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Meeting Report

Abstracts from the International Congress on Neuromuscular Diseases, September 11-14, 2020: A Virtual Event

This collection of invited abstracts is the result of the recent International Congress on Neuromuscular Diseases, held for the very first time as a virtual event, ICNMDigital, on September 11 to 14, 2020. We welcomed 800 registered participants from nearly 50 countries and their enthusiastic participation and positive feedback made this first ICNMD virtual meeting a success of unexpected proportions. We thank everyone who played a part in organizing, supporting, presenting, and attending.

Given the global circumstances, we are very grateful to have been able to come together virtually to share our knowledge and promote advances in the field of neuromuscular diseases for our patients. Our most important goal continues to be to provide accessible opportunities for our colleagues to benefit from scientific content.

We also extend our gratitude to our valued sponsors whose support and participation were an integral part of our success. We will continue to work with them in the coming months to bring even more state-of-the-art content to our Valencia meeting next year.

Our outstanding invited faculty will again join us next year, with the addition of some new sessions and experts addressing breakthroughs in research and clinical trials, as well as special COVID-19 related presentations.

While all accepted abstract submissions remain scheduled in the 2021 programme, we will be reopening our submission site on November 9 to encourage authors to send in their most recent work, or update their initial submissions.

We look forward to welcoming you in person to Valencia, Spain May 28 to June 1, 2021 for four days of great science, fine weather, beautiful surroundings, and an abundance of collegiality.

Dr Juan Jesús Vilchez Padilla, Congress Chair

Scientific Sessions – Day 1
Muscle Diseases

September 11, 2020

Scientific Session 1

Session Chair: Prof Marianne De Visser, The Netherlands

Inflammatory Autoimmune Myopathies
Prof Olivier Benveniste, France

For a long time, the classification of myositis was made according to the binary mode proposed by Peter & Bohan in 1975 on the basis of the existence of skin signs or not, distinguishing only polymyositis and dermatomyositis. Then over the past 50 years, the group of polymyositis has been divided into 3 sub-entities based on clinical phenotypes, histological characteristics of muscle biopsies and the discovery of myositis specific antibodies. The current consensus is that there are 4 subgroups of myositis: dermatomyositis, antisynthetase syndromes, immune mediated necrotizing myopathies and inclusion body myositis. Each of these entities has a different pathophysiology and specific targeted treatments are put in place.

Genetic Therapies
Dr Kevin Flanigan, United States

A growing number of genetic therapies for muscle diseases are available to the neuromuscular physician. The first such approved therapies included antisense oligomer approaches directed toward altering splicing of the *DMD* mRNA to restore an open reading frame by exon exclusion, but antisense therapies now include stimulation of exon inclusion, in the case of the *SMN2* gene, and other targets are under study. The feasibility of adeno-associated virus (AAV)-based gene therapy was demonstrated by the safety and efficacy Zolgensma in SMA patients, leading to its approval. AAV-based microdystrophin studies are underway, with promising early results. In addition to gene replacement, AAV-based strategies for gene modulation, knockdown, and editing will soon reach clinical trials.

Scientific Session 2

Session Chair: *Prof Bjarne Udd, Finland*

MYO-SEQ - Diagnosing Patients with Limb Girdle Muscular Dystrophy

Prof Volker Straub, UK

The limb girdle muscular dystrophies (LGMD) are a heterogeneous group of genetic muscle disease with progressive weakness and wasting of predominantly the shoulder and pelvic girdle muscles. Their nomenclature has recently been changed and it was suggested to call the autosomal recessive forms LGMD R and the autosomal dominant forms LGMD D, followed by a number based upon the order of discovery and the name of the protein affected. The more than 30 different forms of LGMD form important differential diagnoses among one another, but the more challenging task can often be to distinguish them from other neuromuscular diseases with limb girdle weakness. The MYO-SEQ project is a large international exome sequencing project involving more than 50 centres from Europe and the Middle East that exome sequenced >2000 patients with limb girdle weakness older than 10 years of age. The majority of patients showed elevated serum creatine kinase activities. We were able to provide about 54% of patients with a likely genetic diagnosis by testing all genes listed in the GeneTable of Neuromuscular Disorders (http://www.musclegenetable.fr/) for pathogenic variants. The rate of solved cases varied depending on how thoroughly patients were pre-screened for the more common forms of LGMD. Referrals from centres with access to genetic testing may have only shown a solved rate of <30%, whereas the solved rate in patients referred from centres without any pre-screening was as high as 95%. Variants in only eight genes, *CAPN3, DYSF, ANO5, DMD, RYR1, TTN, COL6A2* and *SGCA* collectively accounted for over half of the solved cases. More than 300 patients had conditions with treatment implications, including congenital myasthenic syn-

