence across all intervals and by MedDRA System Organ Class and Preferred Term in the ≤7 mo (n=100) and >7 mo (n=37) age at screening groups were: (1) infections and infestations (76% and 68%, respectively), (2) respiratory, thoracic, and mediastinal disorders (77% and 65%, respectively), and (3) gastrointestinal disorders (21% and 19%, respectively). Most SAEs were related to SMA disease. There were no reports of the MedDRA Preferred Term post lumbar puncture syndrome as an SAE in either age group over the follow-up period. Over the entire follow-up period, 2 (2%) participants in the ≤7 mo group and 3 (8%) participants in the >7 mo group reported non-serious post lumbar puncture syndrome.
Conclusion: The incidence of SAEs appeared higher in the first few years than in the later years of treatment with nusinersen in individuals aged ≤7 mo at screening, and were stable in individuals aged >7 mo at screening, and events were consistent with those expected in the context of SMA. No unexpected or serious treatment-related adverse events have emerged over a median 3.7 years of follow-up.
Supported by: Biogen

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Clinical and genetic spectrum of a large cohort of delta-sarcoglycan muscular dystrophy

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Background: Sarcoglycanopathies comprise four subtypes of autosomal recessive limb-girdle muscular dystrophies (LGMDR3, LGMDR4, LGMDR5 and LGMDR6) that are caused, respectively, by mutations in the SGCA, SGCB, SGCG and SGCD genes. Delta-sarcoglycanopathy (LGMDR6) is the least frequent of all sarcoglycanopaphies and it is considered a ultra-rare disease. Our aim was to characterize the clinical and genetic data of a large cohort of LGMDR6 patients and to investigate whether genetic or protein expression data could predict the severity of the disease.

Methods: We contacted a total of 90 different pediatric and adult neuromuscular units/ neurology departments over the world and collected demographic, genetic, clinical and remaining protein expression in muscle biopsy data of patients with a genetic confirmed diagnosis of LGMDR6

Results: We contacted more than 90 pediatric and adult neuromuscular units/neurology departments around the world and identified 23 patients from 9 different countries after reviewing genetic data of more than 10.000 patients with a neuromuscular disorder. There was a history of consanguinity in 87% of the patients and 52.2% of patients had another affected relative. Ninety one percent of the patients were symptomatic at the time of the analysis. Upper and lower limbs proximal muscle weakness was the most common presenting symptom. Distal muscle weakness was observed early on the progression of the disease. Cardiac involvement was observed in 5 patients (21.7%) and 4 patients (17.4%) required non-invasive ventilation. Sixty percent of patients were wheelchair-bound since a mean age of 14.65 years old. Patients with an undetectable expression of the sarcoglycan complex measure by muscle immunohistochemistry have a significant early onset of the disease and early age of lost ambulation compared to patients with residual protein expression.

Conclusions: This study confirm that delta-sarcoglycanopathy is an ultrarare neuromuscular condition and describes the clinical and molecular data of the largest cohort of patients reported so far. International collaboration has been crucial to collect these data. Our results show that this is a very severe and quickly progressive disease characterized by global muscle weakness affecting proximal and distal muscles of the limbs. As happen with other types of sarcoglycanopathy, there is a correlation between remaining protein expression, age at onset and disease's severity.

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A Spanish Gypsy Family with Charcot-Marie-Tooth type 4D

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We report a Spanish Gypsy family affected with autosomal recessive hereditary motor and sensory neuropathy due to mutation on N-myc Downstream-Regulated Gene 1 (NDRG1). The proband is a 32-year-old woman suffering a progressive neuropathy with onset of symptoms in the first decade of life. She began walking late in infancy. During late childhood she started to have manipulation difficulties. She progressively developed weakness and deformities of the feet (presenting talipes equinovarus) and claw hands. By adolescence she had clumsy gait, with distal sensory loss, symmetrical weakness and distal amyotrophy in all four extremities. When she was 20, she started to suffer progressive hearing loss. Tendon reflexes were absent and sensory and motor nerve conduction studies showed no response in all four limbs. Remarkably, she presented a mild cervical dystonic posturing with associated tremor. Flexor tendon lengthening surgeries were performed in both arms. The distal weakness and gait disorder progressed, leading to a severe disability.

The patient is of gypsy origin. She was born in the city of Madrid. Her grandparent's families were from the Spanish southern region of Extremadura and from Portugal. Her parents were born in Madrid and they were apparently non-consanguineous and healthy. She was the youngest of four siblings, and two of them, a 38-year-old woman and a 36-year-old man, were affected with a similar clinical phenotype. A cervical dystonic position with tremor was also seen in the sister of the proband. Four cousins on the maternal side and four on the paternal side were also affected.

Sequence analysis of PMP22, GDAP1 and SH3TC2 genes were normal on the proband. Sequence on NDRG1 gene found a homozygous mutation (c.442C>T, p. Arg148Ter). Subsequently, genetic analyses were performed on the other five members of the family, confirming the presence of the NDRG1 gene mutation: affected siblings were homozygous and the healthy members were heterozygous.

Charcot-Marie-Tooth (CMT) disease type 4D (also known as Lom type) is a rare autosomal recessive hereditary neuropathy, caused by mutations in the NDRG1 gene. It is characterized by a severe motor and sensory neuropathy with onset in the first decade of life, typically affecting gypsy population. Hearing impairment is usually present. Associated cervical dystonic tremor had not been described before in patients with CMT 4D. This disease was initially identified in Bulgarian Gypsy families, and most cases have been described in Eastern Europe. To our knowledge, this is the second Spanish family reported to have a NDRG1 gene mutation in all

members after performing a complete genetic study, and the first one in the Madrid Region.

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Evaluation of DMD transcripts after Golodirsen treatment of MyoD-converted fibroblasts from 4053-101 clinical trial patients

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Duchenne muscular dystrophy is an X-linked, rare, neuromuscular disease caused by mutations in the dystrophin-encoding gene (DMD) which result in a substantial reduction or absence of dystrophin protein. Genome copy number variations, in particular deletions, that disrupt the transcriptional reading frame are the main cause of the absence of dystrophin. Antisense oligonucleotide-induced exon skipping is able to restore the mRNA reading frame and rescue the dystrophin protein translation, generating a shorter, yet functional, protein and Exondys 51TM is an approved therapy for the treatment of DMD in patients with confirmed DMD gene mutations amenable to exon 51 skipping.

Golodirsen (formerly SRP-4053) is a phosphorodiamidate morpholino oligomer (PMO) developed by Sarepta Therapeutics, Inc., to target exon 53 of the DMD gene. In Study 4053-101, we demonstrated exon skipping and dystrophin restoration in all patients. Some variability in dystrophin protein restoration was observed between different patients, due to a less understood mechanism of delivery of PMOs, and also other not well-identified factors. Here, we aim to assess the specific exon 53 PMO-induced skipping in primary cell cultures from patients recruited into the trial, to better characterise the efficiency of this process in different patients.

Fibroblasts, derived from the patients enrolled in study 4053-101, underwent Myo-D induced differentiation and were subsequently treated with golodirsen. After screening for exon skipping efficiency in cells from treated patients and in healthy controls, we evaluated the transcript 5'-3' imbalance in treated vs non-treated patient cells by custom FluiDMD cards. In addition, to better understand the intracellular RNA dynamics of the deleted and skipped products, we investigated the transcript subcellular localization using specific BaseScope probes. The probes are designed to recognise specific deletions carried by patients involved in the study that had different responses to golodirsen. Subsequently, to provide a more comprehensive assessment of the response to golodirsen, a comparison of the in vitro and the previous in vivo patient data will be performed.

