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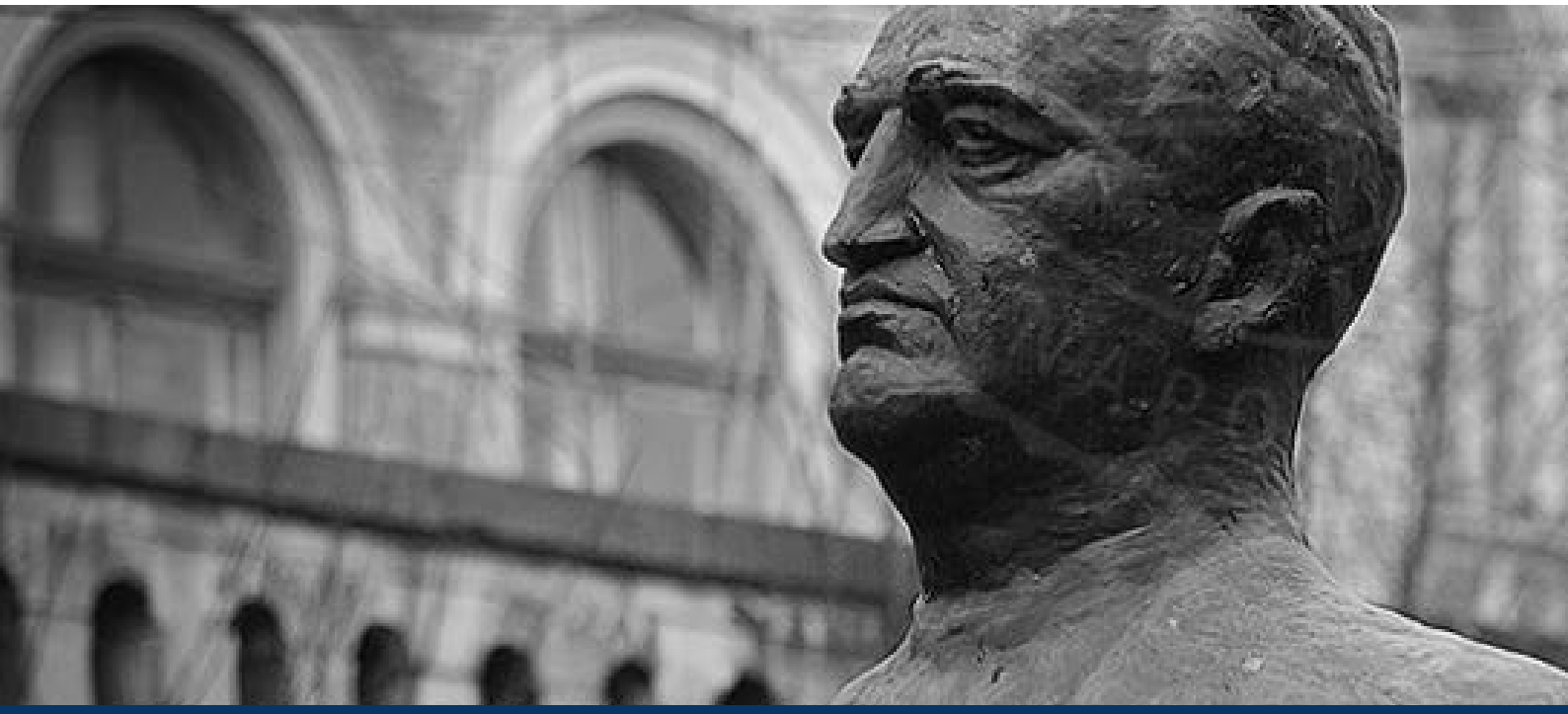

"IULIU HATIEGANU" UNIVERSITY OF MEDICINE AND PHARMACY DOCTORAL SCHOOL

NEUROSCIENCE

PROGRAM

2017-2018 | SECTION 1

14 NOVEMBER | UMF "IULIU HATIEGANU" | CLUJ-NAPOCA | ROMANIA

PhD NEUROSCIENCE PROGRAM COORDINATOR

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Co-Chair EAN Scientific Panel Neurorehabilitation

President of the European Federation of NeuroRehabilitation Societies (EFNR)

Past President of the Romanian Society of Neurology

Professor of Neurology, Chairman Department of Neurosciences "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

INTERNATIONAL GUEST LECTURER

Max Hilz

Professor of Neurology, University of Erlangen-Nuremberg in Erlangen, Germany.

