UDK 616.8

ISSN 1331-5196

Neurologia Croatica

SINCE 1953

SAŽETCI / ABSTRACTS

SUPLEMENT

7. hrvatski kongres:
„Dileme u neurologiji”

s međunarodnim sudjelovanjem

7. 10. – 9. 10. 2020.

Zagreb, Hrvatska

SUPPLEMENT

7th Croatian Congress on
Controversies in Neurology

with International Participation

October 7 – October 9, 2020

Zagreb, Croatia

NEUROL. CROAT. 2020 69 (Supl. 1): 1-52

UDK 616.8

ISSN 1331-5196

Neurologia Croatica

SINCE 1953

SAŽETCI / ABSTRACTS

SUPLEMENT

7. 10. – 9. 10. 2020.

Zagreb, Hrvatska

7. hrvatski kongres:
„Dileme u neurologiji”

s međunarodnim sudjelovanjem

SUPPLEMENT

October 7 – October 9, 2020

Zagreb, Croatia

7th Croatian Congress on Controversies in Neurology

with International Participation

7. hrvatski kongres: „Dileme u neurologiji“

s međunarodnim sudjelovanjem

7th Croatian Congress on Controversies in Neurology

with International Participation

ORGANIZATORI

Klinika za neurologiju, KBC Zagreb
Katedra za neurologiju, Medicinski fakultet Sveučilišta u Zagrebu
Referentni centar za epilepsiju MZ RH
Referentni centar za intenzivnu neurologiju i endovaskularno liječenje moždanog udara i krvožilnih malformacija SŽS-a MZ RH
Referentni centar za neuromuskularne bolesti MZ RH
Referentni centar za demijelinizacijske bolesti SŽS-a MZ RH
Referentni centar za poremećaje pokreta i neurodegenerativne bolesti MZ RH
Referentni centar za kognitivnu neurologiju i eksperimentalnu neurofiziologiju MZ RH
Referentni centar za poremećaje autonomnog živčanog sustava MZ RH
HLZ - Hrvatsko društvo za EEG i kliničku neurofiziologiju
HLZ - Hrvatsko neurološko društvo
HLZ - Hrvatsko društvo za neuromuskularne bolesti i EMNG
HLZ - Sekcija za intenzivnu neurologiju HND

ORGANIZED BY

Department of Neurology, Zagreb University Hospital Centre
Department of Neurology, School of Medicine, University of Zagreb
Reference Centre for Epilepsy, MoH
Reference Centre for Intensive Neurology and Endovascular Treatment of Stroke and Vascular Malformations of CNS, MoH
Reference Centre for Neuromuscular Diseases, MoH
Reference Centre for Demyelinating Diseases of CNS, MoH
Reference Centre for Movement Disorders and Neurodegenerative Diseases, MoH
Reference Centre for Cognitive Neurology and Experimental Neurophysiology, MoH
Reference Centre for Autonomic Nervous System Disorders, MoH
CMA - Croatian Society for EEG and Clinical Neurophysiology
CMA - Croatian Society of Neurology
CMA - Croatian Society for Neuromuscular Diseases and EMNG
CMA - Section of Intensive Neurology of the Croatian Society of Neurology

POČASNA PREDSJEDNICA ORGANIZACIJSKOG ODBORA "DILEME U NEUROLOGIJI" / HONORARY PRESIDENT OF ORGANIZING COMMITTEE − CONTROVERSIES IN NEUROLOGY

Professor Sanja Hajnšek, MD, PhD

PREDSJEDNICA ORGANIZACIJSKOG ODBORA "DILEME U NEUROLOGIJI" / PRESIDENT OF ORGANIZING COMMITTEE − CONTROVERSIES IN NEUROLOGY