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Growth Patterns in Ambulatory Boys with Duchenne Muscular Dystrophy

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Primarily, to analyze retrospective, longitudinal data on weight, height, and BMI in ambulatory boys with Duchenne muscular dystrophy (DMD), either treated with corticosteroids or steroid naïve. Secondly, to consider whether genetic subgroups display different growth patterns.

This analysis extracted patients from the UK NorthStar DMD database (2003-2020) who were ambulant and on one of the following five regimes: "Steroid naïve", "Deflazacort daily" (DD), "Deflazacort intermittent" (DI), "Prednisolone daily" (PD) and "Prednisolone intermittent" (PI). We included 598 patients, with a total of 2604 height, weight, and BMI observations between the ages of 5 and 12 years.

Mixed-effects regression was used to model weight, height, and BMI SD Scores, calculated using the British 1990 national growth data (UK90).

We compared the effects of steroid types, differences between the steroid regimes, and for those on steroids, the effect of steroid starting age. The effect of the dystrophin mutation site on growth was considered, by defining groups according to patterns of affected isoforms expressed in the brain (Dp427, Dp140, and Dp71) and amenability to exon skipping treatments of exons 8, 44, 45, 51, or 53.

Height of ambulant DMD patients was 0.96 SD lower (95% CI: -1.06, -0.86) and BMI 0.68 SD higher (95% CI: 0.56,0.79) than the UK90 paediatric population at age 5, regardless of steroid regime. Those on DD and PD had significant yearly stunting of height ($p<0.001$ and $p=0.001$, respectively) compared to the steroid naïve population. Those on Prednisolone had yearly weight gain 0.13 SD (95% CI: 0.07,0.19) larger than those on Deflazacort, with no significant difference between daily and intermittent. Those on daily regimes experienced a significantly higher yearly increase in BMI of 0.08 SD (95% CI: 0.02, 0.14), compared with those on intermittent regimes. Starting steroids a year earlier was associated with a 0.27 SD (95% CI: 0.18, 0.36) higher weight and 0.27 SD (95% CI: 0.18, 0.36) higher BMI at age 5, but with a lower yearly increase in weight (0.03 SD; 95% CI: 0.01, 0.04) and BMI (0.03 SD; 95% CI: 0.01, 0.05).

Those with affected expression of all three brain isoforms were 0.82 SD (95% CI: 0.36, 1.28) shorter than those with only Dp427 expression affected. There were no differences between those with only Dp427 expression affected and those with both Dp427 and Dp140 expression affected. There were no significant differences in growth between those amenable to any of the exon skipping treatments and those not amenable.

For ambulant boys with DMD, on average those on daily regimes are significantly shorter and have a significantly greater BMI than those on intermittent regimes. The type of steroid (Deflazacort or Prednisone) influences height, weight, and BMI. Starting steroids earlier is associated with higher weight and BMI at age 5, but then the yearly increase is lower than those starting treatment later. Our data confirm that lack of Dp71 expression may cause more severe stunting. As steroid treatment decisions can be guided by adverse effects considerations this analysis provides further insight into the risks associated with specific steroid regimes.

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The Dutch multicenter Duchenne/Becker registry: facilitation of trial readiness and effective use of patient data

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Trial readiness and reduction of patient burden is essential in view of the number of compounds currently in development for Duchenne and Becker (DBMD) patients. National registries play an essential role as they facilitate patient recruitment and are able to give insight in a population's characteristics by collection of natural history data.

The Dutch Dystrophinopathy Database (DDD) was first established in 2008 by the Leiden University Medical Center (LUMC). The structure of this registry was updated in 2019 to meet with the most recent privacy regulations and to function as a multicenter database due to the foundation of the Duchenne Center Netherlands (DCN). DCN is a collaboration between three academic partners (LUMC, Radboudumc, Kempenhaeghe-MUMC+) and the two patient organizations Duchenne Parent Project and Spierziekten Nederland. In this abstract, we introduce the updated DDD structure and provide an overview of the currently registered patients.

Aims: The main goals of the DDD are 1) the ability to approach patients for clinical trials and investigator-initiated studies, 2) the continuous description of epidemiology and natural history, 3) minimalization of patient burden by efficient re-use of data.

Design: Patients with DBMD and carriers can register in the DDD, a database able to capture a cohesive and extensive standardized dataset. To achieve the aims, we have created five registration options (table 1). Only the first option is obligatory and allows for patients to be approached for new trials. The other options provide insight in epidemiology (option 2), enable re-use of data (option 3) and facilitate (inter) national collaborations (option 4 and 5).

Data management system, privacy and informed consent: To allow for efficient (re)use of data, an information model containing meta-level description has been generated and forms the basis for both the registry and investigator initiated studies within DCN. The web-based Castor EDC data management system is used as interface. To meet with privacy regulations, researchers can be granted separate access to (de)coded data and (groups) of patients. This access is supervised by a database manager and approved by the DCN scientific advisory board. All registered patients were asked to provide new informed consent. Informational letters were sent out by post.
Results: 216 patients (out of 473) reregistered five months after first asking consent. Of these, 143 (66%), 63 (29%) and 10 (5%) were Duchenne, Becker and carriers respectively. 41 patients were aged between 3.5-12 years, 24 patients were between 12-15 years, and 151 were 16 years or older. Most patients provided consent for the yearly questionnaire (92%, 98% and 100% for Duchenne, Becker and carriers respectively), 101 out of 104 patients visiting one of the DCN centers consented for registration option three, while consent for exchange of coded data with non-commercial and commercial partners was 89% and 70% respectively.
Conclusion: Patient registries are essential for investigator-initiated studies and clinical trials. The structure of the updated DDD provides an example of how trial readiness, reduction of patient burden, patient preferences and effective (re)use of data can be achieved.

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Spanish Pompe Registry: Analysis of the 100 patients included

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Introduction and Objectives: Pompe disease is a rare genetic disorder produced by a deficiency or absence of alpha-glucosidase enzyme leading to glycogen accumulation in several tissues including but not limited to cardiac and skeletal muscle. Two main clinical phenotypes have been classically described: Infantile Onset Pompe Disease (IOPD) and Late Onset Pompe Disease (LOPD) that share skeletal muscle weakness as the main clinical symptoms but are differentiated by the presence of cardiac involve-

ment restricted to IOPD patients. Epidemiological studies showed that the prevalence of the disease is about 1:40000 individuals although there can be differences depending on the country. There is no data from Spain regarding the existing number of cases, their regional distribution, the genetic and clinical features or the number of patients that are receiving treatment.

Methods: We have developed a Spanish Pompe disease registry which is doctor initiated, whith a dedicated data entry who visits all sites and include data of patients who have signed a consent form. Here we analyzed the data of the first 100 patients included between 2019 and 2020 including LOPD and IOPD phenotypes from 28 sites in Spain. This registry is part of the "Genetic and Rare Diseases Registries" promoted by CIBERER. We collected information about demographics, family history, clinical features, ancillary tests, functional outcomes and response to treatments from each individual clinical report.

Results: Ninety-six patients were classified as LOPD while 4 had an IOPD phenotype. Fifty-seven patients were male (57%). The mean age of our population was of 45.8 years old (SD 18.94). Forty patients had family history of Pompe, being in 35 of them their siblings who were affected. The most common place of birth reported was Andalusia (22 patients) followed by Catalonia (18 patients). The origin of the family was obtained in 65 patients. The most common region of parent's origin was Andalusia (38 progenitors) being the next more frequent region reported Catalonia (10 progenitors). Seventy-eight patients were symptomatic. The most frequent symptom reported was lower limb and axial weakness in 60% of the patients. Eighty-four patients preserved their ability to walk in their last visit recorded. Thirty-six patients required ventilation support being non-invasive in 30 patients and invasive in 6 patients. Ninety three patients had high levels of CK with a mean value of 716 UI/L (SD 457.99). The most common mutation reported was IVS1-13T>G (c.-13-32T>G) in 64 patients of our population followed up by c.2065G>A in 6 patients and c.1551 +1 G>A in 5 patients. None of the IOPD patients carried the IVS1-13T>G mutation. Seventy-seven patients were treated with ERT with Myozyme™ being the mean period of treatment of 8 years (Range 4 months – 18 years).