Adjunct Professor of Neurology, Icahn School of Medicine at Mount Sinai, New York, USA.

Co-chair, Autonomic Nervous System Subspecialty Panel of the European Academy of Neurology, EAN.

Past-President of the European Federation of Autonomic Societies

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2017-2018

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COURSE PROGRAM

COURSE PROGRAM

NOVEMBER 14TH, 2017

"MULTIMEDIA" AUDITORIUM, "IULIU HATIEGANU" UMF CLUJ-NAPOCA

8 VICTOR BABES STREET | CLUJ-NAPOCA | ROMANIA

09:50 – 10:00	Welcome address
10:00 – 10:30	Max Hilz / Germany Diabetic autonomic neuropathy: A diagnostic chameleon with prognostic relevance
10:30 – 11:00	Max Hilz / Germany Mechanisms of cerebral autoregulation, assessment and interpretation by means of transcranial doppler sonography
11:00 – 11:30	Dafin F. Mureșanu / Romania Advances in neurofundamentals
11:30 – 12:00	Coffee Break
12:00 – 12:30	Dafin F. Mureșanu / Romania Brain protection and recovery in stroke
12:30 – 13:00	Max Hilz / Germany Neurological complications in Fabry disease
13:00 – 13:30	Max Hilz / Germany Differential-diagnosis of transient loss of consciousness

INTERNATIONAL GUEST LECTURERS

MAX HILZ
GERMANY

Studied medicine in Cologne and Erlangen-Nuremberg, Germany. After initial training in Anesthesiology and Intensive Care Medicine and in Ear-Nose-and–Throat diseases, he trained 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 held appointments at New York University, New York, NY, as Professor of Neurology, Medicine and Psychiatry. Until 2007, he also served as the Associate Director of the NYU Dysautonomia Evaluation and Treatment Center. He was deeply involved in clinical research regarding the pathophysiology of Familial Dysautonomia, also known as Riley-Day syndrome or Hereditary Sensory and Autonomic Neuropathy Type III, and in studies of Fabry disease.

He is 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. From September 1, 2016 to August 31, 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.

Professor Hilz currently co-chairs the Autonomic Nervous System Subspecialty Panel of the European Academy of Neurology, EAN. He also is Past-President of the German Autonomic Society, Past-President of the European Federation of Autonomic Societies, and Past-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 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. He wrote textbook chapters on basic and sophisticated methods of autonomic testing, and co-authored various autonomic nervous system guidelines and consensus statements, e.g. the guidelines of the German Neurological Society on syncope, the guidelines on erectile dysfunction, the guidelines of the German Diabetes Society on diabetic neuropathy, the consensus statement of the American Academy of Neurology and the American Autonomic Society on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome, as well as the EFNS guidelines on the diagnosis and management of orthostatic hypotension. He served on the expert panel that developed the Autonomic Nervous System subspecialty examination of the American Academy of Neurology. He also served as an advisor to the European Medicines Agency, EMA, on issues related to autonomic nervous system dysfunction.

In summary, Prof. Hilz is experienced in the examination of small nerve fiber diseases and disorders of the autonomic nervous system, including hereditary sensory and autonomic neuropathies, diabetic neuropathies, and Fabry disease, and central autonomic disorders.

DAFIN F. MUREȘANU
ROMANIA

Professor of Neurology, Senior Neurologist, Chairman of the Neurosciences Department, Faculty of Medicine, University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca, Past President of the Romanian Society of Neurology, President of the Society for the Study of Neuroprotection and Neuroplasticity (SSNN), member of the Academy of Medical Sciences, Romania, secretary of its Cluj Branch. He is member of 16 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 (157 papers indexed on Web of Science-ISI, H-index: 17) as well as contributions in monographs and books published by prestigious international publishing houses. Prof. Dr. Dafin F. Muresanu has been honoured with: the University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca, Faculty of Medicine, "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, University of Medicine and Pharmacy "Iuliu Hatieganu" 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.

