Dear Colleagues,

It is our great pleasure to invite you to the **NMD Summer Course Budapest 2019 to the Semmelweis University**. The Summer Course will take place on **29-30 May 2019, in Budapest**, Hungary.

Neuromuscular disorders are experiencing exceptional times. Research in this field has progressed significantly, clinical trials have multiplied, new treatment options will be available for the patients. Despite popular consensus that neuromuscular disorders do not necessitate a prominent place in medical education, knowledge of these conditions can be life-changing for patients and practitioners.

The mission of this Neuromuscular Summer Course is to provide core competency standards of training for the evaluation and treatment of patients with neuromuscular disorders, to improve coordination and treatment of patients with these rare disorders.

Specialists in neuromuscular disorders possess specialized knowledge in the science, clinical evaluation, and management of disorders of the motor neuron, nerve roots, peripheral nerves, neuromuscular junction and muscle that affect patients of all ages. Diagnostic procedures relevant to Neuromuscular Medicine include nerve conduction studies and electromyography, nerve, muscle, and skin biopsy; genetic testing, nerve and muscle imaging, and immunologic testing. Therapeutic modalities include pharmacologic therapies, RNA modifying, enzyme replacement therapies, immunomodulatory therapies and rehabilitation of neuromuscular disorders. The Neuromuscular Summer Course summarizes for the general neurologists both the basic symptomatology of neuromuscular disorders and the newest research of the field, introduce the novel diagnostic opportunities, and gives overview about the present therapeutic options and running clinical trials.

The expected attendance includes neurologists, child neurologists, clinical geneticist, neurophysiologists, academic researchers, medical

practitioners, molecular biologists, health care professionals, case managers, who are interested in this sub-discipline.

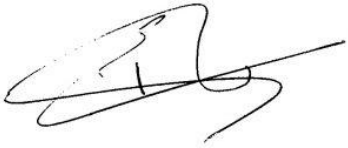
It is a privilege for the Semmelweis University to host the Neuromuscular Summer Course. The best internationally-recognized NMD disease experts from the EAN Muscle and Neuromuscular Junction and Neuropathy Scientific Panels will share their experience and knowledge.

The event will take place in Budapest, at the Basic Medical Science Centre – Semmelweis University. It offers a fabulous environment for high quality, professional meetings. Furthermore, the Summer Course is an ideal base for willing explorers of the beautiful capital of Hungary.

We are looking forward to welcoming you at the Neuromuscular Summer Course, to be held on 29 – 30 May 2019 in Budapest.

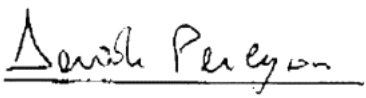
On behalf of the organising committees

Maria Judit Molnar



Peter Van den Bergh

Antonio Toscano



Davide Pareyson

Scientific Committee

Professor **Maria Judit Molnar**

Semmelweis University
co-chair of the Scientific Panel of Muscle and Neuromuscular Junction Disorders

Professor **Antonio Toscano**

University of Messina
co-chair of the Scientific Panel of Muscle and Neuromuscular Junction Disorders

Professor **Peter Van den Bergh**

Université Catholique de Louvain
co-chair of the Scientific Panel of Neuropathy

Professor **Davide Pareyson**

IRCCS Foundation, C. Besta Neurological Institute
co-chair of the Scientific Panel of Neuropathy

General information

Venue

Institute of Clinical Experimental Research, Semmelweis University

Tűzoltó St. 37–47.

1094 Budapest

Registration

Registration will be operating during the course from 08:00 till the end of the course day.

Technical organiser

Diamond Congress Ltd.

1255 Budapest, PO.Box 48.

www.diamond-congress.hu

On site contact number

Mr. Attila Varga

+36 20 936-2969

Official language

Official language of the Course is English.

Badges

All participants will receive a personal badge (and course material) upon registration. Delegates are kindly requested to wear their name badge when attending the meetings and social event.

Presentations

Presentations will be uploaded in the lecture hall. Please be sure that you will upload it lastest in the break before your session. A technician will be at your assistance.

Dinner

Dinner will be served on a boat, named PRIMUS.

Date: Wednesday, 29 May, 2019.

Gathering point: in the **Lobby of Verdi Grand Hotel** (Üllői St. 89/B) **at 18:50.** Bus will take the participants to the boat and back to the Hotel.

Boat departure: Jászai Sq., Pier 9 at 19:30 sharp. Duration of the cruise: 3 hrs.

Liability and insurance

The organisers cannot accept liability for any personal accidents, loss of belongings or damage to private property of participants and accompanying persons that may occur during the Course.

Public transport in Budapest

Public transport in Budapest is provided by Budapest Transport Ltd. (known to all Hungarians simply as **BKV**). Budapest has an efficient public transport network. In general the buses, trams and trolleybuses operate between 4:30 and 23:00. All night bus services operate on the major thoroughfares in the city (night bus timetables are posted at stops and in most metro stations). The three metro lines intersect at Deák Square in the centre of the town, close to the venue. Metro runs at 2-15 minutes intervals from about 4:30 to 23:15.

Advice for your departure

Airport shuttle service:

The company **miniBUD** is the official airport shuttle service provider for Budapest Airport. They provide comfortable, fast and favorable transfer solutions for passengers wishing to travel from the airport to the districts of Budapest, and from the city to the airport. You can buy the ticket at the arrival hall immediately or order it online

miniBUD CONTACT INFORMATION:
E-mail: **info@minibud.hu** Web: **www.minibud.hu**
miniBUD call centre: +36 1 550 0000

How to get to downtown by:
Bus number 200E circulates between Terminal 2 and the Kőbánya-Kispest metro terminal (metro line M3), via the Ferihegy train station (trains to the Nyugati railway station in Budapest). From the Kőbánya-Kispest metro terminal, passengers can take the M3 metro towards Kőbánya-Kispest to reach the city centre. As of 6 April, a direct bus line connecting the airport with the city centre was introduced: the front-door 100E takes passengers to Deák tér. It leaves from Deák tér every thirty minutes from 04:00 to 23:30. A special ticket must be purchased for bus 100E for HUF 900 – other tickets or season tickets are not valid for this service.

Phone number of the official taxi company at the airport:
Főtaxi: +36 1 222-2222

Smoking policy

Smoking is not permitted at the venue. Smoking areas are dedicated outside the building.

Important phone numbers

(English is usually spoken at the emergency numbers listed below. In case English is not spoken, dial 112)

Ambulance:	104
Fire brigade:	105
Police:	107
Central help number:	112
General enquiries:	197
Inland enquiries:	198
International enquiries:	199
Hungarian Automobile Club help number:	188

Wednesday, 29th of May, 2019

08:00	***Registration***
10:00	***Welcome*** **Maria Judit Molnar**, *Local Chair and Co-Chair of the EAN's Scientific Panel of Muscle Disorders* Welcome of the Semmelweis University: **Ferenc Banhidy**, *Vice-rector of the Semmelweis University* Welcome from the EAN's Scientific Panel of Muscle Disorders: **Antonio Toscano,** *Co-Chair of the Panel* Welcome from the EAN's Scientific Panel of Neuropathy: **Peter Van den Bergh**, *Co-Chair of the Panel*
Symptomatology Chair: Marianne de Visser 10:30 – 13:00	10:30 Introduction to clinical myology *Benedikt Schoser* 11:00 How to approach distal muscle weakness? *Marianne de Visser* 11:30 Fatigue *Viktorija Kenina* 12:00 Hypotonia *Anna Kostera-Pruszcyk* 12:30 Myalgia *Judit Boczan*
13:00 – 14:00 ***Lunch Break***	
The role of diagnostic biomarkers in the differential diagnosis of neuromuscular disorders Chair: Antonio Toscano 14:00 – 16:30	14:00 HyperCKemia *Antonio Toscano* 14:30 EMG/ENG: How to solve the problem when interpretation is difficult *Peter Dioszeghy* 15:00 The role of neuropathology in the diagnostic of neuromuscular disorders *Endre Pal* 15:30 The role of genetics in the diagnostic of neuromuscular disorders *Maria Judit Molnar* 16:00 The role of ultrasound in the diagnostic of neuromuscular disorders *Zsuzsanna Aranyi*

Wednesday, 29th of May, 2019

16:30 – 17:00 ***Coffee Break***

Classification, pathomechanism and treatment options in neuromuscular disorders
Disease Groups – I.
Chair: Anna Kostera-Pruscyck
17.00 – 18:00

17:00 SMA pathomechanism and treatment options
Anna Kostera-Pruszcyk

17:30 Classification and differential diagnostic of inherited neuropathies
Angelo Schenone

