E A N

TASK FORCE FOR RARE NEUROLOGIC DISEASES

3RD TEACHING COURSE

11 - 12 JULY 2019

POIANA BRASOV | ROMANIA

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SCIENTIFIC PROGRAM

THURSDAY, 11 JULY 2019

08:50 - 09:00	***WELCOME ADDRESS***

SESSION 1

Chairpersons: Antonio Federico (Italy), Dafin F. Mureșanu (Romania)

09:00 – 10:00	The clinical approach to rare neurologic diseases Antonio Federico (Italy)
10:00 – 10:30	RND-ERN, two years activities Holm Graessner (Germany)
10:30 – 11:15	How artificial intelligence is transforming rare disease care Mária Judit Molnár (Hungary)
11:15 – 11:45	Genetic diagnostic strategies in the differential diagnostic of rare disorders Mária Judit Molnár (Hungary)
11:45 – 12:15	***COFFEE BREAK***

SESSION 2

Chairpersons: Mária Judit Molnár (Hungary), Holm Graessner (Germany)

12:15 – 12:45	Rare neurologic disorders in the context of rare causes of stroke Dafin F. Mureșanu (Romania)
12:45 – 13:15	Stroke in young adults: could this be Fabry disease? Max Hilz (Germany)
13:15 – 14:00	Dominant and episodic ataxias Alessandro Filla (Italy)
14:00 – 15:30	***LUNCH***

SESSION 3

Chairpersons: Max Hilz (Germany), Alessandro Filla (Italy)

15:30 – 16:15	Syndromes of mineral accumulation into the brain: clinical and pathogenetic aspects Antonio Federico (Italy)
16:15 – 17:00	Genetic leucodystrophies as a model of oligodendrocyte dysfunction Antonio Federico (Italy)
17:00 – 17:30	Update on treatment of neurometabolic genetic diseases Antonio Federico (Italy)
17:30 – 18:00	Perspectives for under-diagnosed patients Holm Graessner (Germany)

FRIDAY, 12 JULY 2019

SESSION 4

Chairpersons: Alberto Albanese (Italy), Ovidiu Băjenaru (Romania)

09:00 – 09:30	Mitochondrial encephaloneuromyopathies: new findings Antonio Toscano (Italy)
09:30 – 10:00	Therapeutic perspectives for muscle glycogenoses Antonio Toscano (Italy)
10:00 – 10:30	Relationship between Gaucher disease and Parkinson's disease Ovidiu Băjenaru (Romania)
10:30 – 11:00	***COFFEE BREAK***

SESSION 5

Chairpersons: Antonio Toscano (Italy), Antonio Federico (Italy)

11:00 – 11:30	Distonias Alberto Albanese (Italy)
11:30 – 12:00	Transthyretin amyloidosis neuropathy: still an under-recognized but treatable disease Mihaela Simu (Romania)
12:00 – 12:30	Huntington's Disease: genetic counselling, interdisciplinary clinic and the national registry Andra Ciucă (Romania)
12:30 – 12:45	***CLOSING REMARKS***

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ABSTRACTS

DISTONIAS

ALBERTO ALBANESE
Unità Operativa di Neurologia, IRCCS Istituto Clinico Humanitas, Rozzano, Milano; and Istituto di Neurologia, Universita Cattolica del Sacro Cuore, Milano, Italy

Clinical practice in dystonia has greatly evolved in recent years; a synthetic review on patient management is provided here. Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both. A recent classification has innovated clinical practice and serves as guidance for clinical assessment: Axis I describes clinical features, whereas Axis II indicates etiology. Dystonia presents with different syndromic aggregations with varied somatic involvement and some common features. There are five recognizable physical signs of dystonia: two main signs (dystonic postures and movements) and three additional signs (gestes antagonistes or tricks, mirror dystonia and overflow dystonia). There is still no validation of diagnostic criteria for the different dystonia syndromes, and many cases with mild phenomenology remain undiagnosed. Patients with dystonia also present non-motor features that are variably combined with the movement disorder. The features of the most common inherited and acquired dystonia syndromes are reviewed here. There is clear evidence of genetic-environmental interaction in the determinism of dystonia. The diagnostic process is guided by clinical examination and based on specific laboratory examinations. Symptomatic treatments are available for dystonia: botulinum neurotoxin injections are the primary choice for most focal dystonia syndromes; deep brain stimulation is useful in some generalized and non-generalized syndromes. Additional treatment strategies are currently being assessed.

RELATIONSHIP BETWEEN GAUCHER DISEASE AND PARKINSON'S DISEASE

OVIDIU BĂJENARU
University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania

Gaucher disease manifests phenotypically as a continuum of clinical syndromes, known as GD type 1, 2 and 3. Among these clinical features, neurological manifestations are often present. The clinical picture of Parkinson's disease (PD) has been characterized in study cohorts of GD patients described during the last more than 20 years. Most of these studies have shown a significant higher association of Gaucher disease pathological gene (GBA gene) in patients

with Parkinson's disease phenotype than for other neurodegenerative diseases. Mutations in the GBA gene have now been established as the most common genetic risk factor for developing PD. It is not yet clear what is the magnitude of the risk, nor what is the underlying mechanism for the increased risk. The probability that a patient with type 1 Gaucher disease will develop PD before the age of 70 years, was calculated as 5%–7%, which is considerably higher than estimated for the general population (1% of individuals older than 60 years). PD patients with GD-associated mutations developed dementia and psychosis significantly earlier than those without mutations, but no statistically significant differences were observed for dyskinesia between the groups. Mutations in the glucocerebrosidase (GBA) gene, which encodes the lysosomal enzyme that is deficient in Gaucher's disease, are important and common risk factors for Parkinson's disease (PD) and related disorders. In conclusion, Gaucher patients and Gaucher (GBA) carriers are at an increased risk for Parkinson (PD).

HUNTINGTON'S DISEASE: GENETIC COUNSELLING, INTERDISCIPLINARY CLINIC AND THE NATIONAL REGISTRY

ANDRADA CIUCĂ
VASILE ȚIBRE, CĂTĂLINA CRISAN, RADU POPP, RAMONA MOLDOVAN
Department of Psychology, Babeș-Bolyai University, Romania

Huntington's disease (HD) is a hereditary neurodegenerative disorder caused by a mutation in the HTT gene on chromosome 4. HD has adult onset, between approximately 30 and 50 years, and the symptoms include involuntary movements, cognitive difficulties and psychiatric symptoms. In the European population, approximately 10 out of 100,000 people are affected, and based on these data we can estimate that about 2,000 people are affected in the Romanian population. There are several international guidelines available to support professionals in looking after HD families. Guidelines include clear recommendations on genetic counselling, genetic testing, neurological or psychiatric assessment, pharmacological and non-pharmacological treatment, and quality of life. In Romania, HD is diagnosed and treated primarily in neurology or psychiatry departments. Genetic counselling is not routinely offered before or after genetic testing mainly because testing is not reimbursed therefore usually under private companies policies. Overall, care is at best unsystematic. Babes-Bolyai University and Iuliu Hatieganu University of Medicine and Pharmacy have set up a unique HD clinic in Romania and provide services in line with international guidelines and free of charge for HD families all over the country. The presentation will detail a brief audit of our progress so far as well as the HD national registry our team has set up.