ABSTRACTS

MECHANISMS OF CEREBRAL AUTOREGULATION, ASSESSMENT AND INTERPRETATION BY MEANS OF TRANSCRANIAL DOPPLER SONOGRAPHY

MAX HILZ
Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany

Cerebrovascular autoregulation assures constancy of cerebral perfusion despite blood pressure changes, as long as mean blood pressure remains in a range between 50 - 170 mmHg. Static and dynamic myogenic mechanisms dampen sudden blood pressure changes. Neurogenic influences of sympathetic, noradrenergic fibers modulate primarily proximal, large diameter segments of cerebral arteries, but also small 15 - 20 µm diameter vessels. Parasympathetic, vasodilating impulses are of less influence. Monoaminergic brainstem centers such as the dorsal raphe nucleus, locus coeruleus or nucleus reticularis pontis oralis also influence vessel tone. Metabolic, local parenchymal and endothelial substances have major impact on cerebral vessel tone. Particularly important are nitric oxide, calcitonin gene related peptide, substance P, endothelin, potassium channels and autocoids such as histamine, bradykinin, arachidonic acid, prostanoids, leucotrienes, free radicals or serotonin. The clinical examination of autoregulation is mostly based on brief blood pressure changes induced by drugs such as angiotensin, phenylephrine or sodium nitroprusside, or by challenge maneuvers. Frequently, blood pressure is challenged by a tilt-table maneuver, the "leg-cuff"-method according to Aaslid, or a Valsalva maneuver. The analysis of coherence and phase relation between spontaneous or metronomic breathing modulation of blood pressure and brain perfusion also assesses autoregulatory function. Cerebral blood flow is determined by means of transcranial Doppler sonography, mostly of the proximal segment of the mid-cerebral artery. There is some controversy whether a decrease of cerebral blood flow velocity measured at this segment indicates vasodilatation at the insonated segment or reflects blood flow reduction due to decreased perfusion of down-stream vessel segments. Various clinical and animal studies suggest diameter constancy of the insonated mid-cerebral artery segment and thus indicate that slowing of mid cerebral artery blood flow velocity as assessed by transcranial Doppler sonography is due to a decrease of down-stream perfusion. Direct, intraoperative measurements of vessel diameter confirm this conclusion.

NEUROLOGICAL COMPLICATIONS IN FABRY DISEASE

MAX HILZ[1,2]
1. Clinical Department of Autonomic Neurology, UCL Institute of Neurology, London, UK
2. Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany

In Fabry disease, deficiency of α-galactosidase A results in the accumulation of glycosphingolipids in body fluids and tissues including corneas, blood vessels, kidneys and also structures of the central and peripheral nervous system. Many patients show cardiovascular and cerebrovascular dysfunction. Cerebrovascular dysfunction is particularly associated with a high risk of strokes and of mortality even at a young age. The prevalence and severity of cerebrovascular complications increase with patient age.

Although ischemic strokes and transient ischemic attacks are the most prevalent types of overt cerebrovascular events in FD, cases of intracerebral hemorrhages, subarachnoid hemorrhage, microbleeds, cerebral venous thrombosis, and cervical carotid dissection have also been reported. To our knowledge, no cases of vertebral dissection or spinal cord infarction have been documented in the literature to date. Although silent infarcts are common events, also among young patients with stroke, there are no reports on the frequency of silent brain infarcts in FD. Aseptic meningitis can occur concomitantly in Fabry patients who have had cerebrovascular complications. One case of prolonged transient global amnesia has been reported in a Fabry patient. Dementia, cognitive impairment, and depression occur in patients with FD although additional studies are needed to establish a direct link to FD.

Clinical data as well as histologic and neurophysiologic studies showed predominantly small fiber dysfunction in patients with Fabry disease. Patients with Fabry disease (FD) characteristically develop peripheral neuropathy at an early age, with pain being a crucial symptom of underlying pathology. From our findings, we concluded that small fiber dysfunction is more prominent than large fiber dysfunction in Fabry patients. Clinically, small fiber dysfunction contributes to recurrent episodes of burning and lancinating pain and paraesthesias in the distal extremities. Such episodes can be typically triggered by changes of the environmental temperature, particularly by warming. Moreover, small nerve fiber dysfunction accounts for altered sympathetic and parasympathetic modulation. Sympathetic dysfunction explains the hypohidrosis and a subsequent poor exercise and heat tolerance. However, the diagnosis of pain is challenging due to the heterogeneous and nonspecific symptoms. Practical guidance on the diagnosis and management of pain in FD is needed. To improve treatment outcomes, pain should be diagnosed early in unrecognized or newly identified FD patients. Treatment should include: (a) enzyme replacement therapy controlling the progression of underlying pathology; (b) adjunctive, symptomatic pain management with analgesics for chronic neuropathic and acute nociceptive, and inflammatory or mixed pain; and (c) lifestyle modifications.