Conclusions: The Spanish Pompe Registry give us valuable information about the demographics and clinical features of our population of patients with this rare disease. A better understanding of the disease and its distribution along the country may contribute to improve the quality of their health assistance.

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Bailey-Bloch's congenital myopathy: a rare case reported in Northeastern of Brazil

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A 5-year-old brazilian male from Cajazeiras, Paraíba, son of consanguineous parents, presented generalized muscle weakness since birth with delayed acquisition of motor developmental milestones, in addition, to language delay. His mother reported frequent falls, difficulty walking and swallowing, with progressive worsening through the years. Psychomotor agitation was another finding in the history, requiring the use of risperidone, with good response. Neurological exam evidenced macrocrania, dysarthria due to cleft palate, facial mimic reduction and low ear implantation (Figure 1). When child is sit down, he leans on the body to get up and walks without assistance, with mild anserine gait and normal deep reflexes. Two electroneuromyographies were normal. Exome sequencing was performed and detected a Bailey-Bloch's congenital myopathy (two homozygous copies of pathogenic variants of the STAC3 gene were identified). A Consent form gives written permission to relate the clinical case.

Congenital myopathies are genetic muscular diseases, usually with signs and symptoms present since birth, such as hypotonia, weakness, and a static or slow progression clinical course. The most frequent types of congenital myopathy are differentiated primarily by histological characteristics (Central core and multi-minicore myopathies; Centronuclear myopathy; Nemaline myopathy). Actually, the genetic studies of many different forms of congenital myopathy have been identified, collaborating to trace the genetic profile of these myopathies in our region.

Bailey and Bloch described in 1987, an infant with multiple congenital anomalies and an episode of malignant hyperthermia. This rare autosomal recessive disease was also named as Native American myopathy, because the first patient was from the Lumbee Native American tribe in North Carolina,

USA. This rare condition is characterized by normal intelligence and congenital myopathy with delayed motor milestones, musculoskeletal involvement of trunk and extremities (scoliosis, kyphosis or kyphoscoliosis, contractures, short stature), myopathic facies, ptosis, feeding difficulties and abnormalities of the palate (including cleft palate) are common, as well susceptibility to malignant hyperthermia. Creatine Kinase levels, electroneuromyography and muscle biopsy usually are normal or reveal mild changes.

Currently, the diagnosis of Bailey-Bloch's congenital myopathy is established by molecular genetic testing with biallelic pathogenic variants in STAC3 gene and the clinical findings already reported above. The STAC3 gene is a component of the excitation-contraction coupling machinery of muscles and it is essential for functional skeletal muscle. A higher susceptibility to malignant hyperthermia, maybe result from abnormal calcium ion balance in skeletal muscle, suggesting that this myopathy may affect calcium regulation. Therefore, the importance of diagnosis Bailey-Bloch's congenital myopathy is to avoid certain agents used with general anestesia, such as volatile anesthetic gases and depolarizing muscle relaxants. Our case reported a molecularly confirmed Bailey-Bloch's congenital myopathy (Native American myopathy) in na individual who are not known to have Lumbee tribe Native American ancestry and to our knowledge, the first case reported in the Northeastern of Brazil. We emphasize the importance of clinical features such as facial and generalized weakness, normal or mildly abnormal extraocular movement, hypotonia, cleft palate, scoliosis, and particularly history of malignant hyperthermia should be considered for accurate diagnosis to Bailey-Bloch's congenital myopathy.

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Carey-Fineman-Ziter Syndrome: insights of a very rare congenital myopathy in Northeastern of Brazil

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Introduction: Carey-Fineman-Ziter syndrome (CFZS) is a congenital myopathy linked to an autosomal recessive gene mutation in the MYMK gene that encodes a protein called myomarker, fundamental in muscle formation. We present to the best of our knowledge, the first case of a teenager with CFZS from Pernambuco, Northeastern of Brazil.
Case report: A 15-year-old brazilian female with facial dysmorphisms related to Moebius sequence (facial diplegia and opthalmoparesis) and Robin sequence (mandibular hypoplasia, tongue hypoplasia, ogival palate) since birth. She also presents low ear implantation, tongue fasciculations, proximal muscle hypotrophy, hypotonia, non progressive mild appendicular weakness. Cognition slightly impaired. Recentelly, she has been getting worse with nocturnal dyspnoea. Medical history revealed expousure to misoprostol during pregnancy and delayed acquired motor milestones. Furthermore, in family history, exist a second degree relative with similar facial dysmorphisms and wheelchair user without diagnosis. Brain resonance imaging was normal and electroneuromyography revealed a cronic myopathic with chronic neurogenic pattern with pseudomyotonic discharges in the right genioglossus (Figure 1). Exome sequence was performed and showed a mutation in MYMK (c.271C>A:p Pro91Thr) in heterozygosis. A Consent form gives written permission to relate this clinical case.
Discussion: Carey-Fineman-Ziter syndrome is a very rare myopathy that manifests since birth with weakness in facial muscles (Moebius sequence), global hypotonia and dysmorphisms associated with the Pierre-Robin sequence (mandibular hypoplasia, hypoglossia and cleft palate). Short stature, delayed motor and cognitive development, may also be present, as well as restrictive lung disease and cryptorchidism, in male patients. Muscle weakness is more proximal, with non-progressive or slowly progressive course. Imaging exams of central nervous system, usually, have no findings; however, some reported cases have presented brain malformations, such as brainstem hypoplasia. Muscle biopsy can show a pattern of fatty infiltration or muscle atrophy, which is also common in other myopathies. Exome is necessary for definitive diagnosis, since SCFZ presents an autosomal recessive inheritance pattern. The mutation ocurrs in the MYMK gene which encodes the transmembrane protein myomarker, necessary for fusion of mononuclear myoblasts in multinuclear myocytes in the muscle structure. During embryonic muscle development, the defective

fusion of myoblasts results in a reduced number of muscle fibers with compensatory hypertrophy and muscle weakness identified from early childhood. According to the report, we described a patient in whom a very rare myopathy with clinical features such as Moebius and Robin sequences characterize CFZS, however, ophthalmoplegia of abducent nerve is not always found. We emphasize that her electroneuromyography, there was also a chronic neurogenic pattern, suggesting an impairment of medulla motor nuclei, despite her normal brain resonance imaging. At present, there is no disease modifying treatment available, but prompt diagnosis is essential to prevent contractures, promote motor, respiratory and swallowing rehabilitation, and, in addition, to genetic counseling in family planning. Our case report highlights the importance of a profound facial and tongue muscle weakness in combination with global hypotonia are the clinical hallmark of CFZS. Electroneuromyography can add information about involvement of the motor nuclei of the brain stem and the exome contributes to elucidate the diagnosis.

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Phase 2 RCT Trial Evaluating the FcRn Antagonist Nipocalimab in Adults with Generalized Myasthenia Gravis

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Objective: To evaluate the safety, tolerability, efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity of nipocalimab vs. placebo in patients with generalized myasthenia gravis (gMG) who have had an insufficient response to ongoing, standard-of-care therapy.

Background: Nipocalimab (M281) is a fully human, aglycosylated, effectorless IgG1 anti-FcRn monoclonal antibody that targets the IgG binding site on FcRn with high affinity, thereby interfering with the binding of IgG. IgG that is not bound to FcRn cannot be recycled and thus undergoes lysosomal degradation. This is expected to reduce serum levels of total IgG and pathogenic IgG autoantibodies that cause MG and ameliorate the disease.