A GENERAL APPROACH TO THE DIAGNOSIS AND CARE OF RARE NEUROLOGIC DISEASES AND THE EAN ROLE: A PANDORA BOX FOR NEUROLOGY

ANTONIO FEDERICO
Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy

Rare Neurological diseases are a Pandora Box for Neurology.
The list of the Rare diseases encloses more then 5000 disorders, half of them have a neurological interest, with involvement of the Central and Peripheral nervous system or Muscle or all.
They are underdiagnosticated and a global effort is necessary to improve their knowledge, the possibility to have a correct diagnosis by dissemination of information and culture on them and research, leading to possible treatments (the majority of them are without treatments and in all countries has started a cooperative effort for "orphan drugs".

In USA, since 30 years ago has been stimulated the interest on these disorders, followed 10 year later by the European Community.
Several Scientific Societies have started to have a promoting role on this field.
Since Neurology , as speciality, has the major role in the diagnosis and care of this disease, and basic and applied neurosciences in the research on their pathogenesis, EAN have the main responsibility for the promotion of the knowledge of these disorders, of the informations and of the research within the neurological community in Europe.
The Scientific Committee of the EAN organized a Task Force to Rare Neurologic Diseases, that will have a strict relationship with the Subspecialities Panels. It have members from all the different Panels (the Chairmen (ex officio), another member and a delegate from the Patient Associations) and young Neurologists (from each panels).

This could be an interesting action of the EAN Board, either from the political and ethical point of vue (orphans diseases and orphan drugs) either from a practical point of vue, giving to our members facilities to be informed on this topics and stimulating interactions for the different groups in Europe involved into research .
The aims of the TF is:

- Stimulation the redaction of a list of Rare Neurological Diseases, with main symptoms and diagnostic criteria and guidelines for diagnosis
- Evaluation of the facilities for diagnosis of RND in Europe (produce a list of facilities and address), with the indication where are the main centers interested

in the different disorders, where is possible to do the genetic, biochemical and other laboratory tests, etc

- Promotion of an analysis of the attitude of European Neurologist to RND and which is the state of the art of this issue in the different European countries;
- Stimulation to promotion of registries for RND, data bank and biobanks. These are main aims of the EU, with Research projects in the Biomed Program.
- Stimulation to create European Networks for RND for diagnosis and research.
- Promotion of Teaching courses in Europe.
- Information Service for Rare Neurological Diseases, within the EAN, that will be able, with the collaboration of the different experts present in the WG, to answer to questions from patients, families and doctors (on line). Information service on new data, new findings, research founds, treatments, etc. Discussion on Rare Cases, within the Section on Web page where cases will be described and experts from SSP will answer.

With this activity, the EAN recognizes the primary role of neurologists in the care of these disorders, the necessity to improve the level of the organization of the Neurological Units in Europe and of the formation of neurologists in the care of rare neurological disorders. But also we will stimulate a better integrated relationship with Patient Associations.

We will also focused our attention on the clinical approach to a Rare Neurologic Disease and some guidelines for the diagnosis

GENETIC LEUCODYSTROPHIES AS A MODEL OF OLIGODENDROCYTE DYSFUNCTION

ANTONIO FEDERICO
Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy

Leukodystrophies are a group of orphan genetic diseases that primarily affect the white matter (WM) of the brain. Glial cells play a major role in the structural, metabolic and trophic support of axons.

Diversity of the genetically determined defects that interfere with glial cell functions explain the large heterogeneity of leucodystrophies that may be classified:

- According to neuropathology (staining: ortochromatic, metachromatic, sudanophilic; site of demyelination: sparing U fibres,etc; associated findings)
- According with clinical aspects (peripheral nerve, muscle, eye involvement, macrocephaly, tendinous xanthomas, premature aging,, skin and bone changes,

endocrine involvement: adrenocortical or ovarian insufficiency, diabetes, etc)
- According to biochemical abnormalities
- According to molecular genetic abnormalities.

We will report the main well known forms (Adrenoleucodystrophy, Metachromatic Leucodystrophy, Krabbe Disease) and some rarer conditions as Vanishing White Matter disease, Vacuolating Leucodystrophy, Alexander disease, Spheroid leukoencephalopathy, etc, and also some recently identified forms, describing the clinical findings for clinical suspicion and the pathogenetic mechanisms.

LATE ONSET NEUROMETABOLIC DISEASES: DEMENTIAS, LEUCOENCEPHALOPATHIES, MOVEMENT DISORDERS, ETC

ANTONIO FEDERICO
Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy

The biochemical pathogenesis of many hereditary diseases of the nervous system and muscle has in the recent years been very much investigated: for many diseases an enzyme defect and metabolic substances accumulating in the tissues or in biological fluids have been identified facilitating the diagnosis of a large number of genetic metabolic encephaloneuromyopathies.

Beside the well known infantile- and juvenile-onset diseases, an increasing number of cases with a slowly progressive disease and adult onset have been described, the pathogenesis of which is linked to the same congenital defect of lysosomal, mitochondrial or peroxysomal metabolism as the early onset forms, but in which the onset of the clinical manifestations is delayed in adult age.

We will report the most recent data on the metabolic basis of several disorders mainly involving neurons (characterized by dementia, epipepsy, etc), oligodendrocytes (presented with leucoencephalopathies) , basal ganglia (with particular regards to the different forms of Parkinsonism, dystonia, and other movement disorders etc). From a metabolic point of view, we will summarize the clinical and biochemical aspects of the disorders related to

- Storage material for a primary lysosomal dysfunction of lipid metabolism
- Plasma membrane lipid changes due to peroxisomal impairment
- Cell cholesterol trafficking disturbancies
- Energy metabolism impairment
- Chromosomal instability and Dna repair

- Cell nutrients deficiency
- Small vessel diseases
- Disorders of Heavy Metal Metabolism
- Disorders of Neurotransmitter Metabolism
- Disorders of intermediary metabolism
- Disorders of mechanism of DNA Damage and Repair

For all of them we will describe clinical signs, diagnostic work-up and possible therapeutic strategies.

SYNDROMES OF MINERAL ACCUMULATION INTO THE BRAIN: CLINICAL AND PATHOGENETIC ASPECTS

ANTONIO FEDERICO
Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy

We will report several clinical conditions in which the main characteristic is the mineral accumulation into the brain, mainly in basal nuclei , clinically characterized by different severity of parkinsonism, mental deterioration, psychiatric abnormalities.

Mineral accumulation is due to cooper, in Wilson's disease, a well known epatolenticular degeneration, iron in a recently described syndrome with dystonia/parkinsonism and in patothenate kinase deficiency (Hallervorden-Spatz disease), calcium in several mitochondrial diseases, in the so called Fahr syndrome, now better known as Primary familial brain calcification.

We will describe the different clinical presentations, the pathogenetic aspects and the recent data on the molecular diagnosis.

We will also report several other more rare conditions, useful for the differential diagnosis and we will describe a diagnostic algorithm for diagnosis .

UPDATE ON TREATMENT OF NEUROMETABOLIC GENETIC DISEASES

ANTONIO FEDERICO
Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy

In the recent years numerous new developments in the treatment options to neurometabolic genetic diseases have been obtained. We will report on the most important data, defining symptomatic treatments and therapies able to influence the pathogenetic mechanisms of the disorders, the latter summarized in the following table.