dromes, diseases with associated cardiomyopathies, Pompe disease and other metabolic myopathies. In about 3% of all cases we detected pathogenic copy number variations in both autosomal recessive and X-linked genes, with the *DMD* gene being the most common one. The most important lesson learned from the MYO-SEQ project is that comprehensive phenotypic data will increase the number of solved cases and that the interpretation of genetic data should ideally always be done in the context of clinical, pedigree, electrophysiological, imaging and muscle biopsy data.

Metabolic Therapies
Prof John Vissing, Denmark

Scientific Session3

Session Chair: *Prof Antonio Tascano, Italy*

Novel Image Analysis to Assess Molecular Functionality of Dystrophin in Duchenne Muscular Dystrophy Clinical Trials

Mr Dominic Scaglioni, UK

We used an unbiased, high-throughput digital image analysis platform, to investigate the molecular functionality of induced dystrophin in whole muscle sections of DMD boys who received 48-weeks treatment with exon 53 skipping morpholino antisense oligonucleotide (PMO) golodirsen. We demonstrated that the *de novo* dystrophin induced by golodirsen is capable of conferring a histological benefit in treated patients with an increase in colocalised dystrophin associated proteins at dystrophin positive regions of the sarcolemma in post-treatment biopsies. Additionally, we demonstrated that treatment with golodirsen resulted in a 2.2% reduction in the amount of degenerating myofibres compared to baseline. Furthermore, a significant negative correlation between the amount of dystrophin and levels of regeneration was observed. Our results provide, for the first time, evidence of functionality of induced dystrophin following successful therapeutic intervention in humans.

A Dominant PYGM Mutation Causes a New Class of Glycogen Storage Diseases

Dr Jocelyn Laporte, France

Glycogen storage diseases (GSD) are linked to defect in glycogen storage or usage and all previously described human GSDs segregate as recessive or X-linked traits. Here we describe a dominant GSD family where patients presented with adult-onset proximal muscle weakness and biopsies with fiber size variability, vacuoles, and glycogen accumulations. Exome sequencing uncovered the heterozygous c.1915G>C (p.Asp639His) mutation in *PYGM*, encoding myophosphorylase. Recessive *PYGM* mutations leading to myophosphorylase deficiency cause McArdle disease. However, our patients had a different metabolic profile compared to McArdle disease and a normal protein level in muscle. Immunolocalization uncovered aggregations of myophosphorylase and sequestration of desmin within the myofibers. Myophosphorylase enzymatic activity was normal under high AMP conditions but impaired with low AMP. Overall, we identified a first dominant *PYGM* mutation that causes an adult-onset myopathy involving a different pathomechanism than McArdle disease, and thus defining a novel class of GSDs.

Therapeutic Potential of AntagomiR-23b for Treating Myotonic Dystrophy

Dr Beatriz Llamusi, Spain

ARTHEx develops advanced RNA therapy for Myotonic Dystrophy disease (DM), an orphan genetic disease with no treatment available. Our therapy is based on a portfolio of patent-protected antagomiR molecules. These anti-microRNAs act as long-acting disease modifiers, targeting key pathways that lead to disease through a clearly defined mechanism of action. We obtained proof of concept of the therapeutic activity of antagomiR-23b in a well-known mouse model of Myotonic Dystrophy, and demonstrated that a single subcutaneous injection of the antagomiR produces a long-lasting increase of MBNL proteins and a subsequent rescue of the alternative splicing regulated by this protein. The molecular effects of the antagomiR-23b also rescue the functionality of the muscle, which could be quantified as a reduction in the myotonia levels and relative grip force only in the model mice treated with antagomiR-23b.