19:30 **Dinner on a boat**
Details can be read on the invitation card

Thursday, 30th of May, 2019

08:00 -	**Registration**
Classification, pathomechanism and treatment options in neuromuscular disorders – II. Chair: Peter Van den Bergh 09:00 – 10:30	09:00 Diagnosis and treatment of acquired neuropathies *Peter Van den Bergh* 09:30 Inflammatory myopathies: pathogenesis and treatment options *Marianne de Visser* 10:00 Myasthenia gravis *Viktorija Kenina*
10:30 – 11:00	***Coffee Break***
Case presentations Chair: Maria Judit Molnar 11:00 – 12:40	11:00 Dancing among vacuoles - update on autophagic vacuolar myopathies *Josef Zámečník (University Hospital Motol, Czech Republic) Sponsored by Sanofi Genzyme* 11:25 One year of nusinersen treatment in spinal muscular atrophy (SMA) in Hungary *Lena Szabo (Semmelweis University, Hungary) Sponsored by Biogen Hungary Ltd* 11:40 Recognizing hereditary ATTR – it is not all the same… *Roberta Mussinelli (*Amyloidosis Research and Treatment Centre*, Pavia, Italy) Sponsored by Akcea Therapeutics Germany GmbH* 11:55 Muscular dystrophy, congenital, with cataracts and Intellectual disability identified by WES after a long diagnostic journey *Peter Balicza (Semmelweis University, Hungary)* 12:10 Challenges in FSHD diagnostics: introduction to molecular combing technology to aid the diagnosis of an FSHD patient *Szabolcs Udvardi (Semmelweis University, Hungary)* 12:25 A peculiar isolated vocal muscle paresis: laryngeal myasthenia or autoimmune cranial neuropathy? *Judit Boczan (University of Debrecen, Hungary)*

Thursday, 30th of May, 2019

12:40 – 13:30	***Lunch Break***
Updates in some common neuromuscular disorders Chair: Benedikt Schoser 13.30 – 15:30	13:30 The personalized management of Duchenne and Becker muscular dystrophies *Maria Judit Molnar* 14:00 Update on limb-girdle muscular dystrophies *Antonio Toscano* 14:30 Myotonic dystrophies and non-dystrophic myotonic syndrome *Benedikt Schoser* 15:00 The role of C9orf72 in the background of motoneuron disorders *Zoltan Grosz*
15:30	***Closing remarks*** **Maria Judit Molnar**

PLENARY LECTURE ABSTRACTS

Introduction to clinical myology

Benedikt Schoser

Friedrich-Baur-Institute, Department of Neurology, Ludwig-Maximilians-University Munich, Munich, Germany

The emphasis of this presentation will be on the clinical approach of patients who present with symptoms of a neuromuscular disease. I will provide a Gestalt approach for the phenotyping. The presentation will cover learning from the clinical history and examination in adult-onset inherited and acquired muscle disease. The presentation will be practical and case reports will be presented to highlight key clinical concepts. Furthermore, an integrated diagnostic approach to patients shown on video, to look at muscle MRI imaging, neurophysiology, and muscle biopsies will be given.

How to approach distal muscle weakness?

Marianne de Visser

Department of Neurology, Amsterdam University Medical Centre, Amsterdam, The Netherlands

Pattern recognition is extremely helpful in diagnosing patients suffering from neuromuscular disease. Patients may present with external ophthalmoplegia and/or ptosis, facial/bulbar involvement, distal muscle weakness, axial muscle weakness (dropped head, camptocormia), proximal weakness, and as a floppy infant. Here we will focus on a presentation with distal muscle weakness. Asymmetry of muscle weakness is usually seen in neurogenic disorders but can also be found in some myopathies.

Obviously the age at onset, the family history and the course of the disease are very important. One should always ask and look for associated features, which may be helpful in establishing the diagnosis such as cardiac involvement, the presence of myotonia, fascicualtions, contractures, hyperlaxity, sensory disturbances, ophthalmological abnormalities, or CNS involvement.

Cases from the clinical practice will be discussed as well as the usefulness of assessment of lab investigations, electromyography, muscle imaging, muscle biopsy and genetic testing.

Fatigue

Viktorija Kenina

Riga Eastern Clinical University Hospital, Riga, Latvia

Chronic fatigue is a clinically defined symptom with prevalence in general population characterized by profound disabling fatigue associated with a number of typical symptoms lasting longer than six months. Multiple body systems are affected under chronic fatigue syndrome including immune, neuroendocrine, musculoskeletal systems as well as psychiatric factors that reflect on the heterogeneity of the disease symptomatology. Until now, no effective standardized and reproducible diagnostic tests for evaluation of this symptom. Medical treatment or prevention strategies are not available because the etiology, risk factors, and pathophysiology of the symptom can be different.

Hypotonia

Anna Kostera-Pruszczyk

Department of Neurology, Medical University of Warsaw, Poland

Hypotonia, or decreased muscle tone, is an important symptom related to both neurological and non-neurological conditions, most frequently neuromuscular diseases (NMD).

In the first year of life over 80% of floppy infants have hypotonia due to central nervous system lesions or non-neurological causes, such as Down Syndrome or Prader-Willi Syndrome, endocrinopathies or connetive tissue disorders. Spinal muscular atrophy (SMA) is a leading cause of neuromuscular hypotonia in infancy and can be easily confirmed by *SMN1* gene testing when hypotonia is accompanied by areflexia and finger tremor. Family history, presence of dysmorphic features, artrogryposis, ptosis, feeding problems, organomegally or skin changes can give important clue to diagnosis. Some patients with congenital myotonic dystrophy, SMA, congenital myopathies or myasthenic syndromes may require respiratory support. In others hypotonia will be accompanied by a various degree of muscle weakness. The majority of adult patients presenting with decreased muscle tone have an underlying neuromuscular disease. Acute onset of symptoms is seen mostly in patients with Guillain-Barre syndrome or myasthenia gravis. Inflammatory myopathies, muscular dystrophies or myopathies may present with chronic progressive weakness and CK-emia, lower and upper motor neuron syndromes are seen in Amyotrophic Lateral Sclerosis. Elevated CK, EMG or nerve conduction study results, muscle biopsy and well-chosen genetic tests may be needed to establish diagnosis and offer treatment. Screening for presymptomatic cases may be needed in SMA or some metabolic diseases, when early pharmacotherapy is very effective.

Myalgia

Judit Boczan

Department of Neurology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

Myalgia is a common complaint among patients at neuromuscular outpatient services. In the background both non-neuromuscular and neuromuscular causes may be uncovered. Systemic infections, metabolic and endocrin disorders, medications (eg. statins), rheumatic diseases, and fibromyalgia result in diffuse muscle pain. On the other hand, soft tissue diseases, overuse or ischemia may cause localised myalgia. Detailed history, physical examination, laboratory, and neurophysiologic workup, imaging and muscle biopsy are helpful in diagnosis. Myalgia that is not exercise-induced, and not associated with elevated CK, myopathic EMG, or abnormal clinical muscle examination, is unlikely to be of neuromuscular etiology. This lecture gives an insight into the pathogenesis, etiology, clinical principles of muscle pain of both non-neuromuscular and neuromuscular origin.

HyperCKemia

Antonio Toscano

Neurology and Neuromuscular Unit, University of Messina, Catania, Italy

Creatine kinase is a key enzyme that catalyzes the release of high-energy phosphates from creatine phosphate, mainly present in skeletal muscle. In muscle disorders, there is often a gross elevation of CK (hyperCKemia) because of its leak into serum in large amounts.

HyperCKemia is present in various types of muscle diseases such as muscular dystrophies, limb-girdle myopathies, congenital myopathies and metabolic myopathies, although in the latter case, serum CK may be within the normal range (50-200 U/l) in the interictal periods.

To establish what are the causes provoking hyperCKemia in patients, it is necessary to follow an algorithm including:

a) a very careful personal and family history with an accurate clinical evaluation,
b) routine blood tests,
c) exercise tests,
d) neurophysiological examinations,
e) neuroimaging,
f) muscle biopsy and related morphological studies,
g) biochemical studies,
h) molecular genetic studies to analyse patient's DNA (and sometimes his/her relatives) and confirm clinical suspects

Having variably taken in consideration those diagnostic factors, we will be able to reach, in the majority of cases, the correct diagnosis, also in order to start an appropriate and timeline therapy when available.

EMG/ENG: How to solve the problem when interpretation is difficult

Peter Dioszeghy

Department of Neurology, Teaching Hospital, Nyíregyháza, Hungary

Despite the great development and increasing the availability of molecular genetic diagnostics, neurophysiology (nerve conduction studies (NCS), electromyography (EMG), and special electromyographic methods) remain even nowadays an important tool in the diagnosis of neuromuscular diseases (NMD). Electrophysiology helps to determine the structures involved, the localization and distribution of abnormalities, and can give some support to search for etiology. Important tool for tracking the progress of diseases, and less accurately and with some delay, it can indicate the improvement too.