Design/Methods: 68 patients with anti-AChR or anti-MuSK autoantibodies were randomized 1:1:1:1:1 to 4 nipocalimab treatment groups or a placebo group. Doses of nipocalimab were 5mg/kg Q4W, 30mg/kg Q4W and 60 mg/kg Q2W. A single dose of 60mg/kg was also included to evaluate the duration of IgG lowering and efficacy. To maintain study blinding, all patients received an intravenous infusion (either nipocalimab or placebo) every other week for a total of 5 infusions during the 8-week treatment period. After completion of the follow-up period, patients could enroll in a separate open-label extension study and receive treatment with nipocalimab. On-site visits were temporarily restricted due to COVID-19 restrictions.

Results: Nipocalimab was generally well-tolerated. There were no discontinuations due to TEAEs and no severe AEs with nipocalimab. There was one SAE in the nipocalimab group (shoulder pain) and two SAEs in the placebo group (one case of ischemic stroke and one case of MG worsening). The frequency of infections in the nipocalimab combined dose group vs. the placebo group was 33.3% vs. 21.4%, respectively and there were no severe or serious infections. The percentage of headaches with nipocalimab was comparable to placebo.

Nipocalimab achieved substantial and rapid reductions in serum total IgG and anti-AChR IgG autoantibodies which were correlated statistically significantly with MG-ADL improvement ($P<0.0001$).

Treatment with nipocalimab resulted in a robust and significantly greater mean improvement from baseline in MG-ADL scores across nipocalimab continuous dosing arms vs. placebo at the end of the treatment period (Day 57).

A greater proportion of patients treated with nipocalimab exhibited rapid improvement (within two weeks of treatment) in MG-ADL across all 4 dosing arms vs. placebo.

51.9% of patients who received nipocalimab (all doses) reported a durable MG-ADL response (defined as an MG-ADL improvement of ≥2 points

from baseline for at least 4 consecutive weeks during the first 8 weeks of treatment) vs. 15.4% of those who received placebo (P=0.017).
Conclusion: Nipocalimab was generally well-tolerated and was associated with a meaningful clinical response.

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A familial case of late onset VCP-related proteinopathy

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Objectives: Pathogenic variants in the VCP gene have been associated with progressive autosomal dominant adult onset multisystem proteinopathy with a broad spectrum of phenotypes including inclusion body myopathy, Paget's disease of bone and frontotemporal dementia. Therefore, our aim is to describe a family (father and son) with a previously reported VCP variant presented with a myopathy as the only phenotypic manifestation.
Case report: The proband presented with gradual onset proximal muscle wasting and weakness in all four limbs and axial muscles since 38 years old. Neurological examination at the age of 46 revealed atrophy of shoulder girdle with wasting of both biceps, triceps thinning of thighs and pseudo hypertrophy of both calves, Gower's sign was positive. Scapular winging did not appear. Muscle strength was 4/5 (MRC-scale) at both shoulders, 4/5 at both elbows, 5/5 at both wrists, 3/5 at both hip joints, 3/5 at both knees, 4/5 at both ankles. Facial muscles were not involved. CK level was 1237 U/L. Nerve conduction studies were normal. Needle electromyography showed chronic myopathic changes. Cognitive examination did not reveal any signs of frontotemporal dementia. We did not find any significant abnormalities during single photon emission computed tomography (SPECT) bone scanning, biochemical and rheumatological evaluation. The patient's father presented at the age of 60 with symmetrical pattern of proximal weakness and muscle wasting involving legs, arms, axial muscles. Over a period of 8 years gait disturbances occurred. CK level was normal. Neither bone abnormalities, nor movement or cognitive impairment is present so far. Next generation sequencing identified a known pathogenic missense variant c.277C>T (p.(Arg-93Cys)) in exon 3 of the VCP gene (CM064354; rs1554669087). Segregation analysis confirmed this variant for the father. Pathogenic variant at Arg93 is predicted to induce changes in the tertiary structure of the VCP protein.
Conclusions: The more information about VCP-related patients is collected, the more we can learn about the phenotypic and genotypic variability of these patients. To the best of our knowledge previously reported patients who have the c.277C>T variant display clinical phenotype of complete VCP-related proteinopathy. This report will further contribute to broader analysis of phenotype-genotype correlations of VCP-related proteinopathy.

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Efficacy And Safety Of High, Standard and Low Maintenance IVIG Dosing In CIDP Patients (ProCID)

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IVIG is often considered treatment of first choice in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) because of its rapid onset of action and its relatively safe long-term adverse event profile. Standard dosing regimen includes a loading dose of 2.0 g/kg IVIG and a standard maintenance dosage of 1.0 g/kg IVIG every 3 weeks. No large trials have investigated different IVIG dosing options so far. The ProCID study was a prospective, double-blind, randomised, parallel-group, multicentre, phase III study investigating the efficacy and safety of 10% liquid IVIG (NewGam) in patients with definite or probable CIDP. Patients had to wash-out/reduce their previous CIDP treatment and needed to show deterioration before enrollment in the study.

All eligible patients received a loading dose of 2 g/kg as first IVIG administration. Patients were randomised 2:1:1 to either the standard maintenance dose (1·0 g/kg) or a lower (0·5 g/kg) or higher (2·0 g/kg) maintenance dose every 3 weeks (total duration 24 weeks).

Primary endpoint was the response rate in the 1 g/kg arm at week 24 with a response being defined as improvement in adjusted INCAT score by at least 1 point. In total 142 patients were randomized and 139 subjects were included in the intention-to-treat (ITT) analysis. About 90% of subjects had received corticosteroids and 10% IVIG as prior treatment for CIDP. The primary endpoint was met with a response rate in the standard maintenance arm of 79.7% (55/69 patients; 95% CI: 68.8-87.5) with the lower CI exceeding the predefined threshold of 42%, thus confirming the efficacy of 1·0 g/kg IVIG in the maintenance treatment of CIDP. Although the study was not powered to show dose response, response rates seemed to be dose dependent with a response rate of 64.7% in the 0.5 g/kg arm, and a response rate of 91.7% in the 2.0 g/kg arm. Differences were only statistically significant between the 0.5 g/kg and the 2.0 g/kg arm. Analyses of the secondary efficacy endpoints consistently supported the primary analysis showing a worsening during the wash-out phase and improvements during the IVIG treatment period.

Over half of all patients (56%) had an improvement of ≥1 INCAT point 3 weeks after the loading dose alone. Safety was as expected for IVIG treatment and only headache showed a dose-dependent frequency with higher rates of headache in the high dose arm compared to standard and low dose arms. In summary, the ProCID study demonstrated that 1·0 g/kg IVIg is efficacious and well tolerated as maintenance treatment following a 2·0 g/kg loading dose in patients with active CIDP.

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Benefits of whole exome sequencing data reanalysis in Iranian undiagnosed neuromuscular patients; a pilot study

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The overlapping phenotypes in neuromuscular disorders (NMDs) highlight the role of accurate molecular diagnosis, which itself is confined by their heterogeneous genetic nature. Nowadays, molecular diagnosis is enhanced by implementation of whole exome sequencing (WES) in diagnostic laboratories. However, the diagnostic yield has been still limited to less than 50% in different studies. Besides, hereditary types of NMDs are common in populations with high rate of consanguinity such as Iran. During the past few years, WES has also opened its way as a routine laboratory tool in the work-up of NMDs in this country, displaying higher diagnostic rates up to 73% in some cohorts. However, there are still lots of undiagnosed patients despite having supportive clinical and pathological evidences.