Scientific Sessions – Day 2
Peripheral Neuropathies

September 12, 2020

Scientific Session 4

Session Chair: Prof Peter Van Den Bergh, Belgium

Dysimmune Nodo-Paranodopathies
Dr Luis Querol, Spain

The research in the pathophysiology of theCIDP syndrome has recently been boosted by the description of antibodies targeting proteins at the nodes and paranodes of Ranvier. These antibodies, some of which have been demonstrated to be pathogenic, associate with specific clinical features, including response to therapy that differs from that of typical CIDP patients. In this talk we will revise the Autoimmune Nodopathies, the antibodies associated to them and the clinical implications that their detection determines, both for patient care and to advance in the understanding CIDP pathophysiology.

Painful Channelopathies
Prof Giuseppe Lauria, Italy

Scientific Session 5

Session Chair: *Dr Davide Pareyson, Italy*

Charcot-Marie-Tooth and Related Neuropathies
Prof Mary Reilly, UK

Next generation sequencing (NGS) has revolutionised the diagnosis of the inherited neuropathies. Not only has NGS helped identify over 100 causative genes for CMT and the related disorders, hereditary motor neuropathy and hereditary sensory neuropathy but it has helped identify almost 200 complex inherited neuropathies where the neuropathy is part of a multisystem neurological or systemic disorder.

The recent discovery of bi-allelic SORD (sorbitol dehydrogenase) mutations as a common cause of autosomal recessive CMT2 using whole genome sequencing (WGS) shows the power of WGS in identifying genes which can explain a substantial number of CMT cases and in this case with a potential treatment. Similarly the identification of the bi-allelic pentanucleotide intronic repeat expansion in RFC1 (Replication Factor C1) as the cause of CANVAS (cerebellar ataxia, neuropathy, vestibular areflexia syndrome) and the commonest cause of late onset ataxia highlights the importance of repeat expansions in neurological diseases.

These two examples of recent discoveries have revealed the importance of autosomal recessive genes in inherited neuropathies including late onset disease.

Diabetic Neuropathy: Treatment and Costs
Dr Brian Callaghan, USA

The treatment of diabetic neuropathy has proven to be quite challenging. Glycemic control works better to prevent neuropathy in type 1 diabetes than in type 2 diabetes. Emerging evidence points to obesity as another metabolic risk factor for neuropathy in addition to hyperglycemia. This has led to studies of medical and surgical weight loss, and exercise to prevent and/or reverse neuropathy. Medical and surgical weight loss are associated with stable to improved neuropathy outcomes, whereas exercise is associated with improved neuropathy outcomes. However, randomized controlled trials are needed for a more definitive comparison. The costs of the diagnostic evaluation of diabetic neuropathy is primarily driven by electromyography studies and MRIs, which are often not needed. The costs related to treatments are from medications to treat neuropathic pain including opioiods. Out-of-pocket costs are increasing over time and lead to significant issues with medication adherence.

Scientific Session 6

Sessions Chair: *Prof John England, USA*

Combination of RNA-Interference and Gene Therapy to Treat Charcot-Marie-Tooth Type 2A
Dr Elena Abati, Italy

The presentation highlighted the preliminary results of a project aimed at the evaluation of a new thera-

peutic approach based on the combination of RNA-interference (RNAi) and gene therapy to treat Charcot-Marie-Tooth type 2A (CMT2A), caused by mutations in the MFN2 gene.

The construct was tested on CMT2A induced pluripotent stem cells (iPSC), motor neurons (MN) and in CMT2A mice, and it proved able to successfully silence endogenous MFN2 gene and to restored functional MFN2 protein level in CMT2A iPSCs. Qualitative and quantitative alterations characteristic of CMT2A disease were restored after the therapy in CMT2A MNs. In vivo, the authors managed to successfully deliver the constructs via AAV9 in CMT2A mice with proper silencing of endogenous MFN2 and restoration of basal levels with exogenous construct. Overall, this strategy led to a significant level of rescue in CMT2A motor neurons and mice, suggesting that RNAii and gene therapy combined approach could represent a promising therapeutic strategy for CMT2A.