The presentation provides basic information on electrophysiology and gives general knowledge on the electrodiagnostic of patients with NMDs. One of the first great success of EMG was to reveal the basic differences between the neurogenic and myopathic changes of skeletal muscles. In the evaluation of suspected peripheral neuropathy NCSs allow detailed characterization of the pathology of abnormalities (axonal lesion and/or demyelinisation) and the type of affected nerve fibres (motor, sensory or both). NCS helps to reduce the possible etiologies to an acceptable number that can be used to make a rational investigational program. It can help to differentiate between groups of immune mediated neuropathies and can help in the selection of targeted genetic tests.

The motoneuron diseases (amyotrophic lateral sclerosis - ALS, progressive muscular atrophy, spinal muscular atrophies, postpolio-syndrome etc.) share several electrophysiological features, but there are some differences and their clinical characteristics are different. Diagnostic problems may arise between early ALS and multifocal motor neuropathy as well as other neuropathies. In early ALS the EMG may be normal or only slightly involved and the characteristic signs (chronic neurogenic change, signs of ongoing denervation and reinnervation) appear later. In NCSs the lesion of spinal motoneurons results in signs of axonal damage of motor nerves, but the sensory results remain normal.

Myopathies include muscular dystrophies, congenital, mitochondrial, metabolic, inflammatory myopathies and some channelopathy. The sensitivity of electrodiagnostic is lower comparing to neurogenic diseases, and rarely help to differentiate between these myopathies. However, it is diagnostic in some cases, like acute myositis and channelopathies. Combination of myopathic MUAPs and fibrillation potentials are found not exclusively but most frequently in idiopathic inflammatory myopathies. The source of fibrillation and positive sharp waves is the muscle membrane instability due to presence of inflammation or necrosis. In most

myopathies generally proximal muscles are first involved, consequently the proximal muscles are the best target for EMG in these cases.

Damage of neuromuscular junction (NMJ) may be presynaptic (e.g. Lambert-Eaton myasthenic syndrome) and postsynaptic (e.g. myasthenia gravis). There are two special electrophysiological methods to elucidate the neuromuscular transmission disorders: repetitive nerve stimulation (RNS) and single fibre electromyography (SFEMG). RNS the most relevant test for neuromuscular transmission failure. At a slow frequency stimulation decrement in amplitude of compound muscle action potential (CMAP) is seen, but a normal test does not rule out a neuromuscular transmission defect. If a presynaptic failure is suspected rapid frequency stimulation is done, and there is a significant increment in the amplitude of CMAP. SFEMG measures the variation in time interval between two action potentials of the same motor unit during consecutive discharges. The variation of this interpotential interval is called as "jitter". The jitter is increased both in pre- and postsynaptic NMJ disorders. It is used first in patients suspected of having myasthenia. The method is appropriate to reveal even the subclinical abnormalities.

The role of neuropathology in the diagnostic of neuromuscular disorders

Endre Pal

Neuropathology Unit, Department of Neurology and Pathology, University of Pécs, Pécs, Hungary

Several types of investigations are available during the diagnostic procedure of neuromuscular disorders, including electrophysiology, imaging, biopsy and genetic tests.

Muscle biopsy is a minimally invasive procedure with high diagnostic yield. Specific alterations can be found in about half of the samples, more probably in cases of young patients with high creatine kinase and abnormal EMG study.

Among genetically determined diseases muscle biopsy might be helpful in case of mitochondrial disorders, where characteristic alterations can be seen (such as ragged red- and cytochrome-c oxidase negative fibers), as well as the sample is suitable for genetic studies. Muscular dystrophies are heterogeneous group with wild genetic spectrum, where biopsy findings drive further investigations, such as imaging and genetic tests. Distal myopathy is sometimes challenging, biopsy and imaging is usually unavoidable.

Autoimmune myositis is the most common acquired muscle disease, where biopsy is applied for and ensure pathological classification supporting the clinical diagnosis.

The role of genetics in the diagnostic of neuromuscular disorders

Maria Judit Molnar

Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Budapest, Hungary

Several reports have acknowledged long delays (5 to 7 years or longer, depending on the country and methodology) in arriving at a diagnosis for neuromuscular diseases. Arriving at a molecular diagnosis provides closure, and allows the patient to get the right treatment, to prevent the disease and to seek resources from disease-specific support groups. There is also a positive impact for the physician, who no longer has to contend with diagnostic uncertainty, or the worry of missing an acquired or treatable condition.

Up to this point, one of the chief arguments for deferring genetic testing was that no treatment existed to alter the clinical course. This may be changing, as new treatments are being investigated or actively undergoing clinical trials. Patients without a definite genetic diagnosis will be unable to participate in clinical trials, and subsequently may never be offered future approved therapies. Many recommendations and guidelines exist to direct the rational selection of appropriate genetic testing.

Next generation sequencing (NGS) has revolutionised the diagnostic paradigm in genetic disorders, with the capability to capture and sequence genes, the entire exome or the entire genome. This new approach is dramatically changing the whole diagnostic process, establishing new decision trees and requiring integrated strategies between clinicians and laboratories. To presentation will overview the implementation and benefit of these novel sequencing strategies for the diagnosis of neuromuscular disorders. It will highlight advantages and disadvantages of different genetic strategies in a diagnosis setting, discuss about unresolved cases. It appears important to integrate such novel strategies with clinical, histopathological and imaging investigations, for a faster and more accurate diagnosis and patient care, and to foster research projects and clinical trials.

The role of ultrasound in the diagnosis of neuromuscular disorders

Zsuzsanna Aranyi

Department of Neurology, Semmelweis University, Budapest, Hungary

The high-resolution ultrasonography of peripheral nerves and muscles, a branch of musculoskeletal ultrasound, is a relatively new, but already firmly established complementary tool to electrophysiology in the assessment of neuromuscular disorders. It has been shown that the morphological information provided by ultrasonography influences the diagnostic and therapeutic pathway in the majority of patients. It is an advantage if the ultrasonographer has an expertise in electrophysiology and neuromuscular disorders as well, as the findings can immediately be fit into the broad clinical and neurophysiological picture of the patient, allowing a focused and adaptive examination strategy.

The contribution of ultrasound in neuromuscular disorders is manifold. It may increase diagnostic accuracy, such as in entrapment neuropathies, by showing the increase of size and the change of echostructure of the nerve proximal and/or distal to the site of compression. Moreover, it shows the musculoskeletal environment of the nerve, including anatomical variations such as accessory muscles and musculoskeletal pathologies such as ganglion cysts or synovitis with a possible etiological role in nerve compression. In nerve trauma, ultrasonography can depict neurotmesis (terminal neuroma) or severe intraneural rupture (neuroma-in-continuity), a piece of information needed for an appropriate therapeutic intervention and not provided by electrophysiology. The role of ultrasound in the diagnosis of nerve tumours is evident, and by assessing shape, size, echostructure and vascularity may even help in the differentiation of different types of nerve tumours, such as schwannoma, neurofibroma or intraneural perineurioma. An exciting new field in neuromuscular ultrasound is dysimmune neuropathies. For example, in chronic inflammatory demyelinating polyneuropathy, the findings of marked nerve swelling in proximal arm nerves and the brachial plexus can serve as a valuable piece in the diagnostic puzzle, particularly in dubious cases. Another example is neuralgic amyotrophy, where the hourglass-like constriction of a nerve or nerve fascicle appears to be a specific imaging finding.

In summary, ultrasonography has become an almost indispensable tool in the work-up of neuromuscular disorders. However, as is true for all other auxiliary examinations, its results should always be interpreted in context of clinical and electrophysiological data.

SMA pathomechanism and treatment options

Anna Kostera-Pruszczyk

Department of Neurology, Medical University of Warsaw, Warsaw, Poland

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by mutations of *SMN1* gene. Mutations lead to progressive loss of lower motor neurons, with muscle weakness and atrophy. SMN gene exists in two copies - *SMN1* and *SMN2*. While *SMN1* gene mutation is the primary cause of symptoms, age at onset of symptoms and SMA severity depends to large extend on the number of SMN2 copies. Most SMN1 patients have 2 SMN2 copies, while the majority of people with SMA3 have 4 or more SMN2 copies. Recent years brought delineation and progress in multidisciplinary care (Finkel RS at al.; Mercuri E et al. Neuromuscul Disord. 2018). Recent years brought breakthrough, when Nusinersen, the first drug ever, was licensed for SMA treatment. Nusinersen is an anti-sense oligonucleotide which increases the proportion of exon 7 inclusion in survival motor neuron 2 (SMN2) mRNA transcripts, increasing the amount of functional SMN protein. Nusinersen is given intrathecally, by lumbar puncture. The drug's efficacy has been in demonstrated in clinical trials both in symptomatic and presymptomatic SMA patients. More promising drugs are currently tested in phase 2 and phase 3 clinical trials, including gene therapy and orally administered SMN2 splicing modulators. Early diagnosis and intervention is critical to offer SMA patients optimal treatment.