Over recent years, reanalysis of exome data has allowed genetic diagnosis in patients who have not received positive results from the initial evaluation and has increased the clinical diagnosis in 10-15% of patients. Simultaneous WES-based detection of CNVs plays an important role in this regard as the CNVs explain 10% of all inherited disorders and 5-9% of genetically unsolved myopathic patients. To the best of our knowledge, no specific study is performed to evaluate the added value of WES-reanalysis in molecular diagnosis of NMDs, which is imperative as an average of 28 genes are being introduced annually.

To address this issue, the current study is designed as a pilot phase to assess the effect of WES-reanalysis in improving the diagnostic yield of NMDs, especially in populations with consanguineous background. Therefore, twenty undiagnosed Iranian patients suffering from neuromuscular disorders, who have received a negative result from the initial WES analysis, were selected. WES reanalysis was performed applying the most updated versions of GATK and other algorithms to increase variant detection and annotation. The variants in newly identified NMD genes were reassessed, and WES-based CNV analysis using the GATK GermlineCNVCaller was applied.

Thus far, our initial analysis has shown 20% increase in diagnostic yield based on the identification of pathogenic variants in the following genes; MICU1, MTM1, RYR1 and an intragenic deletion in SGCB. These causal variants were not detected in initial WES analysis; the MICU1 was not a known gene at the time of analysis, the MTM1 gene was not selected for investigation in panel analysis, the

RYR1 variant was reclassified from VUS to likely pathogenic, and CNV analysis was not part of the initial WES evaluation to identify the intragenic deletion of exon 2 in SGCB gene. The identification of this intragenic deletion in such a small cohort is in line with recent studies presenting LGMD2E as the most common type of sarcoglycanopathies in Iranian patients, while this deletion is considered as one of the most frequent mutations in this gene, proposing the possibility of being a founder mutation in Iran.

In conclusion, the current study shows the importance of careful re-evaluation of NGS data in line with multidisciplinary approach to detect different mutation types and achieves significant increase in diagnostic yields of NMDs compared to other Mendelian disorders.

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Risdiplam in adult patients with SMA: first experience from the CUP program

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Introduction: Increasingly, drug therapies are available for 5q spinal muscular atrophy (SMA). The first therapy developed was Nusinersen, which has shown clinically significant improvement in motor function. However, intrathecal administration and the associated technical difficulties is a major obstacle and should not be underestimated. Therefore, therapy with Risdiplam with oral administration route is an advantage for patients with SMA. Data to date from the FIREFISH trial in SMA 1 and the SUNFISH trial in SMA 2 and 3 have shown clinical improvement in motor function. Risdiplam was investigated only in minority of adult SMA patients. Here we present first experience from treatment of adult patients of the the CUP program.

Material/Method: Adult 5q-SMA type 2 patients have been followed during routine visits in our neuromuscular center. Motor performance was assessed using HFMSE, RULM and D2 and D3 subsets of the MFM32.

Results: Between September 2020 and February 2021, 9 patients were treated. HFMSE score, RULM score, and MFM D3 were not significantly increased compared with baseline at 6 months. Mean MFM D2 increased by 3,4 points (SD 2,93) within 6 months. The most common adverse events were headache and nausea. No serious adverse events occurred.

Discussion: Considering the limitations of a small number of patients all of them severely affected prior to treatment and the short observation period, the results to date do not show a significant improvement in motor function of adults with 5q-SMA treated with Risdiplam. Nonetheless, no deterioration of motor functions is registered within this period. Actually, progression of the disease is to be expected in these patients. It should not be underestimated that in all previous studies of Risdiplam (FIREFISH and SUNFISH), patients were treated for at least 12 months. Proving the efficacy of Risdiplam in a real-word cohort of SMA patients would potentially represent and important evidence for adult patients with 5q-SMA.

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Muscle histopathology and functional data in a large cohort of patients with Becker muscular dystrophy

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Age of onset, clinical presentation and rate of disease progression in Becker Muscular Dystrophy (BMD) patients display wide variability. At our Center we are currently performing a randomised, double-blind, placebo-controlled study to evaluate the histological effects, the safety and tolerability, and the efficacy of Givinostat in BMD patients. Ambulant adult male patients with a molecular diagnosis of BMD and a screening 6 minutes walking test (6MWT) between 200 and 450 meters were recruited. All patients underwent other functional tests (4-stair climb, 10 meters walk/run test, rise from

floor, motor function measure MFM, muscle strength) and biceps open muscle biopsy before the randomization visit. The enrolment phase of the study has been closed and we have collected histological specimens from 45 patients, with an average age of 38 years and a mean disease duration of 23 years. Similarly to the wide clinical variability of BMD patients in our cohort, muscle biopsies also showed marked histological variability, ranging from an almost normal morphology to a severe dystrophic pattern with a marked fibroadipose replacement. The correlation analysis between histological parameters and clinical outcomes showed that in BMD patients the percentage of muscle fiber area (MFA) positively correlated with most of the clinical outcomes, while the percentage of adipose and fibrous replacement showed a negative correlation (Figure 1). The in-depth statistical analysis allowed to divide our cohort of BMD patients into three clusters (mild, moderate and severe), according to the clinical and histological features. The severe cluster is characterized by significant increase of both connective (56.26%) and adipose tissue (8%) with a consequent marked reduction of MFA (26.23%). The moderate and mild clusters had 34.44% and 17.83% fibrotic tissue respectively, and no fatty infiltration was detected. In these two clusters, the residual MFA were 64.37% and 80.93% respectively. Marked tissue replacement caused a deterioration of muscle contractile function, which may explain the worst functional performances in more severe patients. Our results underline the importance of the choice of appropriate functional tests to monitor the state of disease progression. At present, this work has collected one of the largest cohorts of ambulant BMD patients, providing relevant information about muscle alterations and allowing significant correlations between them and functional data.

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Chronic Inflammatory Demyelinating Polyneuropathy: Characteristics and Epidemiology in Latvia

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Introduction: Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated disorder affecting peripheral nerves and nerve roots, characterised by progressive or relapsing development of weakness and sensory loss in extremities. As the diagnosis of CIDP may be challenging, the reported prevalence and incidence varies between 0.5-10 cases per 100 000 individuals with a slight male predominance. This is the first study analysing characteristics and epidemiology of CIDP patients in Latvia.

Objectives: To determine incidence (2015-2020) and prevalence (on November 1, 2020) of CIDP in Latvia, as well as describe general characteristics of CIDP patients in Latvia.

Methods: A review of patient files diagnosed with CIDP in a 5-year period (2015-2020) in Pauls Stradins and Riga East Clinical university hospitals. Re-evaluation of clinical and electrophysiology criteria, as well as response to treatment. Neurological examination of all patients identified as definite or probable CIDP patients. Scales and tools used for clinical assessment - MRC scoring scale, grip strength, I-RODS, 6MWT, INCAT, LANSS and COMPASS31 for autonomic dysfunction detection.

Results: In our study 16 patients (6 women and 9 men) were enrolled and identified as CIDP (according to EFNS/PNS electrodiagnostic criteria: 13-definite, 3-probable). At the time of enrolment, the median age was 57,5 years (range 17-79 years). The median age at onset was 52 years with a median disease duration until diagnosis of 9 months. The prevalence and incidence were 0.84 per 100 000 and 0.65 per 100 000, respectively. Sensory disturbances as the initial symptom were reported in 10 patients (62%). One male patient initially had a course that mimicked Guillain-Barre syndrome. According to the clinical symptoms and nerve conduction studies, majority of the patients (n=13) manifested as typical sensorimotor CIDP. CSF analysis was available for 12 patients, verified cytoalbuminologic dissociation was present in 8 samples. Plasma exchange procedure (PLEX) as the first line treatment was performed for 8 patients, intravenous immunoglobulins – for 7 patients, intravenous methylprednisolone – for 1 patient. 75 % of patients (n=12) exhibited a relapsing-remitting course of disease, 25 % - slowly progressive and monophasic. Only 1 of the 16 CIDP patients also had another autoimmune disease - systemic lupus erythematosus. The youngest patient (age 17) had co-existence of CIDP and CMT1A

polyneuropathy. The median I-RODS score for the study group was 36 (summed raw score, range 9-48 points). At the time of evaluation one patient was confirmed to have a long-term remission. According to LANSS results, 5 patients experienced neuropathic pain syndrome.