A) Decrease of levels of toxic metabolites
- diet

B) Removal of toxic substrates
- Transfusions, plasmapheresis, peritoneal dyalisis
- Drugs

C) Substitution of deficient substance
- Leucocyte and plasma infusions
- Organs Transplantations
- Fibroblasts tranplantations
- Bone marrow transplantation

D) Direct supply of deficient metabolite
E) Enzymatic induction by coenzymes
F) Enzyme therapy
G) Gene therapy

We will report our experience in this field in several pathological conditions related to lysosomal, mitochondrial , peroxysomal or to metal disturbancies, also discussing some ethical issues related to early presymptomatic treatments.

DOMINANT AND EPISODIC ATAXIAS

ALESSANDRO FILLA
MARIA LIETO
Full Professor of Neurology and Chairman of the Department of Neurological Sciences at Federico II, Naples, Italy

Polyglutamine expansion diseases are the most frequent cerebellar ataxias or spinocerebellar ataxias or SCAs (SCA1/ATXN1; SCA2/ATXN2; SCA3/ATXN3; SCA6/CACNA1A; SCA7/ATXN7; SCA17/TBP). SCA3/MJD being the most frequent worldwide. Onset usually occurs in the thirties with anticipation in successive

generations. Clinical features include besides ataxia other neurological and extraneurological signs (pyramidal, extrapyramidal, cognitive, seizures, peripheral neuropathy and retinal degeneration).

SCAs may also be caused by non-coding repeats (SCA8/ATXN8OS; SCA10/ATXN10; SCA12/PPP2R2B; SCA31/TGGGAA; SCA36/NOP56) or conventional mutations. The last group include many different mutations that are usually limited to few families. Recently, next generation sequencing widened the last group. Several new SCAs have been identified (SCA42/CACNA1G; SCA44/GRM1; SCA45/FAD2; SCA46/PLD31; SCA48/STUB1). Some SCA genes may cause both dominant or recessive ataxias as SUTB1 that causes SCA48 and SCAR16.

Episodic ataxias are usually dominant with an early onset. Eight forms have been described. The genes have been identified in four (EA/A1; EA2/CACNA1A; EA6/SCL1A3; EA/UBR4). Ion channel are usually involved but not in EA8. EA2 is the most frequent.

SOLVE-RD. SOLVING THE UNSOLVED RARE DISEASES

HOLM GRAESSNER
Managing Director, Rare Disease Centre, University Hospital Tübingen, Germany

The two talks I will be giving will both mainly focus on diagnosis. Using rare neurological disorders patients as examples I will explain how the European Reference Network for Rare Neurological Diseases (ERN-RND) and the H2020 funded project Solve-RD. Solving the unsolved Rare Diseases. contribute finding a diagnosis for a patient with a rare neurological disease.

ERN-RND (ern-rnd.eu) is a network of 32 Healthcare Providers from 13 EU member states. ERN-RDN builds on existing expert centres and mature networks dedicated to rare neurological diseases (RND) as well as established rare disease infrastructures such as Orphanet, EURORDIS and RD-Connect. Through coordination and knowledge transfer, ERN-RND establishes a patient-centred network to address the needs of patients with RND of all age groups, with or without a definite diagnosis, by implementing an infrastructure for diagnosis, evidence-based management, treatment and collection of patient data. The network is active in two main areas: (i) knowledge generation, transfer and dissemination in order to harmonise quality of diagnosis and treatment provided in the network and beyond; (ii) introduction, piloting and role-out of the Clinical Management System (CPMS), an e-health platform provided to the ERNs by the European Commission, to consult on complex cases applying multidisciplinary expert panels.

I will be presenting what means and activities ERN-RND has been implementing to support a better and faster diagnosis for RND patients.

Solve-RD (solve-rd.eu) echoes the ambitious goals set out by the International Rare Diseases Research Consortium (IRDiRC) to deliver diagnostic tests for most rare diseases by 2020. Our main ambitions are thus i) to solve large numbers of rare disease, for which a molecular cause is not known yet by sophisticated combined omics approaches, and ii) to improve diagnostics of rare disease patients through contribution to, participation in and implementation of a "genetic knowledge web" which is based on shared knowledge about genes, genomic variants and phenotypes.

Solve-RD fully integrates with the newly formed European Reference Networks (ERNs) for rare diseases which have begun to operate in 2017. Four ERNs (ERN-RND, -EURO-NMD, -ITHACA, and -GENTURIS) build the core of Solve-RD. Solve-RD will deliver seven implementation steps to address these: i) Collect large amount of RD data , ii) Discover new phenotype patterns, iii) Re-analyse exomes/genomes, iv) Apply novel molecular strategies, v) Facilitate functional analysis, iv) Work towards clinical utility and vii) Towards therapy.

Solve-RD has built a research infrastructure to solve not yet diagnosed patients. I will be presenting the research approach and the established diagnostic research infrastructure, Solve-RD is implementing.

STROKE IN YOUNG ADULTS: COULD THIS BE FABRY DISEASE?

MAX. HILZ
Department of Neurology, Icahn School of Medicine at Mount Sinai New York, NY, USA

Fabry disease is a rare, progressive, and life-threatening lysosomal storage disease that affects both male and female patients. Mutations of the gene that is located on the long arm of the X chromosome at Xq22.1 and encodes the lysosomal hydrolase alpha-galactosidase A (alpha-GAL) cause dysfunction and deficiency of alpha-GAL. The enzyme deficiency results in glycosphingolipid storage, mostly of globotriaoslyceramide [GL-3], in various body fluids and tissues including blood vessels and structures of the central, peripheral and autonomic nervous system. It also causes loss of small myelinated or unmyelinated nerve fibers. Due to glycolipid storage in vascular endothelial cells, in various renal cell types, in cardiomyocytes and neurons, patients are at high risk of early ischemic strokes,

painful peripheral small-fiber neuropathy with burning pain of hands and feet or episodic and excessive pain crises, gastrointestinal problems such as post-prandial pain, cramping, diarrhea. Fabry patients often suffer from early cardiac dysfunction with concentric left ventricular hypertrophy, arrhythmias, and cardiac failure. They develop chronic kidney disease progressing to end-stage renal failure. First clinical signs and symptoms often manifest during childhood or adolescence and reflect dysfunction of peripheral small nerve fibers and of the autonomic nervous system. Typically, first signs and symptoms of Fabry disease include pain in hands and feet, painful crises triggered by heat, fever or physical effort, inability to sweat, tinnitus and hearing loss, microalbuminuria or even proteinuria. With disease progression, there are severe complications involving the kidneys, heart and brain. These complications cause considerable morbidity and premature death. Unfortunately, the disease is often misdiagnosed as most complications of Fabry disease are rather non-specific and may resemble complications of other diseases (1).