PDXK-Related Peripheral Neuropathy With Optic Atrophy. A New Treatable Disease

Dr Viorica Chelban, United Kingdom

We describe a human genetic disorder characterised by primary axonal peripheral neuropathy and optic atrophy leading to patients becoming wheelchair-bound and blind with significant disability if left untreated. For the first time, we mapped the disease to mutations in *PDXK*, which encodes the pyridoxal kinase, the enzyme involved in converting vitamin B_6 to its active form, pyridoxal 5'-phosphate (PLP). We showed conformational rearrangement of the mutant enzyme around the kinase ATP-binding pocket. This renders the mutated PDXK protein unable to bind ATP therefore resulting in reduced plasma levels of activated form of vitamin B_6 concentrations despite a healthy diet in patients. We treated our patients for 12 months with phosphorylated vitamin B_6 and monitored their clinical and biochemical response.

Remarkably, we show that the disorder is reversible and that the phenotype can be rescued by administering the modified phosphorylated vitamin B_6 therefore bypassing the mutation. Following our intervention both patients regained the ability to walk independently after several decades of disability and unsuccessful symptomatic treatment.

De Novo Variants in POLR3B Cause Demyelinating Neuropathy, Ataxia, and Spasticity

Dr Djurdja Djordjevic, Canada

POLR3B encodes the second-largest catalytic subunit of RNA polymerase III, an enzyme involved in transcription of small RNAs. Bi-allelic variants in various POLR3 subunits have previously been reported to cause hypomyelinating leukodystrophy, or 4H leukodystrophy. We described six patients in several different institutions found to have *de novo* missense variants in *POLR3B*, and a clinical presentation significantly different from POLR3-related leukodystrophy. These patients had afferent ataxia, spasticity, variable intellectual disability and epilepsy, and predominantly demyelinating sensorimotor peripheral neuropathy. Protein modelling and proteomic analysis were suggestive of a distinct mechanism of pathogenicity. These variants caused impaired association of individual enzyme subunits rather than affecting overall enzyme formation or stability. Taken together, these findings provide evidence of a novel *de novo* heterozygous POLR3B-related disorder.

Scientific Sessions - Day 3
Neuromuscular Junction Disorders
September 13, 2020

Scientific Session 7

Session Chair: *Prof Zohar Argov, Israel*

Congenital Myasthenic Syndromes
Prof David Beeson, United Kingdom

Next generation sequencing has revealed multiple new genes in which mutations can underlie impaired synaptic transmission at the neuromuscular junction (NMJ). They include presynaptic proteins involved in ACh synthesis and recycling; the SNARE-complex proteins responsible to for vesicle fusion and neurotransmitter release; basal lamina proteins in the synaptic cleft; and proteins affecting the early steps of the N-linked glycosylation pathway. A common feature for many of these newly identified CMS-causative genes is that they have functions outside of signal transmission at the NMJ and thus myasthenia may only be one aspect of a broader clinical picture. Therapy for CMS has been markedly enhanced by the re-adoption of b2-adrenergic receptor agonists as frontline treatments, and studies of disease in animal models illustrate how they stabilise NMJ synaptic structures and counter any adverse effect of long-term cholinesterase inhibitors. However, effective treatment in many cases involving the newly identified CMS genes can be challenging because of the broader clinical picture, and these may need different strategies such as gene therapy.

Randomized controlled trial of thymectomy in myasthenia gravis: a five-year perspective
Dr Gil Wolfe, United States

Background: MGTX, the Thymectomy Trial in Non-thymomatous Generalized Myasthenia Gravis Patients Receiving Corticosteroids, was the first-ever randomized, rater-blinded study of thymectomy in myasthenia gravis (MG). At a three-year time point, the international trial addressed questions regarding the efficacy of thymectomy in non-thymomatous MG that had persisted for 75 years since Blalock's 1941 report. The extension study followed a cohort of MGTX subjects through 5 years.