Professor Ervina Bilić, MD, PhD

PREDSJEDNICA STRUČNOG ODBORA "DILEME U NEUROLOGIJI" / PRESIDENT OF SCIENTIFIC COMMITTEE − CONTROVERSIES IN NEUROLOGY

Professor Zdravka Poljaković, MD, PhD

ORGANIZACIJSKI ODBOR / ORGANIZING COMMITTEE

Organizacijski odbor Kongresa
/ Organizing Committee of the Congress

†Igor Antončić, Bruno Baršić, Silvio Bašić, Vanja Bašić Kes, Fran Borovečki, Marija Bošnjak Pašić, Silva Butković Soldo, Ivan Dubroja, Mario Habek, Jadranka Jurenić, Nataša Klepac, Branko Malojčić, Meri Matijaca, Goran Mrak, Sibila Nanković, Željka Petelin Gadže, Damir Petravić, Marko Radoš, Maja Relja, Marina Titlić, Sanja Tomasović, Vladimira Vuletić

Počasni organizacijski odbor
/ Honorary Organizing Committee

Vesna Brinar, Ante Ćorušić, Vjekoslav Jeleč, Miloš Judaš, Marijan Klarica, Ivica Kostović, Vesna Nesek, Josip Paladino, Ružica Palić Kramarić, Nada Svilokos, Niko Zurak, Marija Žagar

Lektor
/ Language Editor Antonija Redovniković, LinguaMed d.o.o., Zagreb, Croatia

Tisak i dizajn
/ Printing & Design DENONA d.o.o., Getaldićeva 1, Zagreb, Croatia

POKROVITELJI / UNDER THE AUSPICES OF

Ministarstvo zdravstva Republike Hrvatske
/ Ministry of Health of the Republic of Croatia

SPONZORI / SPONSORS

Sanofi Genzyme
Medis Adria d.o.o.
Roche d.o.o.
Merck d.o.o.
Novartis Hrvatska d.o.o.
AbbVie d.o.o.
Makpharm d.o.o.
Boehringer Ingelheim Zagreb d.o.o.
PharmaS d.o.o.
Fresenius Kabi d.o.o.
Alpha-Medical d.o.o.

Na preporuku Uredničkog odbora, urednica časopisa Neurologia Croatica prihvaća objavljivanje sažetaka 7. hrvatskog kongresa: „Dileme u neurologiji" s međunarodnim sudjelovanjem kao suplement časopisa.
Urednici ovoga suplementa pregledali su i odobrili sažetke primljenih radova.
Autori pozvanih predavanja odgovorni su za svoje radove.
Koordinirajući urednik suplementa odgovoran je za sveukupnu kvalitetu suplementa.

The Editor-in-Chief of Neurologia Croatica, as advised by the Editorial Board, has accepted publishing the abstracts of the 7th Croatian Congress on Controversies in Neurology with international participation as a journal supplement.
The editors of this Supplement have been committed to review and accept the abstracts of submitted contributions. The authors of the invited lectures are responsible for their own contributions.
The Supplement Coordinating Editor is responsible for the overall quality of the Supplement.

Glavna urednica
Editor-in-Chief

Pozdravna riječ

Osobita nam je čast i iskreno zadovoljstvo pozvati Vas u ime Organizacijskog odbora na 7. hrvatski kongres "Dileme u neurologiji" s međunarodnim sudjelovanjem.

Svjesni smo da pandemija COVID-19 neprekidno utječe na naš rad i naš život, a neminovno time i na naše stručne i znanstvene sastanke. Kako bismo održali razinu struke, ali i tradiciju izmjene iskustava, ove ćemo Dileme održati u sada već uobičajenom virtualnom prostoru.

Godina 2020. je godina iznenađenja i novih navika pa smo tako koncipirali i ovogodišnje Dileme...

Pozivamo Vas da se uključite u Dileme 2020. kao aktivni sudionici u virtualnom prostoru, kao predavači iz svoje sobe ili pak kao sudionici naših satelitskih simpozija, virtualnih kutaka za diskusiju s vodećim stručnjacima pojedinih područja ili partneri našim stručnim odborima s aktualnom tematikom.