Classification and differential diagnostic of inherited neuropathies

Angelo Schenone

Department of Neurosciences, Rehabilitation, Ophthalmology, Genetic and Maternal Infantile Sciences, University of Genova, Genova, Italy

Inherited neuropathies are rare disorders in which there is a selective involvement of peripheral nerves by the pathological process. However, it is also known that there are neuropathies in which the neuropathy is part of a more widespread neurological or multisystem disorder. Then an efficient way of classifying hereditary neuropathies is to distinguish neuropathies in which the neuropathy is the sole or primary part of the disease from neuropathies in which the neuropathy is part of a more widespread neurological or multisystem disorder. Among the former, hereditary motor and sensory neuropathies also called Charcot-Marie-Tooth (CMT) neuropathies are the most frequent ones. Several types of CMT are known based on the genetic background. Whereas clinical features are sometimes indistinguishable between the different types of CMT, neurophysiological studies allow differentiating demyelinating (CMT1) from axonal CMT (CMT2). Autosomal dominant (AD), autosomal recessive (AR) and x-linked inheritance is observed in CMT. Often, CMT may present with a sporadic onset. To date, mutations in more than 100 genes have been described in patients and families affected by CMT. This makes genetic diagnosis rather difficult. Mutations in three genes are more commonly found in CMT patients: PMP22, MPZ and GJB1. In case mutations in these gene are not found, next generation sequences techniques may be used to identify mutations in known genes or in genes not yet associated to a CMT phenotype. The best yield of genetic testing is observed in patients affected by CMT1. Several animal models of CMT, mainly in rodents, have been developed. The transgenic animals helped in understanding the pathomechanims underlying the different types of CMT and are now used to test innovative pharmacological or genetic therapies. However, to date the only available therapy in human subjects affected by CMT is rehabilitation. Especially, a combination of aerobic, proprioceptive and respiratory exercises proved to be effective in a large population of CMT patients.

Diagnosis and treatment of acquired neuropathies

Peter Van den Bergh

University Hospital Saint-Luc, Brussels, Belgium

Electrophysiology plays a crucial role in the characterization and diagnosis of peripheral neuropathies. It provides insight in the type and mechanism of peripheral neuropathy by giving information on the spatial pattern (generalized, multifocal, focal), the fibre type involved (motor, sensory), pathology (axonal, demyelinating), and the severity and time course (acute, ongoing, chronic). Electrophysiological studies are key in the early detection and characterization of inflammatory demyelinating neuropathies and in differentiating these from primary axonal neuropathies.

Inflammatory demyelinating neuropathies constitute a significant proportion of the acquired peripheral neuropathies. They include Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), multifocal demyelinating neuropathy with persistent conduction block (Lewis-Sumner syndrome), and paraproteinemic neuropathies. A proper diagnosis as early as possible is very important because timely immune treatment can largely reduce morbidity and disability. The diagnosis is based on a constellation of clinical and laboratory features, including electrophysiological studies, spinal fluid examination, and in selected cases serological studies and peripheral nerve biopsy.

In CIDP, electrophysiological criteria for demyelination are designed to exclude abnormalities that can be explained by axonal degeneration (Eur J Neurol 2010). Therefore, lesser degrees of demyelination cannot be defined with certainty. Optimised electrophysiological criteria are capable, however, to support the diagnosis with different levels of probability (possible, probable, definite) in the very large majority of cases. In GBS, much effort has gone into developing criteria which can distinguish axonal and demyelinating subtypes. The discovery of reversible conduction failure (RCF) has led to the concept of nodopathy/paranodopathy, where conduction slowing and conduction block are due to the immune attack mainly at the nodal axolemma level. There is no actual demyelinisation as defined pathologically and if the immune attack continues, conduction failure may not reverse and axonal degeneration will ensue. Recent electrophysiological studies support this pathophysiological mechanism and show that the dichotomous distinction between axonal and demyelinating in GBS is not tenable (Muscle nerve, 2018).

Inflammatory myopathies: pathogenesis and treatment options

Marianne de Visser

Department of Neurology, Amsterdam University Medical Centre, Amsterdam, The Netherlands

Idiopathic inflammatory myopathies (IIMS) are a heterogeneous group of diseases including dermatomyositis (DM), overlap or nonspecific myositis (OM/NSM), antisynthetase syndrome (ASS), immune-mediated necrotizing myopathies (IMNM) and inclusion body myositis (IBM). Except for the latter disease all other IIM subtypes are treatable and therefore an accurate diagnosis is crucial. Thus, the diagnostic armamentarium should include a muscle biopsy.

Histopathologically there is an overlap between DM, NSM and ASS with cell infiltrates mainly at perimysial sites and around blood vessels, but there are also significant dissimilarities particularly between DM and ASS. IMNM is characterized by necrosis of muscle fibres without significant cell infiltration and in IBM cell infiltrates occur at endomysial sites which surround and sometimes invade normal looking muscle fibres.

Currently serological subtyping takes place which in the near future may lead to distinct histopathological patterns amongst the broader subcategories.

IIMs, sIBM excluded, are amenable to immunosuppressive and immunomodulation therapies. Long-term outcome and prognostic factors vary widely. Disease related mortality rates in DM is at least 10%. In adults with DM mortality is attributed to cancer and pulmonary complications. Because chronic immunosuppressive therapy is associated with significant side-effects, and many patients remain (partially) refractory to treatment, novel therapeutic agents that are safe and effective are needed.

Myasthenia gravis

Viktorija Kenina

Riga Eastern Clinical University Hospital, Riga, Latvia

Myasthenia gravis (MG) is an autoimmune disorder in which fatigable muscle weakness occurs as a result of antibody-mediated impairment of neuromuscular transmission. Acetylcholine receptors (AChRs) are the most common auto-antibody target involved in MG pathogenesis, but other targets such as muscle specific kinase (MuSK) and lipoprotein related protein 4 (LRP4) have been identified. MG occurs in patients of all ages and both genders. Advances in the diagnosis and management of MG have resulted in significant improvements in outcomes for patients with this disease. In very mild cases of MG, treatment with acetylcholinesterase inhibitors may be sufficient, but commonly some kind of immunologically active treatment is needed.

The personalized management of Duchenne and Becker muscular dystrophies

Maria Judit Molnar

Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Budapest, Hungary

Duchenne muscular dystrophy (DMD) is a relative common progressive neuromuscular disorder, which is inherited as an X-linked disease that caused by mutations in the dystrophin gene. The lack of functional dystrophin protein in DMD results from mutations which disrupts the reading frame. In Becker muscular dystrophy (BMD) most of the muscle cells contain dystrophin but is function is not perfect. More than 60% of the cases are due to deletions of the dystrophin gene, and in 13% early stop codon mutations are resulting the disease. The genetic diagnosis is the most important diagnostic approach in the diagnostic workup of the disease. Nowadays muscle biopsy has to performed only in very special, peculiar cases.

There is no absolute cure currently for patients with DMD, nevertheless, recent advanced progressions on the treatment of DMD brought hope for these patients.

Care considerations for DMD advocate a coordinated, multidisciplinary approach to the management of DMD in order to optimize management of the primary manifestations of DMD as well as any secondary complications that may arise.

The lecture provides an overview of the multidisciplinary clinical management of DMD with regard to the respiratory, cardiology, orthopaedic, endocrinological and

nutritional needs of patients with DMD. Recent advances in novel disease-modifying treatments for DMD are also discussed with specific reference to gene replacement, exon skipping, suppression of stop codons. More recently, a promising gene editing tool referred to as CRISPR/Cas9 offers exciting perspectives for restoring dystrophin expression in patients with DMD.

Since DMD and BMD are monogenic inherited disorders, they should be treated by replacing the deficient dystrophin copy with a functional one. However, there are different types of mutations in this gene, so such therapeutic approaches are highly mutation specific and thus are personalized. Therefore, DMD has arisen as a model of genetic disorder for understanding and overcoming of the challenges of developing personalized genetic medicines, consequently, the lessons learned from these approaches will be applicable to many other disorders.