DIFFERENTIAL-DIAGNOSIS OF TRANSIENT LOSS OF CONSCIOUSNESS

MAX HILZ
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Transient loss of consciousness (TLOC) is defined as abrupt onset of apparent loss of consciousness. After a short duration (i.e. minutes), there is spontaneous and complete recovery. TLOC can be due to a traumatic cause, such as a concussion, or to non-traumatic etiologies. Non-Traumatic TLOC is most frequently caused by syncope: Syncope may be neurally mediated (such as so-called reflex-syncope), due to orthostatic hypotension, or due to cardiac arrhythmias or structural heart diseases. Other causes of (non-traumatic) TLOC are primary or secondary generalized epileptic seizures, functional (or 'psychogenic') 'pseudoseizures' and 'pseudosyncopes', and rare miscellaneous disorders that may include vertebrobasilar transient ischemic attacks, the subclavian steal syndrome, cataplexy and excessive daytime sleepiness, metabolic disorders (e.g. hypoglycemia) or 'drop attacks'.

TLOCs are characterized by 1) loss of normal motor control with either flaccidity or stiffness that may be accompanied by jerking movements, 2) loss of postural control with falls, and 3) unresponsiveness and amnesia for the event. A solid history and key clinical aspects facilitate the differential diagnosis and help to distinguish epileptic loss of consciousness from syncope and to identify functional or "psychogenic" loss of consciousness which may be rather common in clinical routine of emergency rooms.