Sretni smo što je ovaj znanstveni skup prerastao u tradicionalni hrvatski sastanak neuroznanstvenika i međunarodnih stručnjaka iz područja neurologije, čime je omogućena razmjena iskustava i iznošenje dilema iz područja svakodnevnog praktičnog rada. Napredak struke, kojem smo i nadalje svjedoci, neprekidno donosi mnoštvo novih spoznaja, ali i nedoumica, a zajednički su sastanci, u bilo kojem obliku, ipak najbolji način njihovog rješavanja.

Pozivamo Vas da nam se pridružite i na ovogodišnjem on-line skupu u nadi da ćemo uskoro moći organizirati i naša već tradicionalna druženja uživo!

Prof. dr. sc. Sanja Hajnšek
Počasna predsjednica Organizacijskog odbora
7. hrvatskog kongresa „Dileme u neurologiji"

Prof. dr. sc. Ervina Bilić
Predsjednica Organizacijskog odbora

Prof. dr. sc. Zdravka Poljaković
Predsjednica Stručnog odbora

Welcome address

On behalf of the Organizing Committee, it is our honor and great pleasure to kindly invite you to the 7th Croatian Congress on Controversies in Neurology with International Participation.

We have been witnessing strong and unavoidable impact of the COVID-19 pandemic on our work, our lives, and thus inevitably our professional and scientific meetings. Therefore, this year's Controversies will be held in the currently customary virtual space in order to maintain due level of the profession, as well as the tradition of experience exchange.

As the year 2020 has turned out to be a year of surprise and new routines, this year's Controversies have been conceived accordingly...

We hereby invite you to join the Controversies 2020 as active participants in the virtual space, as lecturers from your room, as participants in our satellite symposia, virtual corners for discussion with the leading experts in particular fields, or as partners in our expert boards on actual topics.

We feel very pleased that this scientific conference has grown into a traditional Croatian meeting of neuroscientists and international experts in the field of neurology, enabling exchange of experiences and presenting dilemmas from daily practice. With continuous advancement of the profession we have been witnessing results in a multitude of novel concepts, as well as dilemmas and such conferences held in any form available still remain the best way to resolve them.

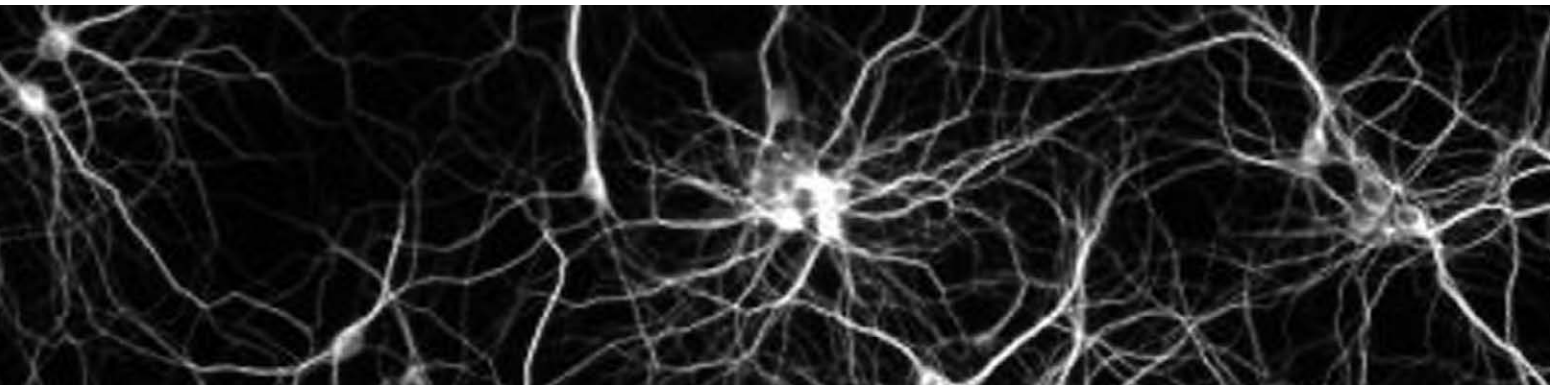
You are invited to join us at this year's on-line meeting, hoping we will be able to organize our traditional in-person meetings soon.