Update on limb-girdle muscular dystrophies

Antonio Toscano

Neurology and Neuromuscular Unit, University of Messina, Catania, Italy

Limb-Girdle Muscular Dystrophies (LGMDs) are a clinically heterogeneous group of Disorders, relatively rare, presenting with a wide spectrum of disease severity because of a large range of symptoms either at infancy, childhood or adulthood. LGMDs include both dominant and recessive forms. Usually, skeletal muscle is primarily compromised but, sometimes, even other organs are involved.

More recently, increased awareness, detailed characterization of the clinical spectrum and improved diagnostic workup have made easier to recognize these clinical entities although this is still a challenge to recognize them either in the infantile or adult cases

Although the clinical evaluation with some traditional diagnostic tools as neurophysiology, muscle morphology and biochemical evaluations is still necessary, a big diagnostic impulse came from some innovative techniques such as use of molecular genetic methods as NGS (Next Generation Sequencing) or whole exome/genome sequencing, that are currently used to better evaluate either known or emerging clinical entities in the field of LGMDs

Nowadays, it is important to update the evaluation of these disorders, also taking into consideration the pathogenic mechanisms, mainly involving the skeletal muscle but sometimes also other organs or apparatuses.

In fact, reaching as early as possible the diagnosis, will allow physicians to start an adequate management of patients and, even, to apply a specific therapy when it is available in an attempt to limit progressive degeneration of organs.

Myotonic dystrophies and non-dystrophic myotonic syndrome

Benedikt Schoser

Friedrich-Baur-Institute, Department of Neurology, Ludwig-Maximilians-University Munich, Munich, Germany

Myotonic dystrophy types 1 and 2 (DM1 / DM2) are the most frequent adult multisystemic neuromuscular disorders characterized by a plethora of symptoms such as progeric muscle weakness, myotonia, cognitive decline, cardiac, and gastrointestinal symptoms. The estimated patient population for both types in Europe is about 150.000 patients. Both types belong to the group of repeat expansion disorders. DM1 is caused by repeat expansion of a trinucleotide sequence (CTG) in the 3'-untranslated region of the myotonic dystrophy protein kinase (DMPK) gene which, when transcribed into CUG-containing RNA, forms aggregates of mutant transcripts that sequester RNA-binding proteins and cause abnormal splicing of downstream effector genes. DM2 is caused by expansion of a complex repeat motif (TG)n(TCTG)n(CCTG)n in the first intron of the CNBP (cellular nucleic acid-binding protein; previously ZNF 9, zinc finger protein 9) gene. A comparable molecular mechanism of common cellular alterations of mRNA splicing has been proposed. Beyond predominant RNA toxicity, other mechanism may effect protein translation and turnover, and activation of cellular stress pathways. A summary of the current state-of-the-art supervision and treatment of both diseases will be given. In addition, latest results of new studies in the field of DMs will be display. The first large European study termed „Observational Prolonged Trial In Myotonic Dystrophy type I to Improve Stamina, a Target Identification Collaboration", OPTIMISTIC : (ClinicalTrials.gov Identifier: NCT02118779) collected prospectively longitudinal data on phenotype, natural history, fatigue, cognition and biomarkers of 256 DM1 patients from four European countries. DM1 patients receive randomised cognitive behavioural therapy or graded physical training for improving their fatigue, and general activity levels including quality of life. In a single centre clinical trial, a GSK3beta inhibitor termed tideglusib is under investigation (ClinicalTrials.gov Identifier: NCT02858908). Furthermore, in 2017 we gained insight in the outcome of a pilot multicentre Northern-American trial testing the antisense oligonucleotide ISIS-DMPKRx (ClinicalTrials.gov Identifier: NCT02312011). For non-dystrophic myotonias mexiletine is re-licenced as orphan drug in the Europe in early 2019.

Conclusion: Myotonic dystrophies and non-dystrophic myotonias are the most variable adult multisystem muscular dystrophies. They are still associated with a premature mortality. We are continuously improving our knowledge on patient´s supervision aiming to reduced morbidity and mortality. Nevertheless, we still need novel avenues integrating the molecular RNA pathogenesis for a specific disease therapy.

The role of C9orf72 in the background of motoneuron disease

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease with the loss of upper and lower motoneurons resulting gradual muscle wasting with a general disease course of 3 to 5 years before death. While the majority of cases are sporadic, approximately 10-15% of ALS cases are familial. To date the most common genetic cause of ALS is a GGGGCC hexanucleotide repeat expansion in the first intronic region of the *C9orf72* gene. The repeat expansion was identified in nearly 40 % of familial ALS (FALS) and 6-10 % of sporadic ALS (SALS) cases. Although, the precise function of the C9 protein awaits for clarification, recent studies show it is mainly located close to the presynaptic terminal and may play a role in the synaptic vesicule function. Our aim was to establish the frequency and genotype phenotype correlation of *C9orf72* hexanucleotid repeats in a Hungarian caucasian cohort diagnosed with motoneuron disease.

Methods

We examined 222 Hungarian caucasian patients diagnosed with motoneuron disease. In all subjects the intronic region of *C9orf72* containing the hexanucleotid repeat was amplified using repeat primed polymerase chain reaction (PCR) technique followed by fragment length analysis performed on Genetic Analyzer 3500 (Applied Biosystems). Samples were analysed using GeneMapper 4.1. Software and compaired to positive and negative controls.

Results

The majority of the patients enroled in this study were sporadic and only the minority had familial ALS. Twenty-one patients out of the 222 tested we had detected a pathological expansion of the hexanucleotid repeats (n>30 repeats). It is noteworthy, that in 19 cases the repeat size fell into the intermedier range.

Conclusion

Pathological *C9orf72* hexanucleotid expansion was found in 9,45 % of an unselected Hungarian cohort diagnosed with motoneuron disease, which confirms the considerable role of C9orf72 intronic hexanucleotid repeat expansion in the genetics of motoneuron diseases. The number from which the repaet expansion pathological still needs to be clarified. With the increasing availability of antisense oligonucleotid therapy in different hereditary diseases the genetic stratification may also be importance for therapy.

CASE PRESENTATION ABSTRACTS

Dancing among vacuoles - update on autophagic vacuolar myopathies

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Deptartent of Pathology and Molecular Medicine, 2nd Medical School, Charles University and University Hospital Motol, Prague, Czech Republic

Autophagy is a highly regulated lysosomal process of cellular "cleaning and restoration" which also provides additional energy to the cell. However, there is also dysfunctional autophagy that accompanies a number of primary lysosomal disorders as well as neurodegenerative diseases, tumors, and also various inflammatory diseases. The disturbance of lysosomal functions leads to so-called "autophagic stress" in the affected cell, which leads to the pathological accumulation of autophagic intermediates in the cytoplasmic vacuoles. Since the autophagy is physiologically escalated in the muscle (skeletal and cardiac) and nervous tissues, the clinical and morphological manifestations of lysosomal dysfunctions tend to be pronounced especially in the respective organs.

There are many myopathies, in which autophagy fails due to lysosomal dysfunction and they have a common morphological manifestation in muscle biopsy - vacuolisation of myofibers. These include several hereditary diseases (especially Pompe's disease, Danon's disease, GNE myopathies), but a similar pattern may be caused by acquired disorders - they most often develop as a toxic effect of some drugs (eg, chloroquine myopathy).

However, the etiology of muscle fiber vacuolisation is much wider. Therefore, the diagnosis of vacuolar myopathies in muscle biopsy requires a comprehensive approach using enzyme histochemistry, immunohistology, and electron microscopy; moreover, further laboratory analyses are usually needed - enzymological tests and molecular genetic analysis.

Establishing the precise etiological diagnosis of vacuolar myopathies is of great importance, especially due to the recently available effective treatment of some of these disorders.

One year of nusinersen treatment in spinal muscular atrophy (SMA) in Hungary

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[2] MRE Bethesda Children Hospital, Budapest, Hungary
[3] Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Budapest, Hungary

Introduction: Nusinersen is an antisense oligonucleotide enhancing the production of the SMN protein. Clinical trials have demostrated its effectiveness in several types of SMA, thus it received EMA approval. In Hungary, nusinersen treatment is reimbursed by the National Health Insurance Fund for all tree types of SMA on a case-by-case basis

Aim: In Hungary, nusinersen treatment was started in April, 2018. Our aim is to summarize our experience with safety, tolerability and efficacy.

Result: By 1st March, 2019, 38 patients have started the therapy in one of the two Hungarian centres. Mean age of patients at the start of the treatment was 6.9 years (0.4-18 y). 8 patients were type I. (5-125 months), 15 patients were type II. (1.3-12 y), 15 patients were type III. (4.5-18 y). 7 patients had severe scoliosis, 4 of them underwent spine stabilizing surgery. Ultrasound guided lumbar puncture was performed in cases of difficult spine with a success rate of 100%.