In patients who suffer a stroke at young age, there are many differential diagnoses to be considered, including for example cervico-cephalic arterial dissection, fibromuscular dysplasia, Moyamoya disease, vasculitis, reversible cerebral vasoconstriction syndrome, Susac's syndrome, Sneddon's syndrome, genetic and hereditary diseases including hematologic conditions with hypercoagulable states such as antiphospholipid syndrome, hyper-homocysteinemia, Sickle cell disease, myeloproliferative disorders, Factor V Leiden mutation, prothrombin G2021A mutation, protein C and protein S deficiencies, antithrombin III deficiency, etc. While CADASIL is often considered a possible cause of stroke at early age, Fabry disease is frequently overlooked. However, in 2005 a study by Rolfs et al. suggested that acute cryptogenic stroke occurring between the ages of 18 to 55 years might be caused by Fabry patients in 4.9% of their male patients and in 2.4% of their female patients (2). In a multi-national, multi-center study of 5023 young patients with ischemic stroke, hemorrhagic stroke, and transient ischemic attacks, the prevalence of Fabry disease was lower. Definite Fabry disease was confirmed in 0.5% of these 18 to 55 year old patients, while probable Fabry disease was considered in another 0.4% of the 5023 patients (3). However, in patients with a confirmed diagnosis of Fabry disease, the risk of stroke is very high. Sims et al. analyzed the stroke incidence using data from 2446 Fabry Registry patients. The authors showed that 6.9 % of the male and 4.3% of the female Fabry patients experienced strokes. The median age at first stroke was 39.0 years in men 45.7 years in women. Often, patients had the first stroke before Fabry disease had been diagnosed (4).

Consequently, the signs and symptoms of Fabry disease should be known in order to assure an early diagnosis. The diagnosis can be confirmed by assessing low

enzyme levels in male patients. Additional genetic testing is needed in female patients since they may have enzyme levels just below or close to normal values. Once the diagnosis has been established, adequate symptomatic, organ- and symptom-specific therapy as well as early, consequent biweekly intravenous enzyme replacement therapy at an adequate and high enough dosage must be initiated (5-9). In patients who have a mutation that is amenable to chaperone therapy, oral treatment with the chaperone migalastat may offer a promising alternative (10). No therapy, inadequate or delayed treatment will usually cause irreversible and life-shortening complications.

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GENETIC DIAGNOSTIC STRATEGIES IN THE DIFFERENCIAL DIAGNOSIS OF RARE DISORDERS

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

For physicians, rare diseases are a unique challenge. Often the diagnostic and therapeutic procedures are complex, and clinical routines are rarely standardized. This is particularly important when multiple organ systems are affected, and the expertise of professionals in many disciplines is required.

Molecular genetic confirmation of a suspected diagnosis often means the end to a year's long odyssey in search of the cause of a medical condition. At the same time, it represents the starting point for more specific information about the progress and prognosis of the disease and for the optimal therapeutic intervention for the patient. Even if there is currently no specific treatments are available, knowledge of the etiology and mechanisms of disease can form the basis for a future treatment strategy or innovative treatment options. The identification of the disease causing mutation provides information on the mode of inheritance and thus probability of other family members inheriting the disease.

New technologies have enabled the simultaneous analysis of large amounts of genetic information for disease-causing changes. This technology is referred to as next-generation sequencing (NGS). The major strength of NGS is that the method can detect abnormalities across the entire genome quickly and cost effectively. Otherwise it has some challenges as well, such as the detection of some types of mutations (especially repeat expansions or structural variations) can not be detected safely. At the commonly used sequencing depth the NGS error rates compared to Sanger sequencing is higher.

The presentation will guide you which genetic test to choose for patients with different rare neurological disorders ranging from single gene testing through NGS panels to whole exome sequencing.

HOW ARTIFICIAL INTELLIGENCE IS TRANSFORMING RARE DISEASE CARE

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

The importance of the use of the artificial intelligence (AI) has increasing importance in these days. Computer processing power is doubling every 18 months and the amount of healthcare data is doubling every 18 months. It has special importance in the field of the rare disorders since in every month a new gene is associated with human disease. Presently we know cc. 8.000 rare human diseases and about 60-70% of them is related to the nervous system.

It would take a physician cc. 160 hours/week of reading to stay up to date on the latest literature. The John Hopkins Study in the USA revealed that cc. 40,500 patients died of misdiagnosis a year. Many of them had rare neurological disorders. The management of this huge amount of data is really challenging for the human brain. On the other side our human cognition has some distortions, such as perception of disease prevalence, recall bias, order effect, framing, anchoring, the management of the potential hypotheses is limited. All these factors support the fact that we have to use the artificial intelligence in the everyday clinical diagnostic and treatment of the rare neurological disorders.
The lecture will offer the introduction into the field of estimation tools, diagnostic tools and therapeutic decisions tools supported by AI. The talk will clarify why AI is needed in the everyday clinical praxis, how we get an Improved diagnosis with help of evidence-based decision support, how we can use different softwares for the interpretation of next-generation diagnostics and disease-gene discovery.

RARE NEUROLOGIC DISORDERS IN THE CONTEXT OF RARE CAUSES OF STROKE

DAFIN F. MUREȘANU
Chairman Department of Clinical Neurosciences
'Iuliu Hatieganu' University of Medicine and Pharmacy, Cluj-Napoca, Romania

According to the World Health Organization, 15 million people suffer stroke worldwide each year. Of these, 5 million die and another 5 million are permanently disabled. Europe averages approximately 650,000 stroke deaths each year.

Stroke is the number one cause of permanent disability globally and the second most common cause of dementia. Although stroke among young adults is generally considered a rare event, with a previous study reporting that about 5% of all strokes in the United States occurred in a young adult population aged between 18 and 44 years, there is growing evidence of an increasing trend of stroke in young adults. It has been documented that stroke incidence in young adults aged between 20 and 54 years has significantly increased between 1999 and 2005.

Many risk factors for cerebrovascular diseases have been established including no modifiable factors such as age, gender, and race, as well as acquired risk factors such as hypertension, smoking, diabetes, and obesity. These factors, however, only account for a portion of the stroke risk suggesting that other variables, including genetics, must be involved in the etiology of stroke. The exact contribution of genetics to the incidence of stroke still remains largely unknown; however, it is clear that stroke can result from both monogenic and polygenic diseases. Common monogenic causes of stroke include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and its autosomal recessive form, CARASIL, as well as sickle cell disease, and Fabry disease.

Among rarer monogenic and polygenic causes of stroke we have: mitochondrial encephalomyopathy, lactic acidosis, and stroke like episodes (MELAS), hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS), homocystinuria, moyamoya disease, and inherited connective tissue disorders, including type IV collagen α1- chain gene (COL4A1) mutation, Marfan syndrome, and vascular Ehlers–Danlos syndrome (VEDS).

Despite all recent advances in neuro-technologies applied for stroke diagnostic, up to a third of strokes are rendered cryptogenic or of undetermined etiology. This number is specifically higher in younger patients. At times, inadequate diagnostic workups, multiple causes, or an under-recognized etiology contributes to this statistic.

The current presentation will give a brief overview related to most studied rare causes of stroke: aortic arch atheroma, cervical dissection, PFO & ASA, hereditary conditions, thrombophilia, acquired hypercoagulable status and vasculitis.