Conclusions: The incidence and prevalence of CIDP in Latvia are similar to previously reported studies worldwide. There is a minor male predominance in our study. All patients had a good response to the first line of treatment.

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SARS-CoV-2 associated Guillain-Barre syndrome cases in Latvia

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Introduction: Guillain-Barre syndrome (GBS) is an autoimmune disorder characterised by sensorimotor polyneuropathy, decreased reflexes and rapidly progressive muscle weakness which can lead to respiratory failure. Upper respiratory tract infections remain one of the most common etiologic factors and several SARS-CoV-2 associated GBS cases were described.

Methods: Case series.

Results: Two female (54 and 79 years-old) and two male (64 and 63 years-old) patients were admitted to clinical university hospitals with progressive sensory loss and motor weakness in limbs. Previous medical history revealed positive SARS-CoV-2 RT-PCR nasopharyngeal swabs in both males and females, as well as signs of pre-existing upper respiratory tract infection in both females and one of the male patients. The diagnosis in male patients was complicated by co-existing severe hyponatremia (111 mmol/L) in one case and severe thrombocytopenia (PLT 15000) in another. In male patient with thrombocytopenia autoimmune hematologic disease was suspected and he received therapy with glucocorticosteroids. Subsequent deterioration of motor symptoms occurred, and patient was referred to neurologist. Neurological examination revealed asymmetric tetraparesis of different degree, reduced tendon reflexes and sensory polyneuropathy. All the patients underwent lumbar puncture and increased protein level were observed in all cases (0,53, 0,6, 2,0 and 2,1 g/L respectively). According to Brighton criteria Level 2, GBS diagnosis was confirmed. Nerve conduction study was performed only in one male patient, showing severe sensorimotor axonal demyelinating polyneuropathy prevalent in hands. Both female patients underwent 5 plasma exchange procedures; IVIG 0,4 g/kg for 5 days was used for the male patients. Immunomodulatory therapy resulted in slight improvement of sensory and motor symptoms in all patients, and they were discharged to continue further rehabilitation.

Conclusion: Muscle weakness and tingling sensations are non-specific symptoms which occurs in various neurological and systemic conditions. SARS-CoV-2 virus is associated with wide spectrum of provoked disorders especially of autoimmune origin. The onset of characteristic new neurological symptoms early after the respiratory illness should raise suspicion of Guillain-Barre syndrome. We describe first SARS-CoV-2 associated GBS cases in Latvia with equally successful response to different immunomodulatory treatment.

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The evidence of altered mitochondrial respiration in skeletal muscles of premanifest Huntington's disease

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Introduction: Huntington's disease (HD) is a neurodegenerative disease caused by CAG trinucleotide repeat expansion in the huntingtin gene. Along with the affected nervous system, muscle pathology stands out as a well-recognized hallmark of HD and manifested in muscle wasting and atrophy, and accompanied by defects in energy metabolism. However, it has not yet been determined whether changes in mitochondrial respiratory function cause muscle atrophy in HD patients.

Material and Methods: Muscle samples were acquired by a fine-needle biopsy method from the middle part of the m. rectus femoris of 8 HD premanifest patients (age, mean±SD, 27±3.25 years), and 8 age and sex-matched controls (age, mean±SD, 28.5±3.21 years). Following mechanical preparation and permeabilization with saponin, respiration of muscle samples was measured using high-resolution respirometry (Oroboros Oxygraph-2k, Oroboros Instruments, Austria). The data were normalized to the wet weight of samples; results (pmol O2/s/mg, means±SD) were statistically analyzed using the Mann-Whitney test.

Results: The study revealed that coupled respiration rates were decreased in HD premanifest in comparison to controls. In particular, when studying respiration during oxidative phosphorylation (OXPHOS) with the involvement of different metabolic pathways (CI, CII, and CI+CII), lower values in HD premanifest were shown for OXPHOSCI (20.7±2.7 vs. 26.6±2.0, $p<0.001$) and OXPHOSCI+CII (34.3±4.4 vs. 44.8±7.5, $p=0.007$), but not for OXPHOSCII. The tendency to decreased electron transfer system capacity and respiratory acceptor control ratio was also observed in HD premanifest. No significant difference between HD patients and controls was observed in citrase synthase activity.

Conclusion: We demonstrated alterations in mitochondrial respiration of skeletal muscles observed on the premanifest stage of HD.

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Late adult onset spastic paraplegia in ABDC1 mutation

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Background: X-linked adrenoleukodystrophy (ALD) is one of the most common peroxisomal disorders characterized by abnormal accumulation of very long-chain fatty acids (VLCFA) in plasma and tissues. It is caused by mutations within ABCD1 gene.

ABCD1mutations have variable penetrance in males, and several clinical presentations are distinguished: childhood and adolescent cerebral ALD, adrenomyeloneuropathy (AMN), olivopontocerebellar form, adult cerebral ALD, Addison-only form, and asymptomatic ; female heterozygotes may exhibit AMN.

AMN represents the second most common subtype, about 27% of cases in Spanish samples. AMN is an adult-onset form characterized by progressive spastic paraparesis, sensory dysfunction and urinary symptoms . The age at onset is between 20 and 30 years old.

Hereditary spastic paraplegia (HSP) is a clinically and genetically heterogeneous group of disorders characterized by a slowly progressive spastic paraplegia. Complicated and pure HSP are distinguished by the presence of associated clinical features.

Case report: Our patient was a 49-year-old male, with rigidity complain. He has noticed in last two years pain and rigidity in legs after long walks. He had no weakness in lower limbs, gait difficulty, gait unsteadiness or urinary dysfunction. The upper limbs were intact, and no skin hyperpigmentation, cognitive impairment, afebrile seizures, muscle atrophy or extrapyramidal disturbances was observed.

Neurological examinations revealed no enhanced muscle tone but brisk tendon reflexes, positive Babinski signs and clonus in lower limbs. Vibratory sensation, light touch, pain, temperature and position sense were normal. His gait was normal. Electromyography was also normal. Brain MRI and whole spine MRI revealed no obvious lesion. The results of routine screening were normal. VLCFA was not considered for this adult onset case with pure spasticity and without leukodystrophic changes on brain MRI.

His brother had a diagnosis of spastic paraplegia with negative genetic tests. This brother had suffered from progressive gait difficulty since age 26. The disease progressed slowly and the symptoms were severe enough to require a walking aid. He could no longer run or walk long distance at age 40. We used exome sequencing (ES) and we identified a hemizygous pathogenic variant c.448G>A (p.Arg163His) in ABCD1 gene.

The genetic test was performed in his affected sibling and confirm the same mutation. Laboratory examinations showed normal levels of plasma cortisol and adrenocorticotropic hormone (ACTH) in both

patients. Measurement of VLCFA in the plasma of both brothers revealed that the values of C24:0, C26:0, C24/C22and C26/C22 were all at higher-level when compared with normal, which was consistent with the biochemical defect of X-ALD.
Conclusions: ABCD1 mutations can cause a mild "pure HSP" phenotype in males without neuropathy. This phenotype can have a late onset . Plasma concentration of VLCFAs should be considered in HSP without neuropathy or changes on MRI. ES give us the possibility to broad the clinical-genetic spectrum of ABCD1 mutations.