We performed approximately 150 injections. The most frequent side effects were headache (10%), backache (12%) and vomiting (12%). We have not yet met drug specific side effects. There were no treatment terminations because of any side effects.

By now, 14 children have received the first six treatments. Motor function has improved in most of the children. In type II-III. patients, on average 4,2 point improvement was shown by the Hammersmith Functional Motor Scale Expanded (HFMSE) version and 1-14 point increase was found in the Revised Upper Limb Modul score. The 6 minute walk test results also increased by 32 m on average in type III. patients. In type I. patients, the change in the CHOP-INTEND score was between 16 and 21 points (18,7 on average).

Conclusion: Outside of clinical trials, nusinersen seems to have the same safety and tolerability profile. In a heterogenic patient population of all types of SMA nusinersen has demonstrated the same efficacy in everyday clinical practice.

Recognizing hereditary ATTR – it is not all the same…

Roberta Mussinelli, Laura Obici

Amyloidosis Research and Treatment Centre, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Hereditary transthyretin amyloidosis (hATTR) is characterized by high genetic and phenotypic variability, with differences in disease presentation and progression across different populations and geographical regions. The most common *TTR* pathogenic variant, Val30Met, clearly exemplifies such significant heterogeneity in clinical presentation and disease course, being associated with two different phenotypes, indicated as early-onset and late-onset respectively. Differences include not only the age at disease onset but also the pattern of organ involvement, with small-fibre neuropathy, severe autonomic dysfunction and nephrotic renal damage dominating in the first case, whereas in patients with the late-onset phenotype the disease is heralded by bilateral carpal tunnel syndrome and usually manifests with early involvement of larger sensory and motor nerve fibres and mild autonomic neuropathy. Moreover, a progressive cardiomyopathy with a hypertrophic phenotype typically occurs in late-onset patients but it is not observed in the early-onset population. Neuropathy progression occurs relentlessly in the absence of treatment, with walking impairment and wheel-chair requirement within a few years. The rate of disease progression and outcome may vary according to the underlying *TTR* mutation. We will discuss a clinical case that clearly exemplifies the diagnostic challenges in patients with apparently sporadic late-onset ATTR amyloidosis and highlights important red flags.

Muscular dystrophy, congenital, with cataracts and intellectual disability identified by WES after a long diagnostic journey

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Here we are reporting a very rare congenital muscular dystrophy, which was diagnosed after a 12 years diagnostic journey.

The 32 years old female patient has delayed motor development, epileptic seizures, cataracts and secunder glaucoma in her childhood. At age 16 years muscle weakness started, CK was elevated (1000-2000 U/l). A few years later diabetes mellitus developed and behind her hip pain bilateral hip dysplasia was detected. At age 20 she was suffering from secunder amenorrhea and generalized severe lipomatosis started.

Neurologial examination revealed several facial dysmorphic features, cervial lymphadenopathy, multifocal large lipomas. The limb muscles were atrophic especially in the lower limbs. In the thighs spastic muscles were observed. In the hips and knees extension type contractures were present. The Achilles tendons were in contractures as well. She had severe proximal type muscle weakness in all limbs. She was able to walk a few steps with bilateral aid. She had very mild mental retardation.

Muscle biopsy revealed myopathic features, intermyofibrillary homogenous material was accumulated. Several, large lipid vacuoles were present in the muscle. In the urine slightly elevated GAG was present and the heparansulfat level was increased beside increased level of mono- and disaccharids. Abdominal ultrasound found enlarged liver. ECG revealed abnormal repolarization and left ventricle hypertrophy. Targeted. MPS pane sequencing was negativ. WES detected homozygous pathogenic mutation c.67G>A (p.Val23Met) in the INPP5K (inositol polyphosphate-5-phosphatase K) gene indicating the diagnosis of Muscular dystrophy, congenital, with cataracts and intellectual disability (MDCCAID).

Our case demonstrate the usefulness of the whole exome sequencing in multisystemic muscle disorders.

Challenges in FSHD diagnostics: introduction to molecular combing technology to aid the diagnosis of an FSHD patient

Szabolcs Udvardi

Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Budapest, Hungary

FSHD is the third most common form of muscular dystrophy. Its genetic cause is very unusual, it is caused by a contraction of the 3,3kB D4Z4 repeat units in the telomeric region of chromosome 4. Common PCR technologies cannot be applied efficiently to identify the genetic background of FSHD, the most common protocol used to diagnose FSHD is Southern Blot. We routinely use this method to identify the genetic background of FSHD in our patients.

In some cases there are difficulties to interpret the result of the Southern Blot, as there is a similar (non-pathogenic) region in chromosome 10 and frequent translocation events occur between the homologous C4 and C10 regions. There is an additional Southern Blot analysis, called Dosage Test, which can be used to detect translocation events, but it may be insufficient to offer definitive diagnosis of particular cases.

A recently developed technique, Molecular Combing, offers an alternative method to diagnose the disease. In this presentation we show how an inconclusive Southern Blot diagnosis was complemented by Molecular Combing to establish a clear diagnosis for one of our patients.

A peculiar isolated vocal muscle paresis: laryngeal myasthenia or autoimmune cranial neuropathy?

Judit Boczan

Department of Neurology, Faculty of Medicine, University of Debrecen, Hungary

A 47-year-old woman with primary antiphospholipid syndrome developed sudden onset dysphonia in June, 2010, with no detectable cause. She complained about generalized skeletal muscle weakness, muscle pain, and mild dysphagia 6 months later. Brain CT and MRI, laboratory workup, chest CT, and repetitive nerve stimulation of the axillary nerve were negative. Physical examination revealed pressure sensitive skeletal muscles, no dysphonia, dysphagia or muscle weakness. EMG was characteristic for acute myositis. Muscle biopsy and MRI showed negative result. She was categorized as having a 'possible myositis.' Symptomes improved with methylprednisolone therapy. Azathioprine, hydroxychloroquine, and cyclosporine were not effective. In 2013 symptoms were worsening, mild weakness of the facial muscles and hip flexors, medium severity weakness of the neck flexors, mild dysphagia, mild atrophy of the tongue, and medium severity dysphonia was detected. RNS test of the axillary nerve was negative again, but the edrophonium-chloride test resulted in marked improvement, especially in her dysphonia. Laboratory tests for antibodies against AChR and MUSK were negative. SF-EMG of the right EDC muscle showed mild impairment of neuromuscular transmission, and normal NM function in the right orbicularis oculi muscle. Initially isolated laryngeal myasthenia gravis was diagnosed and pyridostigmine was started which resulted in significant improvement. Due to deterioration (bulbar signs and dyspnoea) she was treated with steroid, PLEX and IvIg several times. In order to avoid exacerbations subcutaneous immunoglobulin (SCIG) treatment was started in June 2014, which was effective for 3 years. Then, due to deterioration, she was treated with PLEX or IvIg therapy again, which was completed with mycophenolate mophetil for one year. Rituximab therapy was started in March, 2018 with mild effect. In 2017 monoclonal gammopathy of unknown significance was diagnosed in her sera, and paraprotein was also found in her CSF in March, 2019. Autoantibodies against gangliosides, repeated muscle biposy were negative. Phoniatric examination in April, 2019 revealed a dominant vocal muscle paresis. Recently the patient is on PLEX or IvIg and rituximab therapy, and has deteriorations every month with dysphonia, mild dysphagia, and generalized weakness.

COMPANY PROFILE

Sanofi Genzyme

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CV-S OF THE SPEAKERS OF THE PLENARY SESSIONS

Professor Zsuzsanna Aranyi

Zsuzsanna Arányi, MD, PhD, Doctor of Science of the Hungarian Academy of Sciences is an Associate Professor of neurology and clinical neurophysiology, the Head of the Laboratory of Clinical Neurophysiology and the tertiary referral centre for neuromuscular disorders at the Dept. of Neurology, Semmelweis University in Budapest, Hungary. She is a member of the governing body of the Hungarian Society of Clinical Neurophysiology, the Hungarian Society of Neurology, the Public Body and the Clinical Neuroscience Committee of the Hungarian Academy of Sciences, and the European Academy of Neurology (EAN) Scientific Panel Neuropathies.

After graduating from Semmelweis University, she has held a continuous position at the Dept. of Neurology, Semmelweis University. She has also spent time in training and research in clinical neurophysiology at Inselspital, University of Bern, Switzerland. Her initial research interest focused on transcranial magnetic stimulation, which later turned to electromyography and neuromuscular disorders, and lately to neuromuscular ultrasound. As one of the pioneers of neuromuscular ultrasound in Hungary, she has been devoted to advocating the method as a complementary diagnostic tool to electrophysiology, both in Hungary and abroad. She received a National Brain Research Program research grant as the head of the joint Peripheral Nervous System Research Group of the Hungarian Academy of Sciences and Semmelweis University. She has been an invited lecturer in numerous national and international courses and conferences on neuromuscular ultrasound, and provides hands-on training in neuromuscular ultrasound. Her present research areas include the ultrasonography of entrapment neuropathies, neuralgic amyotrophy, and thoracic outlet syndrome.