MITOCHONDRIAL ENCEPHALO-NEURO-MYOPATHIES

ANTONIO TOSCANO
Department of Clinical and Experimental Medicine of the University of Messina, Italy

Mitochondrial diseases (MDs) are a heterogeneous group of inborn errors of metabolism, caused by nuclear or mitochondrial DNA (nDNA or mtDNA) genes mutations, leading to specific clinical abnormalities. Different phenotypes may range from single-organ involvement to multisystemic syndromes, mainly affecting brain, peripheral nerve and skeletal muscle as encephalo-neuro-myopathies.
Two of the most diffuse multi-organ MDs are MELAS and MERRF, due to point mtDNA mutations. MELAS is mitochondrial encephalomyopathy with lactic acidosis, and stroke-like episodes, presenting with focal and diffuse brain damage, sensorimotor polyneuropathy and muscle weakness. MERRF is myoclonic epilepsy associated with the presence "ragged-red fibers" in the skeletal muscles, characterized by myoclonus and generalized epilepsy, ataxia and myopathy.
mtDNA depletion syndromes are more rare mitochondrial disorders, related to nDNA genes mutations as Thymidine phosphorylase (TYMP). TYMP mutations results in a Mitochondrial Neuro-Gastro-Intestinal Encephalomyophaty (MNGIE). This syndrome occurr in patients with gastrointestinal dismotility and cachexia, leukoencephalopathy, progressive external ophtalmoplegia, peripheral neuropathy and muscle weakness.

The pathogenesis of the above mentioned MDs has been quite clearly elucidated and their diagnosis is now possible, although a defined therapy remains a challenge.

THERAPEUTIC PERSPECTIVE FOR MUSCLE GLYCOGENOSIS

ANTONIO TOSCANO
Department of Clinical and Experimental Medicine of the University of Messina, Italy

Glycogen storage diseases (GSDs) are metabolic disorders, caused by an enzyme deficiency of either glycogen degradation or synthesis. Depending on the enzyme tissue-expression, GSDs involve liver (hypoglycemia), striated muscle (weakness with possible rhabdomyolysis and cardiomyopathy) or both

Therapy is limited to dietary modification or organ transplantation for most of them. In fact, although gene therapy studies are ongoing for GSD I, II and V; on the other

hand, the exception is GSD II (Pompe disease), for which an enzyme replacement therapy (ERT) has been already developed and commercialized since 2006.

Pompe disease is caused by acid alpha-glucosidase (GAA) enzyme deficiency due to over 400 mutations and produces a lysosomal accumulation of glycogen in several tissues, especially in cardiac and skeletal muscles. Several studies have demonstrated the efficacy of recombinant human GAA ERT on motor, cardiac and respiratory functions. In fact, ERT has dramatically changed the natural course of the disease (especially in infants), guaranteeing a longer survival.

A potential alternative to ERT is the gene therapy: systemic and intradiaphragmatic delivery of rAAV1-hGAA leading to a respiratory improvement in KO mice, but human preclinical studies results are still minimal. An additional attempt by a different approach with the gene therapy technique is trying to exploit GAA hepatic synthesis and AAV8 hepatic cells tropism in GAA−/− mice. All these approaches are still in progress and the results will come in the next months.

TRANSTHYRETIN AMYLOIDOSIS NEUROPATHY: STILL AN UNDER-RECOGNIZED BUT TREATABLE DISEASE

MIHAELA SIMU

Department of Neurology, County Clinical Emergency Hospital "Pius Brinzeu", Timisoara, Romania; University of Medicine and Pharmacy "Victor Babes" Timișoara, Romania

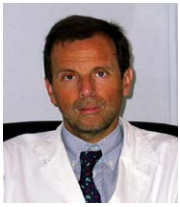
Hereditary transthyretin (ATTR) amyloidosis is a rare genetic disorder with autosomal dominant inheritance, caused by the misfolding of protein monomers derived from the tetrameric protein transthyretin (TTR). In Europe, the incidence is estimated as 0.003 cases per 10,000 per year, with a prevalence estimate of 0.052 per 10,000.

Clinically, it characterized by a slowly progressive peripheral sensorimotor or autonomic neuropathy, cardiomyopathy, nephropathy, vitreous opacities, and CNS amyloidosis. The disease begins in the third to fifth decade in persons from endemic foci in Portugal and Japan; onset is later in patients from other areas. Typically, sensory neuropathy starts in the lower extremities with paresthesias and hypesthesias of the feet, followed within a few years by motor neuropathy. In some patients, particularly those with early-onset disease, autonomic neuropathy is the first manifestation, with orthostatic hypotension, constipation alternating with diarrhea, attacks of nausea and vomiting, delayed gastric emptying, sexual impotence, anhidrosis, and urinary retention or incontinence. Cardiac amyloidosis

is mainly characterized by progressive cardiomyopathy. The leptomeningeal amyloidosis may present with dementia, psychosis, visual impairment, headache, seizures, paresis, ataxia, myelopathy, hydrocephalus, or intracranial hemorrhage. The diagnosis is established in a proband with characteristic clinical features, amyloid deposits identified on biopsy, and identification of a heterozygous pathogenic variant in TTR by molecular genetic testing.

Orthotopic liver transplantation halts the progression of peripheral and autonomic neuropathy, being recommended in individuals younger than age 60 years with: duration less than five years, polyneuropathy restricted to the lower extremities or with autonomic neuropathy alone, and no significant cardiac or renal dysfunction. Additional treatment options include TTR tetramer stabilizers and gene-silencing therapies. Surgery is indicated for carpal tunnel syndrome, surgical treatment for glaucoma and vitrectomy for vitreous involvement. Cardiac pacemaker is indicated in patients with sick sinus syndrome or second degree or third-degree AV block.

CURRICULUM VITAE



ALBERTO ALBANESE
ITALY

Alberto Albanese is Professor of Neurology and Head of the Department of Neurology at the Humanitas Research Hospital in Milan. Is certified in Neurology and in Psychiatry and has published over 250 publications, including more than 200 scientific papers on indexed journals and several chapters on multi-authored books. Is Editor in Chief of Frontiers in Movement Disorders and Associate Editor of the European Journal of Neurology. He is a member of the Faculty of 1000, and has peer reviewed for a number of neurological journals.

Prof. Albanese has been President of the International Neurotoxin association and is a honorary member of the French Neurological Society and of the Swiss Neurological Society. He is regular member of several scientific societies.

OVIDIU BĂJENARU
ROMANIA

Corresponding Member of the Romanian Academy

Member of the Romanian Academy of Medical Sciences of Romania

Professor of Neurology and Director of the Clinical Neuroscience Department at the

University of Medicine and Pharmacy "Carol Davila" Bucharest, Chairman of the Department of Neurology – University Emergency Hospital Bucharest

- Graduate of the Faculty of Medicine – University of Medicine and Pharmacy (UMF) „Carol
- Davila" Bucharest (1983)
- Specialist in Neurology (1989), Senior Neurologist (1994); competence in MRI
- diagnostic in neurologic disorders (1991)
- PhD (1993) - UMF „Carol Davila" Bucharest
- 2006: Doctor Honoris Causa –University „Ovidius" – Constanta
- Postdoctoral specialization at the University „René Descartes" (Paris) during 1993-
- 1994, in clinical Neurology (CHU „Saint-Anne" and „Kremlin-Bicetre") and research
- grants in Clinical and Experimental Neurophysiology (CHU „Cochin-Port Royale" and
- Faculté de Medecine Paris V)
- 2001-2013: President of the Romanian Society of Neurology
- Since 2013: Honorary President ad vitam of the Romanian Society of Neurology
- Since 2001: Coordinator and Chairman of all annual National Congresses of the
- Romanian Society of Neurology and many other scientific events and teaching courses organized for neurologists in Romania
- Visiting Professor in Vietnam (2013) and Kazakhstan (2015), on behalf of WFN
- Member of the Executive Committee of ENS (European Society of Neurology) between 2005-2009, of the Scientific Committee of ECTRIMS (2004-2009)
- Member of European Academy of Neurology (since 2014), American Academy of Neurology, International Parkinson's Disease and Movement Disorders Society,
- European Stroke Organisation, Danube Neurological Association (member of the Scientific Board and Deputy Secretary General), and others
- Since 2008: official representative of Romania for UEMS - European Board of Neurology (secretary of the Executive Committee between 2010-2015) and member of the examination board for the title of European Neurologist
- Author of more than 1000 scientific papers reported and published in scientific journals, among 147 cited in ISI Web of Science (Hirsch index 22) and Pubmed. Author of chapters in 2 international books of neurology and author and co-author in more than 15 medical books published in Romania.
- Coordinator of the National Diagnostic and Treatment Guidelines in Neurological Disorders