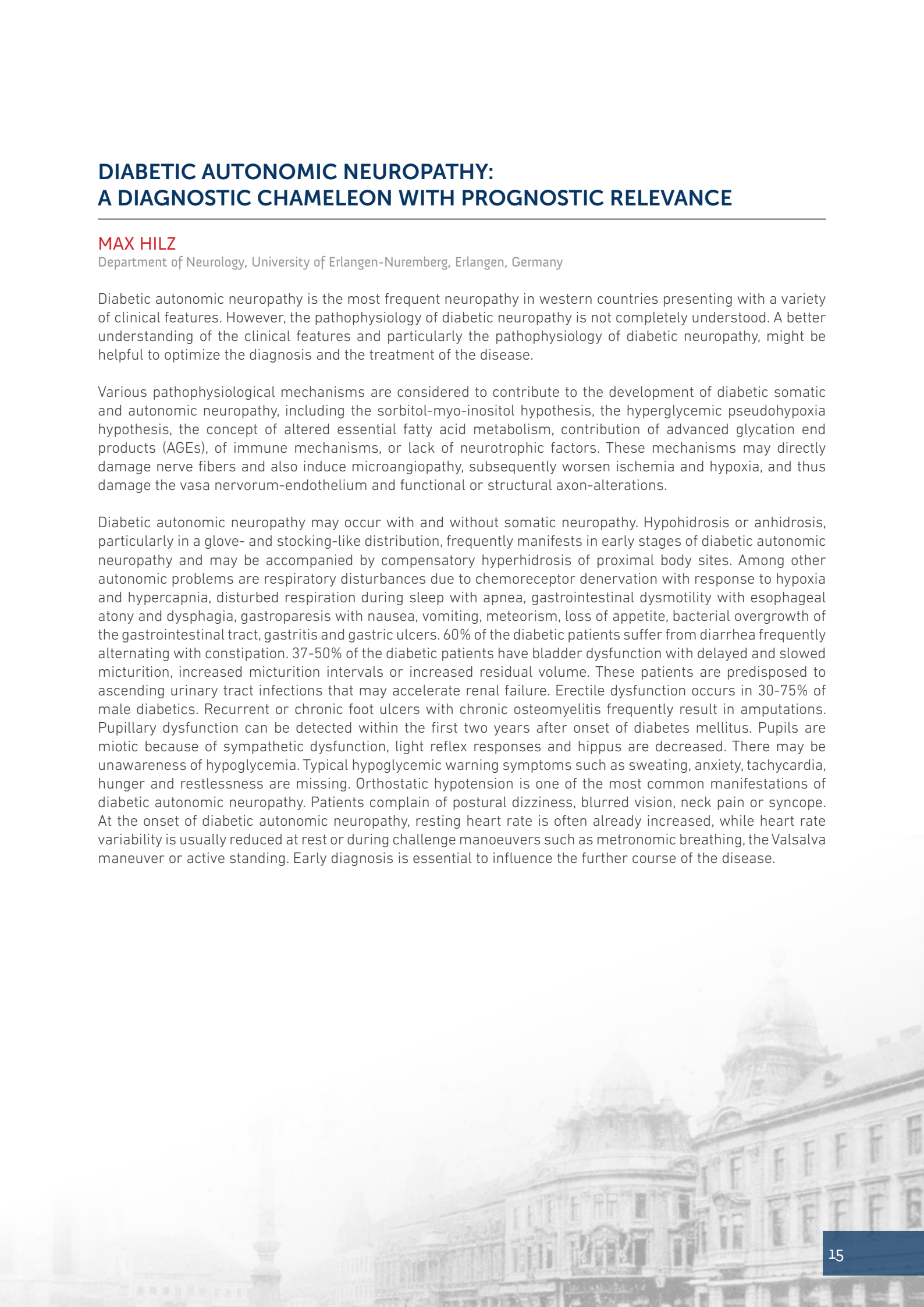
DIABETIC AUTONOMIC NEUROPATHY: A DIAGNOSTIC CHAMELEON WITH PROGNOSTIC RELEVANCE

MAX HILZ
Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany

Diabetic autonomic neuropathy is the most frequent neuropathy in western countries presenting with a variety of clinical features. However, the pathophysiology of diabetic neuropathy is not completely understood. A better understanding of the clinical features and particularly the pathophysiology of diabetic neuropathy, might be helpful to optimize the diagnosis and the treatment of the disease.

Various pathophysiological mechanisms are considered to contribute to the development of diabetic somatic and autonomic neuropathy, including the sorbitol-myo-inositol hypothesis, the hyperglycemic pseudohypoxia hypothesis, the concept of altered essential fatty acid metabolism, contribution of advanced glycation end products (AGEs), of immune mechanisms, or lack of neurotrophic factors. These mechanisms may directly damage nerve fibers and also induce microangiopathy, subsequently worsen ischemia and hypoxia, and thus damage the vasa nervorum-endothelium and functional or structural axon-alterations.

Diabetic autonomic neuropathy may occur with and without somatic neuropathy. Hypohidrosis or anhidrosis, particularly in a glove- and stocking-like distribution, frequently manifests in early stages of diabetic autonomic neuropathy and may be accompanied by compensatory hyperhidrosis of proximal body sites. Among other autonomic problems are respiratory disturbances due to chemoreceptor denervation with response to hypoxia and hypercapnia, disturbed respiration during sleep with apnea, gastrointestinal dysmotility with esophageal atony and dysphagia, gastroparesis with nausea, vomiting, meteorism, loss of appetite, bacterial overgrowth of the gastrointestinal tract, gastritis and gastric ulcers. 60% of the diabetic patients suffer from diarrhea frequently alternating with constipation. 37-50% of the diabetic patients have bladder dysfunction with delayed and slowed micturition, increased micturition intervals or increased residual volume. These patients are predisposed to ascending urinary tract infections that may accelerate renal failure. Erectile dysfunction occurs in 30-75% of male diabetics. Recurrent or chronic foot ulcers with chronic osteomyelitis frequently result in amputations. Pupillary dysfunction can be detected within the first two years after onset of diabetes mellitus. Pupils are miotic because of sympathetic dysfunction, light reflex responses and hippus are decreased. There may be unawareness of hypoglycemia. Typical hypoglycemic warning symptoms such as sweating, anxiety, tachycardia, hunger and restlessness are missing. Orthostatic hypotension is one of the most common manifestations of diabetic autonomic neuropathy. Patients complain of postural dizziness, blurred vision, neck pain or syncope. At the onset of diabetic autonomic neuropathy, resting heart rate is often already increased, while heart rate variability is usually reduced at rest or during challenge manoeuvers such as metronomic breathing, the Valsalva maneuver or active standing. Early diagnosis is essential to influence the further course of the disease.