Dr. Judit Boczan

Judit Boczan has graduated in Medicine at the Faculty of Medicine in Debrecen, Hungary, in 1996. She conducted her PhD study about the role of Protein kinase C isozymes in the regulation of the regeneration of human skeletal muscle cells. She was a postdoctoral fellow with Fogarty Fellowship at the National Institutes of Neurological Diseases and Stroke, NIH, in Bethesda, USA between 2001 and 2003, where she had a research about the regulation of synaptic vesicle exocytosis by Protein kinase A. She was trained in neurology and clinical neurophysiology, and currently, she is leading the regional Neuromuscular outpatient services at the Department of Neurology, Debrecen, Hungary. She also performes neurophysiological examinations, organizes genetic testing, and neuropathological investigations for patients. Between 2014 and 2018 she was the secretary, and currently she is the president of the Hungarian Society of Clinical Neurogenetics. Her main interests are: immunological alterations in neuromuscular diseases, paraneoplastic neurological syndromes, clinical neurophysiology of the neuromuscular junction in children.

Professor Peter Dioszeghy

Peter Dioszeghy gave his medical studies at the Medical Faculty of Debrecen University. He was awarded his doctorate degree in medicine in 1973. As a first job he obtained an appointment in the Department of Debrecen University. After his residency he passed the board exam in 1977 in neurology later in psychiatry and in 2008 in clinical neurophysiology. His training in neurophysiology was done under direction of professor Ferenc Mechler in the Laboratory of Electrophysiology, Debrecen University. He received a grant of Swedish Institute and worked in the laboratory of Erik Stalberg in the Department of Electrophysiology, Uppsala. He had other scholarships: 1993 Wadham College, Oxford, 1994 Institute of Neuropathology, Freie University, Berlin, 1995 Department of Neurology, Karolinska Institute, Stockholm. After successfully defending his thesis, he obtained the PhD degree. Title of his thesis: „New data on the pathomechanism and diagnosis of neuromuscular diseases". Habilitation was performed in 1996. From 1996 until present, he is the head of Department of Neurology, Teaching Hospital, Nyiregyháza.

Dr. Zoltan Grosz

Zoltán Grosz works as a consultant neurologist. He is head of the outpatient clinic and Laboratory of Clinical Neurophysiology of the Institute of Genomic Medicine and Rare Disorders at Semmelweis University. He is conducting his PhD studies on motoneuron diseases.

After graduation from the Faculty of Medicine at the University of Debrecen, he spent his residency and gained experience working at the Neurology and Stroke Center of „Szt. Imre Hospital" He achieved the title „expert in neurosonology" in 2006, took the Board Exam on Neurology in 2007. Passed the European thrombolysis exam in 2008. He became a specialist in clinical electrophysiology in 2011. In 2014 he achived the title „specialist in health management" at the Faculty of Corvinus University. Recently, his focus turned toward rare diseases. His interests covers the distinct fields of neurodegenerative and neuromuscular diseases. He is also inolved in the education and holding lectures both undergraduate and postgraduate level. He has great experinece as a subinvestigator in clinical trials ranging phase II-III.

Viktorija Kenina MD, PhD

Riga, Latvia

Neurologist, immunologist

The Latvian Society of Neuroimmunologists, Chairperson of the Board

Centre of Neuroimmunology and immundeficiencies, Chairperson of the Board

Head doctor of neuromuscular unit in Eastern Clinical University Hospital

Member of EAN managment group Muscle and NMJ disorders

Member of EAN managment group Neuropathies

Professor Anna Kostera-Pruszczyk

Anna Kostera-Pruszczyk is Professor and Head of the Department of Neurology at the Medical University of Warsaw, Poland. She received the MD and PhD in Medical Sciences from the Medical University of Warsaw. She is involved in patients care, including intensive care, teaching, supervising medical students and neurology residents. She published over 75 refereed journal papers mostly on neuro- muscular disorders. She is a member of Expert Panel of European Academy of Neurology for NMD. She is a member of Polish Neurological Society, Polish Pediatric Neurology Society, Peripheral Nerve Society and of European Academy of Neurology.

Professor Maria Judit Molnar

Maria Judit Molnar MD, PhD, Professor of Neurology, Psychiatry, Clinical Genetics, and Clinical Pharmacology, Doctor of the Hungarian Academy of Sciences is the director of Semmelweis University's Institute of Genomic Medicine and Rare Disorders, among others president of the Hungarian Medical College of Clinical Genetics, elected president of the Hungarian Human Genetic Society, Co- Chair of the Neuromuscular Scientific Panel and management board member of the Neurogenetic Scientific Panel of the European Academy of Neurology, past president of the Hungarian Society of Clinical Neurogenetics, secretary of the Hungarian Society of Personalized Medicine.

She was the vice-rector for Scientific Affairs at Semmelweis University (Budapest, Hungary) between 2012 and 2015, where she was also responsible for International Affairs.

After spending 2 years in Aachen Technische Universitat (Germany) as Humboldt fellow, she has been adjunct professor at the Montreal Neurological Institute, McGill University, between 1999 -2012. She is the member of the steering committee of the Association of Academic Health Centers Internationals. Dr. Molnar is the Facilitator of a Challenge Group of the International Consortia of Personalized Medicine initiated by the European Commission.

Dr. Molnar is recognized as a leading experts on the diagnosis and treatment of neurological and psychiatric disorders. The Institute of Genomic Medicine and Rare Disorders lead by her offers a comprehensive state of the art, patient-centered multidisciplinary care for patients with rare neuropsychiatric disorders including genetic testing, neuropathological investigations and genetic counselling as well. Dr. Molnar's research covers a broad range of basic and clinical studies on rare neurological disorders, utilizing a broad spectrum of technologies including clinical science, molecular genetics including next generation sequencing and bioinformatics as well. The Institute of Genomic Medicine and Rare Disorders is the part of the European Reference Network of Rare Neurological Disorders (ERN-RND) and Neuromuscular Disorders (ERN-NMD). Dr. Molnar is the member of the management board of the ERN-RND as the work package leader.

She plays important role in the organization of rare disease management in Hungary and acts as an ambassador promoting the personalized healthcare. She is the President of the Advisory Board of Rare Disorders, the official advisory board of the Hungarian Insurance Fund. She is the member of the advisory board of several pharmaceutical companies (AOP Orphan, Biogen, Greenovations Biotech GmbH, Sanofi Aventis, Sarepta, Stealth Health Biotherapeutics). She was the principal investigator of 11 clinical trials, and 13 research grants, published 1 book, 21 book chapters, 140 papers with more than 1500 citations. Hirsch Index is 20. She owns 2 patents. She is active in postgraduate education, 7 PhD students defended their thesis and 5 are active in their education. Several neurologists and clinical geneticist has been trained by her.

Dr. Endre Pal

Work:

1991-1996 Resident, Dept. of Neurology, University of Pécs (UP)

Since 1996 Contributor in the Neuropathology Laboratory, Dept. of Neurology, UP

1996-1998 Assistant professor, Department of Neurology, UP

1998-2000 Research associate, National Institute of Neuroscience, Tokyo, Japan

2000-2005 Associate professor, Department of Neurology, UP

2005-2010 Chief neurologist, Baranya County Hospital, Pécs

2010 Associate professor, Department of Neurology, UP

2013- Head, Division of Neuropathology, Dept. of Pathology, UP

Qualifications:

1985–1991 Medical University, Pécs, Hungary

1991 MD

1996 Board exam of neurology, UP, Hungary

2001 Degree of Ph.D., UP, Hungary

2009 Board exam of neuropathology, Semmelweis University, Budapest, Hungary

2010 Habilitation, University of Pécs, Hungary

Memberships:

1992- Hungarian Society of Neurology

1996- Hungarian Society of Stroke

1996- Hungarian Society of Neurosonology

1997- Hungarian Clinical Neurogenetical Society

2006- Hungarian Society of Neuropathology

2013- Hungarian Academy of Sciences (MTA), Medical Sciences, Committee on Clinical Neurosciences

Professor Angelo Schenone

Prof. **Angelo Schenone** was born in Genoa, on August 29th 1956.