- National Principal Investigator and Investigator in more than 50 international, multicentric, controlled clinical trials in: stroke, Parkinson's disease and movement disorders, multiple sclerosis, dementia, epilepsy, and others.
- Director of more national research grants
- 9 awards of excellency in medicine from different socio-professional national and international organizations, the Romanian Ministery of Health and the Romanian Orthodox Patriarchate
- Initiator and coordinator of the National Medical Programs of the Ministery of Health and National Health Insurance System for the treatment of: acute stroke, multiple sclerosis, rare neurological diseases, advanced Parkinson's disease (1999 – 2015)
- President of Consultative Commision of Neurology of the Ministery of Health and National Health Insurance System (2008 – 2015)

ANDRADA CIUCĂ
ROMANIA

Andrada Ciucă is currently a PhD candidate at the Department of Psychology, Babeș-Bolyai University, Romania, with a thesis on genetic counselling. She previously graduated from the same university with a B.A. in Psychology and a M.Sc. in Genetic Counselling. Her research interests include genetic counselling for various conditions such as cancer, psychiatric or rare disorders. Her professional training includes specialisations in genetics and rare disorders such as psychiatric genetic counselling from Bournemouth University, medicine development in rare disorders form European Rare Disorders Organisation, genomics and variant interpretation from Wellcome Genome Campus, Cambridge, and patient advocacy from European Federation of Neurological Associations. During the past several years she has developed a special interest in Huntington's disease by participating in numerous conferences and meetings of patients' organisations from across Europe. She is a volunteering at the Romanian Association for Huntington's disease working to raise awareness and improve quality of life for the affected families.

ANTONIO FEDERICO
ITALY

Prof. Antonio Federico, born in Polla (Sa) on the 25.08.48, from 1990 is full professor of Neurology at the University of Siena , Director of the Unit Clinical Neurology and Neurometabolic Disease.

He was Director of the Department of Neurological, Neurosurgical and Behavioural Sciences, University of Siena (2002-2008).

He received the degree in Medicine and specialization in Nervous and Mental Diseases, summa cum laude, at the University of Naples in 1972 and 1975 respectively. He received the Lepetit Award for the best degree dissertation in 1972.

His biological training was in the Institute of Biochemistry as student and after in Physiology of the University of Naples, and in the Centre de Neurochimie of CNRS, in Strasbourg, directed by prof. Mandel where he worked in the years 1973-75. He also collaborated with many international research groups, in different countries where he spent in the past years some times: in Montreal (Prof. Andermann, Karpati and Shoudgbridge), in London (dr A. Harding and prof. Morgan-Hughes), in Toronto (dr.Robinson), in Bonn (prof. von Bergmann), in Paris (dr.Baumann), in Baltimore (proff. Moser and Naidu), in Oxford (prof. Matthews), etc. His clinical formation was made at the Medical School of the University of Naples, in the Dept, Neurology, and after in Siena, where he moved on 1980 with his mentor, prof. G.C. Guazzi. Associated professor in Neurology in 1982, since 1990 he is full professor of Neurology, Medical School, University of Siena. In 2013, he received honoris causa degree in Medicine at University Carol Davila, Bucharest, Rumania.

In the years 1990-96 he was Secretary of the Italian Society of Neurology. In the years 2006-08 was President of the Italian Society of Neurology. He coordinated the Study Group on Clinical Neurogenetics of the Italian Society of Neurology. He has been referee for projects evaluation in the area of Orphan drugs and Orphan diseases for Biomed Projects from EU, for MURST, CNR and Istituto Superiore di Sanita, and other national and international funding agencies, etc.

He is member of the Second Opinion Group of the American Leucodistrophy Association. Associated editor of Neurological Sciences , Springer-Verlag Editor from 2000. From 2012, he is Editor-in Chief.

He is author of more than 500 article quoted by Pubmed. He is author of a chapter on Cerebrotendinous Xanthomatosis, Vinken and Bruyn Edts, Handbook of Clincal Neurology, vol 49, Neurodystrophies and Neurolipidoses.

On the book McKusick's Mendelian Inheritance in Man,. Ed.1992, Catalog of Autosomal Dominant and Recessive Phenotypes he is cited for 3 different diseases. He was editor of the book Late Onset Neurometabolic diseases (A.Federico, K. Suzuki and N.Baumann Edts), Karger 1991, and many other books from Italian and international.

Publishing Companies. Recently he published (2015) Manuale di Neurologia Pratica and Neurologia and Assistenza infermieristica, for students.

His main field of interest is related to neurometabolic, neurodegenerative and rare diseases, investigated from a genetic, metabolic, neuroimaging and clinical point of vue. Summary of the academic involvements: - Director of the Section Neurological Sciences, Dept Neurological , Neurosurgical and Behavioural Sciences (2000-2012) - Director of the Research Center for the Diagnosis, Therapy and Prevention of the Neurohandicap and Rare Neurological Diseases, until the 2010 - Vice-Dine of the Medical School, University of Siena (2003- 2006) - Director of the Postgraduate School of Neurology, University of Siena, from 2006 up to 2014. - Director of the PhD School in Cognitive and Neurological Sciences, University of Siena (from 2000 up to date) - Coordinator of the Section of the Univ. Siena of the PhD Program Neurosciences, Univ. Florence. - Research delegate for the Dept Medicine, Surgery and Neurosciences (2013-2018) - Vice-Rector of the University of Siena, from 1st april 2016 to november 2017.

Medical Involvements – Until November 2018 (date of retirement) Director of the OU Clinical Neurology and Neurometabolic Diseases, University Hospital of Siena Medical School. –He is still Director of the Regional Reference Center for Rare Diseases - Regional Coordinator of the Network for Rare Neurological Diseases, Tuscany Region. - Member of several Ministry of Health and Regional Committees National and International Commitments - President of the Italian Society of Neurology (2009-11) - Italian delegate to the World Federation of Neurology - Italian Delegate to the European Union of Medical Specialists (Section Neurology) - Italian Delegate and Chairman of the Neuromediterraneum Forum and President - Consultive Member of the European Brain Council - Editor – in – Chief of Neurological Sciences, Springer Verlag Editor. He is in the Editorial Board of many national and international journals. - Member of the American Panel United Leucodystrophies. – Member of the Scientific Committee of AISM (Associazione Italiana Sclerosi Multipla) - Chairman of the Scientific Committee of the European Academy of Neurology (2014-2018) - Chairman of Neuromediterraneum Forum - Co-Chairman of Research group of WFN Migration Neurology. Member of the Scientific Societies: - Societa Italiana di Neurologia (Past Secretary, President, Past-President and Member of the Committee) - Society for the Inborn Errors of Metabolism - Italian Association of Neuropathology - SINDEM (Italian Association of Dementias) - Italian Association for Parkinson's disease - Italian Association of Neurogeriatrics (Member

of the Scientific Committee) - Italian Stroke Forum - European Academy of Neurology (Member of the Board and Chairman of the Scientific Committee) - American Academy of Neurology - World Federation of Neurology (Co-Chair Section of Migration Neurology) - Neuromediterraneum Forum (President).

