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Wearable inertial sensors for longitudinal follow-up of patients with amyotrophic lateral sclerosis.

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by the loss of motor neuron leading to weakness and death often resulting from failure of the respiratory muscles. There have been numerous recent discoveries in ALS research leading to potential therapies that will need testing in clinical trials. Due to outcome measures limitations, trials, especially for neurodegenerative disorders, require large sample sizes, long durations and have a high risk for failure. Digital biomarkers collected with wearable devices could provide powerful outcome measures through an objective assessment performed in real-life. Remote continuous monitoring is an innovative method for quantifying disease progression in ALS patients providing for motor function assessment through patients' loss of ambulation. This opportunity for shorter and less burdensome clinical trials should be confirmed by further data collection. We designed a longitudinal natural history study in ALS. Participants were assessed with standard evaluations including the amyotrophic lateral sclerosis functional rating scale, six-minute walk test, Medical Research Council scores, Ashworth score, hand dynamometer, pulmonary function and cognitive tests every 3 months for 1 year. After each visit, patients were asked to wear for one month one inertial sensor at the ankle and one at the wrist for continuous assessment of motor function in real-life. These data will be compared with already acquired normative data. At the present time, 11 patients with ALS (3 females, 8 males) aged from 44 to 72 years old were included. Four patients discontinued the study due to death or permanent ventilation. Initial results suggest that upper and lower limb variables are lower in patient with ALS than in controls and show a downward trend over time. We will present longitudinal data along with correlation between change in traditional and digital outcome measures. We will show comparison between patients and controls.

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Electrophysiologic evidence of *MORC2* pathogenic variant with motor neuron involvement: a case report

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MORC2 pathogenic variants have been reported in patients with CMT2Z (MIM 616688) and developmental delay, impaired growth, dysmorphic facies, and axonal neuropathy (MIM 619090). A few reports have been published supporting an SMA-Like phenotype caused by *MORC2* variants. We report a patient with de novo, heterozygous c. 1164 C>G (p. Ser388Arg) *MORC2* pathogenic variant, who presented with globally delayed development, toe walking, bilateral sensorineural hearing loss, microcephaly, precocious puberty, and delayed myelination and mild cerebellar volume loss on magnetic resonance imaging of the brain. Interestingly, sensory and motor nerve conduction studies were within normal limits. Electromyography revealed high amplitude motor unit action potential (MUAP) resembling motor neuron diseases. We provide electrophysiologic evidence that *MORC2* pathogenic variants can exclusively affect motor neurons, suggestive of a distinct motor neuron phenotype as part of the spectrum of MORC2-related disorders.

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Non-5q spinal muscular atrophy in twin sisters with SPG11/CMT2X associated spatacsin gene mutation

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We present the case of two twin sisters who came to our attention for progressive walking difficulties with falls and hand cramps. Symptoms emerged at the age of 22 for both. There was no overt consanguinity between their parents, although they came from the same little town. A cousin with post-anoxic tetraparesis was reported. Electrophysiological exams showed a diffuse chronic neurogenic EMG pattern compatible with a motor neuronopathy, while brain and spine MRI did not find pathological findings. At neurological examination they presented rather asymmetrical distal limbs weakness, moderate in the upper limbs, while severe in feet dorsiflexion, alongside bilateral pes cavus and stepping gait. A first NGS panel for distal SMA/motor hereditary neuropathies and genetic analysis for 5q-SMA did not find damaging mutations. Clinical exome NGS sequencing was then performed disclosing the presence in the probands of a heterozygous pathogenic variant (c.255G>A) on SPG11, coding for vesicle trafficking spatacsin and known in association to Spastic Paraparesis 11 and axonal sensory-motor CMT2X, both characterized by and autosomal recessive transmission pattern, variable age at onset, slowly progressive, this also present in the unaffected father, often with preservation of walking capability, distally asymmetric the latter. As the second variant has not been found yet, based on these findings, sequencing of SPG11 is ongoing in the two probands in order to identify eventual non-coding sequence mutations and further define diagnosis.

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A novel variant of *DYNC1H1* mutations in spinal muscular atrophy lower extremity predominant in an Indonesian patient: a case report

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Spinal muscular atrophy (SMA) is a hereditary motor neuron disorder caused by aberrant development and/or early loss of spinal motor neuron. SMA lower extremity predominant (SMALED) is characterized by congenital or early childhood onset of muscle weakness and atrophy predominantly in lower extremities. Mutations in dynein, cytoplasmic 1, heavy chain 1 (*DYNC1H1*) have been associated with SMALED. In this report, we present a 3 years 10 months old Javanese girl from nonconsanguineous parents who attended our clinic with unsteady gait and difficulties in running and climbing stairs. The clinical features were weakness of the lower extremities with lower motor neuron phenotype. A novel variant c.1867T>C in *DYNC1H1* gene was identified using whole exome sequencing.

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KEYNOTE LECTURE

I.15

Neuromuscular Disorders with Founder Effects in French Canada: why, where and how they contribute to the NMD field

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The French settlers of North America during the French Regime (1604-1763) were few and sparse on a vast continent. Understanding the early pioneer period and the subsequent growth of their descendants is key to explain the higher regional prevalence of certain Neuromuscular Disorders (NMD) in Canada. We will review the genetic impact of the various population bottlenecks that shaped the French Canadian gene pool. We will present a history of the identification of NMD with Canadian regional founder effects to emphasize how these large cohorts played a role in gene identification. Using oculopharyngeal muscular dystrophy (OPMD) as a prototype of FC founder diseases, we will chart how large FC cohorts disproportionally continue to contribute to our knowledge of these conditions. Myotonic muscular dystrophy type 1 (DM1) and Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) will also be discussed to underline the value of large cohort characterizations for granular clinical phenotyping and natural history studies. Lastly, we will discuss the contribution of rare recessive mutations and dominant mutations with variable prevalence to the identification of novel mutations relying on the mixed European and First Nation backgrounds of the French Canadian population.

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