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Two novel SH3TC2 mutations . Extending the genotype spectrum

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Background: Mutations in the SH3TC2 gene, cause a recessive demyelinating CMT type 4C and it is characterized clinically by demyelinating peripheral neuropathy frequently associated with spinal deformities and cranial nerves involvement . Carpal tunnel syndrome in CMT4C is reported infrequently and it is uncertain whether heterozygous mutations of SH3TC2 confer susceptibility to carpal tunnel syndrome due to toxic gain of function.
Case report: We studied a 54-year-old female with no consanguineous parents, with early-onset motor and sensory neuropathy, deformities of the hands and feet, and severe bilateral carpal tunnel syndrome. At the age of 15 years she developed insidious difficulty running due to bilateral foot drop without sensory impairment. She observed a deformity in her hands at the age of 30.

Neurological examination revealed the following: severe symmetrical distal muscle weakness and atrophy of lower limbs ; asymmetrical distal atrophy in thenar eminences and interosseous muscles; moderate asymmetrical muscle weakness in hands and positive bilateral Tinel and Phalen signs at the wrists. Deep tendon reflexes were decreased in upper limbs and absent in lower limbs. Superficial and vibration perception were absent in distal lower extremities. She had gait instability. Deformities of the hands (claw hand) and feet (pes planus) were also observed. There was no scoliosis or cranial involvement . She had 3 siblings, one of them with similar symptoms . Both affected siblings were studied several years ago with negative PMP22 duplication or deletion and both underwent extensor tendon transfers for treatment of foot drop about ten years before.

Electrophysiological studies yielded several significant findings. In nerve conduction study (NCS), sensory nerve action potential (SNAP) were absent in lower and upper limbs and compound muscle action potential (CMAP) were absent in lower limbs. CMAPs in upper limbs showed relatively diffuse and homogeneous slowing of conduction velocity (around 25m/s) without conduction block. In median NCS, distal latencies of motor nerves were more prolonged than the distal latencies of cubital nerve. These focal conduction delay were presumably caused by concomitant bilateral carpal tunnel syndrome.

An asymptomatic sibling underwent an electrophysiological studies that was normal, without median neuropathy.
Results: We used exome sequencing and we identified in both siblings a compound, heterozygous pathogenic variants c.2640del (p.N881fs*4) and c524_529+56del in the SH3TC2 gene (NM_024577.3) . The asymptomatic sibling was heterozygous for c.2640del variant.
Conclusions: We identified two new pathogenic variants in the SH3TC2 gene. These variants causes a severe phenotype of demyelinating peripheral neuropathy with carpal tunnel syndrome without scoliosis or cranial involvement. Our finding extend the genotype and phenotype spectrum of the SH3TC2 gene.

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Charcot-Marie-Tooth disease: a portuguese case series

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Introduction: Charcot-Marie-Tooth (CMT) disease encompasses a heterogeneous group of peripheral nervous system genetic disorders with different patterns of inheritance and a growing list of genes contributing to their clinical picture. Nonetheless, CMT

patients share a clinical phenotype composed by distal weakness, atrophy and sensory loss, pes cavus and hammer toes.

Objective: Characterize an adult population with diagnosis of CMT in a national reference center.

Materials and Methods: Analysis of prospective records of patients followed in neuromuscular disorders consultation from January 2000 to December 2020; selection of those with genetically confirmed CMT and collection of demographic, clinical, neurophysiological and genetic data.

Results: We identified 120 patients of 62 different families with slight predominance of females (53,3%) and an average age of 48,5 years. In the majority, symptoms initiated in infancy (up to 3 years old, 44,3%) with foot deformities (39%) and gait disturbances (32,2%). Cranial nerve involvement was noted in only 5 patients (3 – bilateral facial palsy; 2 – vocal cord paresis; 1 – diplopia; 1 ptosis). CMT1 was the most prevalent form (89,2%), subdivided in CMT1A (56,7%), CMT1B (21,7%), CMT1E (1,7%) e CMTX (9,2%). A large proportion of patients had family history (82,2%), reflecting the commonest pattern of inheritance (autosomal dominant, 85,8%). In neurophysiologic studies, demyelinating features predominated (79,1%) over axonal forms. With an average evolution disease time of around 32 years, 40% of patients needed gait assistive devices, 10,7% moved on a wheelchair and 20% were submitted to some type of surgical intervention. In our cohort, nerve biopsy was performed in just 10 patients, including those with rarer forms of CMT, severe illness at presentation and older patients with longtime diagnosis. We would like to point two distinct cases.

Case 1: A 60-year-old male had late onset sensory and motor neuropathy with intermediate motor conduction velocities due to a heterozygous variant in HOX10 gene; so far, mutations in this gene were only described in a family with CMT and isolated congenital vertical talus phenotypes.

Case 2: The neurophysiologic study of a 27-year-old male showed sensory and motor neuropathy with markedly low amplitude of compound muscle action potentials and conduction velocities only slightly reduced in lower limbs; genetic testing disclosed a heterozygous variant in gap junction beta-1 protein (GJB1) gene and family history was compatible with X-linked inheritance. Interestingly, neurological examination revealed subtle signs of central nervous system involvement, even though unremarkable brain and spinal cord MRI.

Conclusion: We describe a hospital series of CMT with similar features to those described in literature and composed mainly of patients with CMT1. Although cranial nerve involvement is present in 5 cases, no patient in our cohort presented hypoacusia (a frequent symptom in patients with CMT1). Advances in molecular biology techniques had allowed accurate genetic diagnosis and simplified etiological research by reducing the recurrence to invasive methods such as nerve biopsy.

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IGNITE-DMD: One-year Safety and Efficacy Evaluation of SGT-001 Microdystrophin Gene Therapy for Duchenne Muscular Dystrophy

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IGNITE-DMD is the first-in-human open-label Phase I/II ascending dose study investigating safety and efficacy of intravenous SGT-001, an adeno-associated virus (AAV9) microdystrophin gene therapy, in patients with Duchenne muscular dystrophy (DMD). DMD is caused by mutations in the DMD gene that result in the absence of dystrophin protein in skeletal and cardiac muscle, leading to muscle fiber deterioration, progressive motor decline, and premature death. SGT-001 is designed to deliver microdystrophin, a functional surrogate of dystrophin, to improve muscle fiber stability and function. The microdystrophin transgene of SGT-001 is composed of actin and dystroglycan binding domains and uniquely includes the nNOS binding domain thought to protect muscle from ischemic damage. Skeletal and cardiac muscle expression is driven by the CK8 promoter. Primary outcomes of this study include safety evaluations and measurement of microdystrophin expression in muscle biopsies by Western blot. Secondary outcomes include serum creatine kinase (CK), functional evaluations (6MWT; NSAA); pulmonary function tests, and quality of life assessments (PedsQL, PODCI, Modus Outcomes). The study is currently ongoing.