He obtained the classical high school diploma with 54/60 in 1975 and the degree in Medicine and Surgery at the University of Genoa in 1981 with marks 110/110 cum laude, discussing a thesis on the pharmacokinetics of antiepileptic drugs. In 1985 he specialized in Neurology at the University of Genoa, with 50/50 cum laude discussing an experimental thesis on: "Demyelinating polyneuropathies in the course of idiopathic monoclonal gammopathy: literature review and personal cases". In 1991 he specialized in Neuropathology at the University of Verona, discussing an experimental thesis on: "Lead Neuropathy: clinical and neuropathological study of two cases of experimental intoxication".

Prof. Schenone has held a position as Assistant professor (1989-2005) and Associate professor in Neurology (2005-2018)at the Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal Infantile Sciences (DINOGMI) of the University of Genoa. Since 2018 he is Full Professor in Neurology at the DINOGMI.

He served as Director of the Residency program in Physical and Rehabilitation Medicine (2004-2010)and since 2018 he is Director of the Residency program in Neurology at the DINOGMI.

Since 1997 he is Ordinary Member of the Italian Association of Neuropathology, Ordinary Member of the Italian Society of Neurology, Ordinary Member of the Peripheral Nerve Society. From 1997 to 2000 he served as advisor to the Italian Association of Neuropathology. He was president of the Italian Association of Neuropathology (2006-2007) and a member of the board of the Peripheral Nerve Society (2005-2009). He was secretary (2010-2013) and president (2016-2019) of the Italian Association of the Peripheral Nervous System.

Prof. Schenone's academic-scientific career is enriched by three extended stays in the USA: 1985-1986 "Visiting scientist" at the "Peripheral Nerve Center, Mayo Clinic and Mayo Foundation, Rochester, MN, USA"; 1993-1994: Visiting scientist, Molecular Neuroscience Program, Mayo Clinic and Mayo Foundation, Rochester, MN, USA; 2004 (June-August) Visiting scientist, Department of Neurology, Wayne State University, Detroit USA.

He serves as reviewer of several international journals and is Coordinator of the Editorial Committee of the Genova University Press and associate editor of the International Journal Frontiers in Neurology.

The scientific activity of Prof. Schenone is attested by 201 publications in national and international journals. H-Index 36. Citations: 5336.

Professor Benedikt Schoser

Benedikt Schoser started his career with training in muscle pathology by Hans Goebel and finishing his medical thesis at the Institute of Neuropathology in Mainz, Germany in 1993.

He started his career in neurology at the University Hospitals Mainz, Frankfurt, and Hamburg, Germany, in 1993, where he was trained in general neurology, intensive care neurology, psychiatry, and clinical neurophysiology. After spending a year in Thomas Jentsch's laboratory at the Institute of Neuropathophysiology in Hamburg, he was nominated as fulltime senior neurologist in 2001 at the Friedrich-Baur-Institute, Department of Neurology, Ludwig-Maximilians-University Munich. Additionally in 2016 he received his diploma in palliative medicine. He received his post-graduate degree (Habilitation) from Ludwig-Maximilians-University Munich in 2004.

He is currently senior consultant neurologist and co-chair of the Friedrich-Baur- Institute, the major national referral centre for rare neuromuscular diseases in Germany. Dr Schoser's clinical and research interests are in the field of multisystemic neuromuscular diseases and metabolic and myotonic myopathies.

He has authored and co-authored more than 225 articles in peer reviewed journals and contributed more than 25 chapters to books on neurology and muscle pathology, mainly in the field of diagnostic features and translational therapeutic trials in myotonic dystrophies, myasthenic syndromes, inflammatory myopathies, and metabolic myopathies.

He serves as member of the Editorial Board of Neuromuscular Disorders, Journal of Neuromuscular diseases, and Jounal of Rhematology and was the past chair of the Scientific Board of Neuromuscular Centers (Deutsche Gesellschaft für Muskelkranke e.V.) in Germany till February 2017. Dr Schoser is co-founder and chair of the European Pompe consortium (EPOC). Since June 2016 he served as co-chair of the Scientific Muscle and Neuromuscular panel of the European Academy of Neurology (EAN). In 2018 I became fellow of the European Academy of Neurology (FEAN)

Professor Antonio Toscano

Antonio Toscano is Professor of Neurology, since 2009, at the Department of Clinical and Experimental Medicine of the University of Messina, Italy.

He received his MD "cum laude" in 1981 and, then, he specialized in Neurology in 1985 in the University of Messina.

From 1986 to 1987, he attended as a fellow "The National Hospital for Nervous Diseases, London, UK, under the guide of dr. John Morgan-Hughes, studying Mitochondrial Disorders.

Since 2016, he is responsible of a ERN Reference Center for Rare Neuromuscular disorders at the University Hospital of Messina, Italy.

He has been President and past President of the Italian Association of Myology (AIM) (2009-2015) Since 2016, Chairman of the EAN Panel for Muscle and Neuromuscular Junction Disorders.

Since 2017, Treasurer of the Italian Society of Neurology (SIN).

Since 2018, Dean of the Faculty of Medicine of the University of Messina.

He is also member of:

a) National Board of the Italian Neurological Society (SIN),
b) Board of the European Consortium for Pompe Disease (EPOC),
c) International board of the Pompe registry,
d) several other National and International Scientific Societies and Groups

His main research interests are focused on Neuromuscular and Neurodegenerative Disorders with particular attention to Metabolic Myopathies and, more specifically, to pathogenic, clinical and therapeutic aspects of muscle glycogenoses (i.e. Pompe disease), lipid storage myopathies and mitochondrial encephalomyopathies or other rare neurodegenerative disorders. In these fields, he has published over 200 papers.

Professor Peter Van den Bergh

Professor of Neurology at the Université Catholique de Louvain and Director of the Neuromuscular Centre of Reference of the Cliniques Universitaires Saint-Luc, Brussels, Belgium.

Academic and clinical responsabilities: Head of the neuromuscular diseases and neuromuscular rehabilitation clinic, of the electromyography lab, and the neuromuscular pathology lab; Teaching of clinical neurophysiology and neuromuscular pathology.

In 1999, creation of the *Reference Centre For Neuromuscular Diseases* at the Cliniques Universitaires St-Luc, of which he is director and coordinator.

Current **research interests** are pathogenesis and treatment of inflammatory neuropathies (founding member of the Inflammatory Neuropathy Consortium, a standing committee of the Peripheral Nerve Society)
electrodiagnostic criteria of demyelinating neuropathies development of functional scales for neuromuscular disorders
Organizer of an International Symposium on Neuromuscular Disorders – December 1999, Brussels, Belgium
Organizer of an International Symposium of Neuromuscular Diseases – October 2005, Brussels, Belgium
Organizer of WMS11 – October 2006, Bruges, Belgium
Organizer of Progress in Neuromuscular Disorders, the 10th Anniversary Symposium of the Neuromuscular Centre UCL St-Luc – November 2010, Brussels, Belgium
Member of the Treat-NMD Alliance (coordinator for the 6 Belgian Neuromuscular Centres) (since 2008)
Chairman of the EFNS and since 2016 the European Academy of Neurology (EAN) Scientific Neuropathy panel (since 2009)
Member of the European Affairs Subcommittee of the EAN (2016), delegate to the BioMedAlliance Europe (2017)
Member of the AFM Pathophysiological Basis of the Muscular Dystrophies commission (2012-2017)
President of the Belgian-Dutch Neuromuscular Study Group (since 1998)
Member of WMS since 1997, participated at all WMS congresses except two
Editorial Board member of Neuromuscular Disorders since 2001
Executive Associate Editor of Neuromuscular Disorders since 2016
Member of the WMS Executive Board since 2007
Member of the WMS Program Committee since 2007
President-elect of the Inflammatory Neuropathy Consortium (INC) of the Peripheral Nerve Society
Executive Board member of Euro-NMD and leader of the Neurophysiology Group (2017)

Marianne de Visser, MD PhD

Marianne de Visser is an adult neurologist at the Amsterdam University Medical Center in Amsterdam, The Netherlands and emeritus Professor of neuromuscular diseases at the University of Amsterdam.

She graduated from the University of Amsterdam and was trained at the Academic Hospital of Amsterdam. She was a visiting scientist at Dr. Andrew Engel's lab at Mayo Clinic, Rochester, Minnesota where she performed ultrastructural studies on skeletal muscle in dermatomyositis.

Her research interests are neuromuscular disorders, and in particular myositis, ALS, and hereditary neuropathies. She participated in numerous ALS trials and undertook an investigator-initiated trial on inflammatory myopathies. She wrote more than 400 peer-reviewed articles and contributed to more than 30 text books, H-factor is 55.

She is a member of the Governing Board of the European Academy of Neurology, first as Treasurer and more recently as Secretary-General.

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