ADVANCES IN NEUROFUNDAMENTALS

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

Brain damage affects all three levels of structural and functional organization: cellular and molecular level, circuitries level and dynamic network level and launches an endogenous continuous brain defense response which consists in neuroprotection (the immediate response) and neurorecovery (a later response).

Endogenous neuromodulation represents at the cellular and molecular level the optimization of common biological processes that could potentially generate cell death or promote neurodegeneration. At the circuitries and dynamic network levels, it represents the tendency in reinbalancing of functional connectivity in resting-state netwoks.

In the last years, there has been a substantial effort in understanding the brain functioning and how to enhance endogenous neuromodulation and neurorehabilitation in general, by using a large spectrum of neurotechnologies such as imaging techniques (functional magnetic resonance imaging, ligant-based positron emission tomography, diffusion-tensor imaging), quantitative electroencephalogram, magnetoencephalography, eye tracking, optogenetics, transcranial magnetic stimulation, transcranial direct current simulation, deep brain simulation, computational neuroscience and brain-computer interfaces. The combination between these technologies provide valuable information about the structure-function relationship underling resting-state networks, about the dynamic cross-talk between networks and about the abnormalities in the functional connectivity in different pathologies.

Neurorecovery can be enhanced by pharmacological intervention, physical activity, electromagnetic stimulation, psychological support, environmental stimulation or any demonstrated combinations of these factors capable of improving the patient's condition after brain and spinal cord injuries. From the pharmacological perspective, it is clear that the focusing on molecules that are capable of mimic the function of endogenous molecules with multimodal and pleiotropic neuroprotective effects is the best approach in neurorecovery, especially when they are associated with intensive physical training.

Biological agents (e.g., neurotrophic factors and related molecules) with modulating and multimodal effects are better pharmacological agents for brain and spinal cord protection and recovery, because they usually have also pleiotropic neuroprotective effect. That is why they are capable of pharmacologically bridging acute neuroprotective processes with the long-term recovery processes.

There are many animal and human studies trying to elucidate the cellular and molecular mechanisms of plasticity of the nervous system. A better understanding of the mechanisms underlying the neuroplasticity will reflect in a more efficient and comprehensive treatment.

BRAIN PROTECTION AND RECOVERY IN STROKE

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Over the last decades, therapeutic approaches for stroke have significantly evolved and improved as a consequence of the implementation of modern stroke units, improvement of general medical care and more structured and early administered rehabilitation schemes.

Thrombolytic therapy with rt-PA (recombinant tissue plasminogen activator) has been developed and a number of clinical trials have recently confirmed the effectiveness of thrombectomy to be better than rtPA alone.
Except thrombolytic therapy and thrombectomy there is still no widely accepted therapy for acute ischemic stroke. Current data shows that even if advanced procedures can be used, 60% of stroke patients die or remain with a certain level of deficit. As it is widely accepted that immobilization-related complications cause over 50% of stroke patients' deaths, rehabilitation plays an important role in stroke care.

It is getting clearer that multimodal drugs may play an important role in pharmacological support of neurorehabilitation after stroke.

The results of recently published large and well-controlled clinical studies show a positive effect of neurotrophic factors on neurological recovery after acute ischemic stroke.

The newly published CARS study assessed the efficacy and safety of neurotrophic factors in combination with a standardized rehabilitation program. The primary study endpoint was the Action Research Arm Test (ARAT) at day 90, assessing upper-limb motor functions. Neurotrophic factors treatment was administered for 21 days, starting within 48-72 hours after ischemic stroke.

The study showed a statistically significant group difference in the upper-limb motor function (ARAT) at day 90 – primary end point. Neurotrophic factors were also superior over placebo in most of the secondary endpoints like the NIHSS, Barthel Index and mRS. Also, at day 90, patients treated with neurotrophic factors showed less depressive symptoms and better quality of life. In addition, the most important measure for early benefit, the NIHSS at day 21, showed statistically significant superiority of neurotrophic factors. Analysis of the safety parameters did not show any clinically statistical significant differences between the treatment groups. The trial indicates that early combination of rehabilitation with a multimodal medication of neuroprotective and recovery properties is a valid therapeutic approach.

Furthermore, CARS 1 and CARS 2 meta-analysis provides evidence that neurotrophic factors treatment has a beneficial effect on motor function recovery in early rehabilitation patients after stroke. All pre-planned primary meta-analytic results were statistically significant.

NOTES


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