Methods: MGTX was designed to answer three questions: does the combination of alternate-day prednisone and extended transsternal thymectomy after 3 years compared to an identical dosing protocol of prednisone alone, (1) lead to better outcomes in MG as measured by a time-weighted average of the Quantitative MG Score (QMG), (2) reduce the time-weighted average alternate-day prednisone requirements, and (3) reduce side-effect burdens on patients primarily arising from medications used to treat the disease? Patients age 18 to 65 years with generalized non-thymomatous acetylcholine receptor antibody-positive MG of less than 5 years duration and MG Foundation of America Clinical Classification 2 to 4 were enrolled. Dual primary outcomes were the time-weighted average of the Quantitative MG (QMG) score and prednisone dose over 3 years. The extension study followed the same outcomes for an additional 2 years.

Results: A total of 126 MG patients underwent randomization at 36 sites. Subjects who underwent thymectomy showed significant improvements in MG status (time-weighted average QMG 6.15 vs. 8.99, $p<0.001$) and reduced alternate-day prednisone requirements (32 mg vs. 54 mg, $p<0.001$) at 3 years with benefits observed as early as 9 to 12 months. The ability to withdraw completely from prednisone and remain off it at 3 years also favored the surgical arm (58% vs. 20%, $p<0.01$). The ability to withdraw from prednisone did not correlate with duration of disease, age at MG onset or trial enrollment. On secondary outcomes, fewer thymectomy patients required immunosuppression with azathioprine (17% vs. 48%, $p<0.001$) or hospitalization for exacerbations (9% vs. 37%, $p<0.001$). The thymectomy group had fewer treatment-associated symptoms ($p<0.001$) and lower distress levels related to symptoms ($p=0.003$). The extension study enrolled 68 subjects (33 prednisone alone; 35 prednisone plus thymectomy). Of the 68, 50 (74%) completed the 60-month assessment (24 prednisone alone; 26 prednisone plus thymectomy). At 5 years, patients ran-

domized to thymectomy continued to demonstrate improved clinical status compared to patients on prednisone alone based on time-weighted average QMG (5.47 vs. 9.34, p=0.0007) and lower average alternate-day prednisone requirements (24 mg vs. 48 mg, p=0.0002). Requirements for hospitalization, steroid-sparing immunosuppression and intravenous gammaglobulin continued to be significantly lower in the thymectomy arm. The proportion of patients in minimal manifestation status (MMS) at month 60 was significantly higher (23/26, 88% vs. 14/24, 58%, p=0.0236) in the thymectomy group, and nearly twice as many thymectomy patients achieved MMS with complete withdrawal of prednisone (64% vs. 38%).

Conclusions: MGTX provided a definitive answer sought by the MG community since the middle of the last century. Extended transsternal thymectomy performed within the first 5 years of disease improves clinical outcomes, reduces immunosuppressive medication requirements, and decreases side-effect burdens in generalized acetylcholine receptor antibody-positive MG patients without thymoma. The benefit of thymectomy over medical therapy alone persists at 5 years, and based on some measures may even widen after the first 36 months.

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Scientific Session 8

Session Chair: Prof Angela Vincent, UK

Immununoactive Drug Therapy in Myasthenia Gravis

Prof Nils Erik Gilhus, Norway

Myasthenia gravis (MG) is an autoimmune disease with antibodies against the acetylcholine receptor, MuSK or LRP4 in the postsynaptic muscle membrane. This immune attack induces muscle weakness. The therapy is symptomatic to increase the amount of acetylcholine in the synapse, immunosuppressive drugs, thymectomy, and supportive measures including physical training programmes. The outcome in the great majority of patients is excellent, very good or good, and so the treatment should have ambitious aims.

Most patients need long-term immunosuppressive drug treatment. The combination of prednisolone (or prednisone) and azathioprine is commonly used as the primary treatment. Mycophenolate mofetil represents an alternative to azathioprine. Rituximab is increasingly used, has promising results, and is regarded as safe. Tacrolimus, methotrexate, cyclosporine and cyclophosphamide are established drugs for MG treatment. Intravenous immunoglobulin (IVIg) and plasma exchange are given for acute exacerbations, but also as continuous treatment in selected patients. Complements inhibitors and FcRn inhibitors represent new and emerging treatments. Their place will depend on clinical effect, safety, and not least cost – benefit considerations.