Three untreated control subjects (one non-ambulant: 15.3 years; two ambulant: 6.2, 9.5 years), and three low dose (5E13 vg/kg) subjects (one non-ambulant: 14.4 years; two ambulant: 5.2, 6.9 years) were initially enrolled. After evaluation of microdystrophin expression at Day 90, a four-fold increased dose of SGT-001 (2E14 vg/kg) was administered to three additional ambulatory subjects (6.8, 7.7, 10.7 years) in the high dose group. The most common treatment emergent adverse events were nausea, emesis and pyrexia within 72 hours of dosing. Activation of the terminal pathway (C5b9) of the classical complement system occurred in all subjects resulting in two serious adverse events (SAEs); two other SAEs included an episode of transaminitis and hyperbilirubinemia 4 weeks post dosing, which resolved after a transient increase of corticosteroids, and one unrelated to SGT-001. Other adverse events included thrombocytopenia, elevation of D-dimer associated with microangiopathy, and acute kidney injury in two subjects. All SAEs are resolved. In Day 90 biopsies, microdystrophin expression in the high dose group ranged from approximately 5-17.5% of normal dystrophin by Western blot and sarcolemmal microdystrophin protein was observed in 20-70% of muscle fibers by immunofluorescence. Importantly, colocalization with β-sarcoglycan and nNOS was also observed in microdystrophin positive fibers. At the one-year timepoint, high dose subjects showed a persistent decline in serum CK levels. In addition to protein expression and biomarker results, positive results were observed in functional and quality of life assessments at the one-year timepoint and will be described. These preliminary findings suggest the potential for SGT-001 to confer meaningful benefit to patients with DMD and support its continued study as a therapeutic candidate.

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Multineuritis as clinical manifestation of leukemia relapse. A case report

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Introduction: Neuroleukemiosis (NLK) is a rare affectation of the peripheral nervous system (PNS) caused by the infiltration of leukemic cells. One of its forms of manifestation is as an isolated multineuritis. We present a case of multineuritis due to NLK in a patient with a treated mielomonoblastic acute leukemia.

Case report: A 34-year-old woman with history of mielomonoblastic acute leukemia treated with chemotherapy and allogeneic hematopoietic stem cell transplantation in remission phase since three months ago. She presented to the neurological service with progressive right hand paresthesia, left facial numbness and gait impairment due to right/left foot palsy. Neurophysiological examination confirmed a multineuritis involving right median, facial and peroneal nerves. On physical examination bilateral preauricular masses were noted. A facial MRI study showed large bilateral laterocervical masses that infiltrate the parotid glands, and a thickening of the left facial nerve. An ultrasound-guided parotid biopsy showed infiltration by monocytes morphologically suggestive of malignancy. A lumbar puncture ruled out a central nervous system (CNS) infiltration. The PET-CT showed hypercaptation of sciatic nerves, facial nerves and right median nerve (Figure 1).

A bone marrow aspirate confirmed a systemic leukemia relapse. The patient was treated with a new chemotherapy schema including cytarabine, fludarabine and mitoxantrone with an improvement of the neurologic deficit.

Discussion: Neuroleukemiosis can simulate multiple pathologies of the PNS depending on the structure it affects. It is a rare entity that has only been described in a few cases.

It is suspected that the leukemic infiltration occurs because the blood-nerve barrier acts as a defense for leukemic cells against chemotherapy and immune system. Since the PNS could act as a "reservoir" for leukemic cells, NLK usually presents as a form of disease relapse months or years after remission. However, it can also appear during the disease course or as the first manifestation.

Another theory suggests that it is produced by direct dissemination from the CNS, since it rarely occurs without its involvement.

NLK as a form of extramedullary leukemia relapse predicts a poor long-term prognosis. However, in the absence of bone marrow involvement, it has a better short-term prognosis. In absence of systemic involvement, local treatment with radiotherapy can be performed with good response. In presence of systemic relapse, a chemotherapy regimen that contains agents capable of crossing the blood-nerve barrier is required. Neurological prognosis is uncertain,

with described cases of complete recovery after treatment.

Differential diagnosis of NLK is made with infectious complications, vasculitic neuropathy, chemotherapeutic neurotoxicity, Guillain-Barré syndrome and paraneoplastic neuropathies. Multineuritis has never been described as a form of graft versus host disease (GVHD). If suspected, must take into account that neurological GVHD can only be diagnosed if the patient has involvement of other organs and other more common causes of the pathology have been ruled out.

Symptoms suggestive of peripheral neuropathy in leukemia patients should be considered as a "red flag" even in the remission phase and an urgent consultation to Neurology is mandatory. If NLK is confirmed, CNS involvement and systemic relapse must be ruled out.

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MBNL loss of function in motoneurons leads to motor unit dysfunction in myotonic dystrophy

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Myotonic dystrophy type 1 (DM1) is a neuromuscular disease characterised by myotonia, progressive muscle weakness and atrophy, cardiac defects as well as cognitive impairments. DM1 is an RNA dominant disease caused by the expression of CTG repeat expansions in the 3'UTR of the DMPK gene. Thus, mutant transcripts containing expanded CUG repeats aggregate as ribonuclear inclusions that sequester Muscleblind-like (MBNL) RNA-binding proteins, impairing their functions in various tissues. MBNL proteins have a pivotal role in DM1 pathology and RNA metabolism abnormalities observed in affected tissues are mainly attributable to MBNL loss of function. MBNL family is composed of three paralogs: MBNL1, mostly expressed in skeletal muscles but also found in the brain; MBNL2 predominantly expressed in the brain and MBNL3 during embryonic development. While most studies on DM1 muscle pathology have focused on the skeletal muscle itself, prior reports suggest an impaired communication between motor neurons (MN) and skeletal muscle. Here we aim to determine the consequences of MBNL functional loss on motor unit physiology and its latter contribution to DM1 muscle alterations. To assess the effects of MBNL1 and MBNL2 loss-of-function specifically in MN to skeletal muscle, we have generated a conditional mouse model invalidated for Mbnl1 and Mbnl2 in the MN. These mice develop progressive motor abnormalities but also neuromuscular junction (NMJ) alterations indicating that MBNL compound loss-of-function in MN significantly affects NMJ structure and function. As NMJ are unaltered in young transgenic mice, deficiency in NMJ maintenance rather than development may be responsible for NMJ abnormalities observed in older transgenic mice. Identification of molecular alterations in MN of this mouse model as well as MBNL RNA targets in MN is ongoing. Altogether our work will help for a better knowledge of DM1 physiopathology.

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Impaired 6-minute Walk Distance and Lower-trunk Accelerometry Outcomes in Glycogen Storage Disease Type IIIa

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Introduction: Glycogen storage disease type IIIa (GSDIIIa) is an autosomal recessive disorder caused by mutations in the AGL gene coding for the glycogen debranching enzyme. The symptoms start in childhood with liver involvement and progress at adulthood with skeletal muscle weakness that can lead to ambulation loss. However, walking has never been studied in this pathology. This cross-sectional

study focusses on the 6-minute walk distance (6MWD) and accelerometry outcomes in patients and healthy controls.

Methods: Lower-trunk accelerations during the 6-minute walk test around cones 25 meters apart were measured using a portable triaxial accelerometer (Locometrix®, Centaure Metrix, Evry, France). The sampling frequency was set at 100 Hz. Raw data processing and gait parameter extraction were performed using custom software developed in LabView.

Results: Forty-four patients (aged 9.5-49, 55% female) were compared to 53 healthy individuals matched for age, sex, height, weight and body mass index.

The 6MWD expressed in meters or as a percentage of predicted value (%pred) was reduced in patients compared to their healthy peers ($P<0.001$). This was explained by their reduced speed ($P<0.001$) and frequency of step cycles ($P<0.001$). The power along the 3 axes (antero-posterior, vertical, mediolateral), and therefore the total power resulting from the sum of the powers along the 3 axes, were lower in the GSDIII ($P<0.001$).

The step symmetry ($P<0.01$) but not the regularity was impaired in GSDIII.

No correlation was found between the 6MWD (%pred) and patient age. Whatever the age of the patients, their 6MWD varied between 50 and 100% pred, except for 2 patients around their thirties who presented a 6MWD of about 30% pred.

Conclusion: The 6MWD and accelerometry outcomes are altered in the GSDIII. Correlations with muscle torques of the lower limbs will make it possible to map the muscle weaknesses responsible for the walking deficit. A longitudinal study on the evolution of gait disorders in patients with GSDIII is ongoing.