ALESSANDRO FILLA
ITALY

Full Professor of Neurology and Chairman of the Department of Neurological Sciences at Federico II, Naples, Italy.

EDUCATION:
1972 Medical Degree at the University of Naples
1973 Educational Council for Foreign Medical Graduates Certification
1975 Board Certification in Neurology

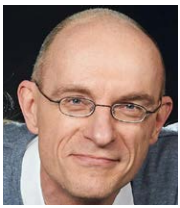
CLINICAL TRAINING/RESEARCH EXPERIENCE:
1976-78 Fellow of Research at the Department of Neurobiology of the Institute of Clinical Research of Montreal (Dr. A. Barbeau)
1992 Stage at the National Hospital, Queen Square, London (Dr. A. Harding)
1994 Stage at Columbia University, New York (Dr. S. Fahn)
1996 Stage at Hopital de la Salpetriere (Dr. Y. Agid)

ACADEMIC AND PROFESSIONAL DUTIES
1973 Assistant Professor of Anatomy
1974 Lecturer of Neurology at the Federico II University, Naples
1982 Senior Lecturer of Neurology
1982 Visiting Professor of Pharmacology and Neuropediatrics at University of Arizona
1992 Associate Professor of Neurology
2001 Full Professor of Neurology
2003-09 Chairman of the Clinical Department of Neurological Sciences
2007-12 Chairman of University Department of Neurological Sciences
2007 to date Director of the School of Neurology Residents
2018 co-chairman Neurogenetic Panel of the European Academy of Neurology

RESEARCH FIELDS
Molecular genetics and molecular pathogenesis of the recessive and dominant ataxias;
Molecular genetics and molecular pathogenesis of the hereditary spastic paraplegias;

Molecular genetics and molecular pathogenesis in Parkinson disease and parkinsonisms;
Epidemiology of hereditary ataxias and spastic paraplegias;
Clinical studies in hereditary ataxias;
Trials in hereditary ataxias.

280 pubblications, H-Index=46



HOLM GRAESSNER
GERMANY

POSITION TITLE:
Managing Director, Rare Disease Centre, University Hospital Tübingen

EDUCATION/TRAINING

Institution and location	Degree	Completion date	Field of study
Technical University Ilmenau, Germany	Dipl.Ing.	1993	Biomedical Engineering
University of Rostock, Germany	M.A.	1999	German language and literature / philosophy
University of Rostock, Germany	PhD	2004	History of Science
University of Reutlingen, Germany	MBA	2008	International Marketing

BIOGRAPHY
Holm Graessner has been Managing Director of the Rare Disease Centre, since 2010, at the University and University Hospital Tübingen, Germany. www.zse-tuebingen.de
He is Coordinator of the European Reference Network for Rare Neurological Diseases (ERN-RND). www.ern-rnd.eu
Together with Olaf Riess, he coordinates the H2020 Solve-RD project on "Solving the unsolved rare diseases". www.solve-rd.eu

He received his PhD "Summa cum laude" in 2004 and, then, he obtained his MBA degree in 2008.

From 2003 until now, he has been coordinating and managing more than 10 EU funded collaborative projects. The main focus of these projects are rare and neurological diseases, among them EUROSCA, MEFOPA, SENSE-PARK, MULTISYN, NEUROMICS and PROOF.

He has been co-leading one of the four working groups of the German Action Plan for Rare Diseases.

Since 2017, in his function as the coordinator of ERN-RND, he is a member of the Rare Disease Task Force of the European Academy of Neurology. In the Coordinator's Group of the European Reference Networks, he leads the cross-border healthcare working group.

PUBLICATIONS

1. RD-Connect, NeurOmics and EURenOmics: collaborative European initiative for rare diseases. Lochmüller H, Badowska DM, Thompson R, Knoers NV, Aartsma-Rus A, Gut I, Wood L, Harmuth T, Durudas A, Graessner H, Schaefer F, Riess O; RD-Connect consortium; NeurOmics consortium; EURenOmics consortium. Eur J Hum Genet. 2018 Feb 27. doi: 10.1038/s41431-018-0115-5. [Epub ahead of print] PMID: 29487416
2. European Reference Networks : Consequences for healthcare in Germany. Graessner H, Schäfer F, Scarpa M, Wagner TOF. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2017 May;60(5):537-541. doi: 10.1007/s00103-017-2533-x. German.
3. Participatory design in Parkinson's research with focus on the symptomatic domains to be measured. Serrano JA, Larsen F, Isaacs T, Matthews H, Duffen J, Riggare S, Capitanio F, Ferreira JJ, Domingos J, Maetzler W, Graessner H; SENSE-PARK Consortium. J Parkinsons Dis. 2015;5(1):187-96. doi: 10.3233/JPD-140472. PMID: 25588357

Since 2017, in his function as the coordinator of ERN-RND, he is a member of the Rare Disease Task Force of the European Academy of Neurology. In the Coordinator's Group of the European Reference Networks, he leads the cross-border healthcare working group.

MAX HILZ
GERMANY

He studied medicine at the Universities of Cologne and Erlangen-Nuremberg in Germany. He first trained in Anesthesiology and Intensive Care Medicine and in Ear-Nose-and–Throat diseases, and then started his residency in Neurology and Psychiatry at the University of Erlangen-Nuremberg.

He specialized in Neurology, Clinical Neurophysiology, Neurological Intensive Care Medicine and Disorders of the Autonomic Nervous System (ANS). He holds German board certificates in Neurology and Psychiatry and in Psychotherapy. He also passed the board examination of the American Board of Electrodiagnostic Medicine.

He is licensed to practice medicine in Germany, the United Kingdom, and in the State of New York, USA.

From 1992 until 2013, he was Attending and Full Professor of Neurology, Medicine and Psychiatry at New York University, New York, NY. Until 2007, he also served as the Associate Director of the Dysautonomia Evaluation and Treatment Center at New York University. In 2006, he was offered an Endowed Chair and tenured Professorship at New York University. From September 2016 to August 2017, he was the Chair in Autonomic Neurology, and Director of the Clinical Department of Autonomic Neurology at the University College London, Institute of Neurology, Queen Square, London, UK. Until April 2019, he was Professor of Neurology at the University of Erlangen-Nuremberg in Erlangen, Germany. Since June 2015, he is also Adjunct Professor of Neurology at Icahn School of Medicine at Mount Sinai, New York, NY, USA.

In December 2018, he received the academic degree of Doctor honoris causa (Dr. h.c.) from the "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania,

Professor Hilz is the current Chair of the Autonomic Disorders Research Group in the World Federation of Neurology. He also co-chairs the Autonomic Nervous System Subspecialty Panel of the European Academy of Neurology, EAN. He was President of the German Autonomic Society, President of the European Federation of Autonomic Societies, and Chair of the Autonomic Section of the American Academy of Neurology. He is a member of the editorial board of Clinical Autonomic Research, and Associate Clinical Editor of Autonomic Neuroscience: Basic and Clinical. He also served as an advisor to the European Medicines Agency, EMA, on issues related to autonomic nervous system dysfunction.