Drug-induced worsening in myasthenia gravis

Amelia Evoli, Italy

Highlights:

- Several medications can exacerbate myasthenia gravis (MG) or can unmask subclinical MG, by interfering with neuromuscular transmission
- With few exceptions, the use of these agents is not banned, but should be evaluated individually, taking into consideration therapeutic needs and patient's MG status
- MG can be worsened or, more commonly, triggered by medications acting on the immune system. Toxicity is not MG-specific, as these agents may be associated with a variety of immune-related adverse effects

- MG associated with these medications, particularly with immune checkpoint inhibitor treatment, is rare but potential fatal. Early diagnosis and prompt aggressive treatment are crucial.

Scientific Session 9

Session Chair: Prof Susana Quijano-Roy, France

Clinical Characteristics and Outcomes of Thymoma Associated Myasthenia Gravis
Mr Rodrigo Alvarez Velasco, Spain

We compared clinical characteristics of 147 patients with thymoma associated anti-AChR myasthenia gravis (MG) with those of 817 patients with non-thymoma anti-AChR MG. Median follow-up time was 4.6 years. At onset, thymoma-associated MG patients were younger (52.0 vs 60.4, p<0.001), had more generalized symptoms (OR: 3.02, 95%CI: 1.95-4,68, p<0.001) and more severe disease (MGFA scale) (OR: 1.6, 95%CI: 1.15-2.21, p=0.005). Disease severity based on the MGFA-PIS scale was higher in thymomatous patients at 1 year, 5 years and end of follow-up. Treatment refractoriness and mortality were also higher (OR: 2.28; 95%CI: 1.43-3.63; p=0.001). (HR: 2.27; 95%CI: 1.36-3.80; p=0.002). Myasthenic symptoms worsened in 13 of 28 patients with recurrences but differences in severity at 1 year, 5 years and end of follow-up were not significant. Seven thymomatous patients had non-resectable lesions, 4 had severe myasthenic symptoms, and one died because of MG.

Treatment Impact on Specific Symptom MG-ADL Domains in Myasthenia Gravis Patients: Phase 2 Efgartigimod Study Analysis
Dr James Howard, United States

The neonatal Fc receptor (FcRn) is a ubiquitous molecule present throughout life that acts by recycling IgG, extending its half-life and abundancy. Efgartigimod, a first-in-class small molecule inhibits function of FcRn and outcompetes endogenous IgG, preventing IgG recycling and promotes lysosomal degradation.

A phase 2 study in generalized AChR+ myasthenia gravis (MG) demonstrated a 70% mean reduction in IgG subtypes, reduction in circulating AChR antibodies without effect on IgM, IgA or albumin. This was accompanied by a ≥2 point change in MG-ADL score in 75% of efgartigimod treated patients vs. 25% placebo-treated patients. The phase 3 ADAPT trial, unique in design, randomized AChR+ and AChR- MG patients. 67.7% of treated patients achieved the primary endpoint vs. 29.7% of the placebo arm; 84.1% of responders became so in the first 2 weeks. More than 50% of patients maintained a response >8 weeks. Adverse events were mild or moderate in severity and balanced in the two arms.

Fatigue in Patients with Myasthenia Gravis: A Severe, Common Problem
Dr Martijn Tannemaat, Netherlands

Although a hallmark of myasthenia gravis (MG) is muscle fatigability due to dysfunction of the neuromuscular junction, a large number of MG patients also report symptoms of central fatigue, defined as an experienced lack of energy, physically and/or mentally. Our results show that fatigue is indeed highly prevalent in Dutch MG patients and has a negative impact on quality of life. It is associated with female sex, BMI, disease severity and depression. Fatigue was negatively correlated with higher age and frequent strenuous physical activities. In addition, we observed different coping strategies between fatigued and non-fatigued patients. These observations provide a rationale for future studies on aerobic exercise and cognitive behavioral therapy as novel treatments for fatigue in MG.

Scientific Sessions – Day 4
Motor Neuron Diseases
September 14, 2020

Scientific Session 10

Session Chair: Prof Marianne De Visser, The Netherlands

New Guidelines for the Design and Implementation of ALS Clinical Trials
Prof Leonard Van Den Berg, Netherlands

Advances in Genetics & Epigenetic of ALS
Dr Bryan Traynor, United States

To date, approximately 20 genes and loci have been identified as relevant to the pathogenesis of ALS. Overall, we now know about two-thirds of ALS's genetic etiology and about 10% of sporadic cases. Large-scale efforts and data-sharing will be required to identify the remaining genetic causes. We can also use existing genetic data to unravel other aspects of ALS, such as which pathways and cell types are involved in the disease process. Ultimately, the hope is that we will develop gene therapies against each of these individual causes.

Scientific Session 11

Session Chair: Prof Benedikt Schoser, Germany

Therapeutic Considerations in SMA 2020: Who, When and How to Treat
Dr Richard Finkel, United States

Spinal muscular atrophy (SMA) represents a paradigm for targeted translational research. Three drugs designed to increase SMN protein have now received regulatory approval: an antisense oligonucleotide (nusinersen, all ages and types of SMA) and a small molecule (risdiplam, ≥2 months of age , all types) that modulate splicing of *SMN2*, and gene replacement of *SMN1* (onasemnogene abeparvovec, <2 years of age, all types). Accumulating real-world data demonstrate that virtually all patients with SMA (types 0 to 4, infants to adults, and recently diagnosed to chronic) have the capacity to respond to nusinersen and risdiplam, but that the therapeutic expectations among these populations are quite different. Early treatment, especially pre-symptomatic, provides the most robust response. Choosing the optimal drug for a particular patient remains a challenge for the clinician as comparative data is limited at present. Combinatorial treatment may provide added benefit, albeit with added cost and higher risk.

Newborn Screening
Prof Laurent Servais, UK

Yet three different disease-modifying treatments are approved for Spinal Muscular Atrophy, it is very clear that their efficacy mainly depends on disease duration before treatment onset. In this context, several newborn screening programs have been initiated in different countries. So far, all these programs have been demonstrated to be successful in identifying and early-treating patients with an homozygous deletion. Open questions remain on the management of patients with 4 copies of SMN2, long term efficacy and health-economic impact

Scientific Session 12

Session Chair: Prof Enrico Bertini, Italy

A Longitudinal Natural History Study for Type 2 and 3 Spinal Muscle Atrophy
Ms Jesica Maria Exposito Escudero, Spain

Since new SMA therapies approval, the natural history becomes essential for a better understanding of the heterogeneity in the progression and the real impact of new available treatments. Results of our prospective monocentric study on 99 SMA late onset patients followed during 30 – 36 months, where is being identified natural history's characteristics and modifier factors to be considered in the protocols to assess new therapies effectiveness.

Disease progression has a slow and not linear course, needing a follow-up beyond two years to identify the potential stabilization effect of new treatments. Different scales should be used to have a wider vision over disease progression and the stratification of SMA type II: by age (older and younger than 6 years) and type III by subtype (IIIA / IIIB). A better understanding of natural history will improve

definition of the indication, response, and continuity criteria for the new therapies in real world.

Cervical Spinal Cord Atrophy: An Early Marker of Survival Time in Amyotrophic Lateral Sclerosis

Miss Virginia Reyes Garrido, Spain

Our aim is to evaluate cervical spinal cord volume (CSCV) as a biomarker of survival and disease progression in Amyotrophic Lateral Sclerosis (ALS).

We performed a retrospective study with 65 patients with ALS (37 had deceased). JIM software was used to calculate the CSCV in MRIs acquired at diagnosis.

Our results revealed a correlation ($p<0,01$) between CSCV and the survival time from symptom onset ($r=0,46$) and from diagnosis ($r=0,49$). A significant difference ($p<0,01$) was found for the mean CSCV according to survival time, stratified as longer than one, three or five years. The mean CSCV was lower for patients with lower survival. We found a correlation ($p<0,01$) between CSCV and the higher progression rate in ALSFRS-R score during the diagnostic delay($r=-0,41$) and in the first three years of evolution($p<0.01$)($r=0,5$).

Our study suggests that CSCV could be a useful biomarker for predicting survival and severity of progression in ALS.