He co-authored the guidelines of the German Neurological Society on syncope, the

guidelines on erectile dysfunction and the guidelines of the German Diabetes Society on diabetic neuropathy. He has published more than 300 original and review articles in peer-reviewed journals and chapters in textbooks and presented his work at several hundred scientific conferences.

Prof. Hilz is experienced in the examination of small nerve fiber diseases and disorders of the peripheral and central autonomic nervous system, including hereditary sensory and autonomic neuropathies, diabetic neuropathies, and Fabry disease, and central autonomic disorders. He studied the pathophysiology of Familial Dysautonomia, also known as Hereditary Sensory and Autonomic Neuropathy Type III, of Fabry disease, and the effects of brain lesions of various etiologies on the central autonomic network and on autonomic function. He also described long-term changes in the central autonomic modulation of the cardiovascular system in patients with a history of traumatic brain injury, stroke, epilepsy, multiple sclerosis and other diseases.

MÁRIA JUDIT MOLNÁR
HUNGARY

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.

DAFIN F. MUREȘANU

ROMANIA

Professor of Neurology, Senior Neurologist, Chairman of the Neurosciences Department, Faculty of Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, President of the European Federation of Neurorehabilitation Societies (EFNR), Co-Chair EAN Scientific Panel Neurorehabilitation, Past President of the Romanian Society of Neurology, President of the Society for the Study of Neuroprotection and Neuroplasticity (SSNN), Member of the Romanian Academy, Member of the Academy of Medical Sciences, Romania, secretary of its Cluj Branch. He is member of 17 scientific international societies (being Member of the American Neurological Association (ANA) - Fellow of ANA (FANA) since 2012) and 10 national ones, being part of the executive board of most of these societies.

Professor Dafin F. Muresanu is a specialist in Leadership and Management of Research and Health Care Systems (specialization in Management and Leadership, Arthur Anderson Institute, Illinois, USA, 1998 and several international courses and training stages in Neurology, research, management and leadership). Professor Dafin F. Muresanu is coordinator in international educational programs of European Master (i.e. European Master in Stroke Medicine, University of Krems), organizer and co-organizer of many educational projects: European and international schools and courses (International School of Neurology, European Stroke Organisation summer School, Danubian Neurological Society Teaching Courses, Seminars - Department of Neurosciences, European Teaching Courses on Neurorehabilitation) and scientific events: congresses, conferences, symposia (International Congresses of the Society for the Study of Neuroprotection and Neuroplasticity (SSNN), International Association of Neurorestoratology (IANR) & Global College for Neuroprotection and Neuroregeneration (GCNN) Conferences, Vascular Dementia Congresses (VaD), World Congresses on Controversies in Neurology (CONy), Danube Society Neurology Congresses, World Academy for Multidisciplinary Neurotraumatolgy (AMN) Congresses, Congresses of European Society for Clinical Neuropharmacology, European Congresses of Neurorehabilitation). His activity includes involvement in many national and international clinical studies and research projects, over 400 scientific participations as "invited speaker" in national and international scientific events, a significant portfolio of scientific articles (193 papers indexed on Web of Science-ISI, H-index: 21) as well as contributions in monographs and books published by prestigious international publishing houses.

Prof. Dr. Dafin F. Muresanu has been honoured with: „Dimitrie Cantemir" Medal of the Academy of The Republic of Moldova in 2018, Ana Aslan Award 2018 - "Performance in the study of active aging and neuroscience", for the contribution to the development of Romanian medicine, National Order "Faithful Service" awarded by the President of Romania in 2017; "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Faculty of Medicine, the "Iuliu Hatieganu Great Award 2016" for the best educational project in the last five years; the Academy of Romanian Scientists, "Carol Davila Award for Medical Sciences / 2011", for the contribution to the Neurosurgery book "Tratat de Neurochirurgie" (vol.2), Editura Medicala, Bucuresti, 2011; the Faculty of Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca "Octavian Fodor Award" for the best scientific activity of the year 2010 and the 2009 Romanian Academy "Gheorghe Marinescu Award" for advanced contributions in Neuroprotection and Neuroplasticity.

ANTONIO TOSCANO
ITALY

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)i

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 190 papers.

MIHAELA SIMU
ROMANIA

Mihaela Simu is presently working as Professor and Chairman of the Neurology Department II of University of Medicine and Pharmacy "Victor Babes" - Timisoara.

Professor Simu is currently Vicepresident of the Romanian Society of Neurology, one of the coordinators of the National Programme for the treatment of Multiple Sclerosis in Romania, active member of ENS, EFNS, American Academy of Neurology, and MDS.

Professor Simu has been and is involved as principal investigator in more than 20 international and national multicentric trials and 4 national research grants, and is presently the Romanian project leader in the BIOMARK HURO project (cooperation between Szeged and Timisoara medical Universities). Her interests are directed mainly in clinical neurology, in particular in multiple sclerosis, Parkinson disease, dementia, cerebrovascular and focal dystonias.
As author or co-author, has published and reported more than 100 national and international scientific papers, 3 medical books and 2 neurology courses in a bilingual (Romanian / English) version.

GENERAL INFORMATION

GENERAL INFORMATION

REGISTRATION DESK

All materials and documentation will be available at the registration desk located at SSNN booth.
The staff will be pleased to help you with all enquiries regarding registration, materials and program. Please do not hesitate to contact the staff members if there is something they can do to make your stay more enjoyable.

LOGISTIC PARTNER:

SYNAPSE
TRAVEL

Synapse Travel

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Scientific Secretariat

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Contact Details

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LANGUAGE

The official language is English. Simultaneous translation will not be provided.

CHANGES IN PROGRAM

The organizers cannot assume liability for any changes in the program due to external or unforeseen circumstances.

NAME BADGES

Participants are kindly requested to wear their name badge at all times. The badge enables admission to the scientific sessions and dinners.

FINAL PROGRAM & ABSTRACT BOOK

The participants documents include the program and abstract book which will be handed out at the registration counter.

COFFEE BREAKS

Coffee, tea and water are served during morning coffee breaks and are free of charge to all registered participants.

MOBILE PHONES

Participants are kindly requested to keep their mobile phones turned off while attending the scientific sessions in the meeting rooms.

CURRENCY

The official currency in Romania is RON.

ELECTRICITY

Electrical power is 220 volts, 50 Hz. Two-prong plugs are standard.

TIME

The time in Romania is Eastern European Time (GMT+2).

ACADEMIC PARTNERS

European Academy
of Neurology
www.ean.org

Foundation for the
Study of Nanoneurosciences and
Neuroregeneration

Academia de
Științe Medicale
din România

Romanian Academy of
Medical Sciences
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ORGANIZERS

Institute for Neurological Research and Diagnostic
www.roneuro.ro

Foundation of the Society for the Study of Neuroprotection and Neuroplasticity
www.ssnn.ro

Foundation of the Journal for Medicine and Life
www.medandlife.org

"Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania
www.umfcluj.ro

Romanian Society of Neurology
www.neurology.ro

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for rare or low prevalence complex diseases
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