Prof. Sanja Hajnšek, MD, PhD
Honorary President of Organizing Committee
Controversies in Neurology

Prof. Ervina Bilić, MD, PhD
President of Organizing Committee
Controversies in Neurology

Prof. Zdravka Poljaković, MD, PhD
President of Scientific Committee
Controversies in Neurology

Sadržaj / Contents



When to test autonomic nervous system in a patient with transient loss of consciousness?

Ivan Adamec

Department of Neurology, Referral Centre for Autonomic Nervous System Disorders, Zagreb University Hospital Centre, Zagreb, Croatia

Syncope is an episode of transient loss of consciousness caused by global cerebral hypoperfusion. The loss of consciousness develops quickly, lasts shortly and is followed by full recovery. During their lifetime, about one-third of the population will experience syncope. In most cases, syncope can be diagnosed based on typical clinical presentation with corroboration of the event circumstances from a bystander. If the loss of consciousness episodes are atypical or are frequently repeating, autonomic nervous system testing should be performed. In the context of syncope, the most important part of autonomic nervous system testing is the tilt table test. With this test, the subject is exposed to orthostatic stress by passive lifting of the table in controlled laboratory conditions. After 10 minutes of lying down, the table is raised to 70° from the horizontal and the subject spends the next 10 to 40 minutes in this position, depending on the specific protocol, with possible provocation by painful stimuli or nitroglycerin. A positive response is orthostatic hypotension or vasovagal syncope, which can confirm the diagnosis. The tilt table test has a special value in the differential diagnosis of syncope and epileptic seizures, as well as psychogenic pseudosyncope. Since cardiovascular inhibitory syncope can cause additional symptoms during loss of consciousness, such as tonic cramps, myoclonic limb twitching, head and gaze deviation, urination, this type of syncope can be mistaken for an epileptic seizure and tilt table testing is useful for confirmation of such a form of syncope.

Migraine in women of reproductive age

Koraljka Bačić Baronica

Sveti Duh University Hospital, Zagreb, Croatia

Migraine is the most common neurological disorder. Women are three times more likely to have migraine than men, and it is most common between the ages of 18 and 55. These are the peak productive years in life, so migraine has a great personal, familial and societal impact and represents a big burden. However, migraine in women of reproductive age is associated with some specific issues such as using hormonal therapy as contraception or for medical reasons, family planning and using prophylactic and abortive therapy during pregnancy and lactation. Clinical experience points to the role of hormones in migraine and studies have elucidated their effects on migraine pathophysiology and clinical features. The lecture will cover the role of sex hormones in migraine. Current expert opinion for choosing the right contraceptive or sex hormones required for medical reasons in each migraine subtype according to the associated risk of ischemic stroke will be presented since there are no guidelines based on high-quality evidence. Family planning and using specific and nonspecific prophylactic therapy for migraine will also be discussed. Guidelines about prescribing abortive therapy, specific and nonspecific prophylactic therapy in pregnancy and lactation period will also be evaluated.

Acute inflammatory demyelinating syndromes

Barbara Barun

Department of Neurology, Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Zagreb, Croatia

Acute inflammatory demyelinating syndromes are rare disorders that differ from multiple sclerosis (MS) by unusual clinical or magnetic resonance imaging findings or poor response to treatments used for MS. Acute demyelinating encephalomyelitis (ADEM) is an acute monophasic inflammatory demyelinating disease of the central nervous system. It can occur at any age but it mainly affects children and young adults. The disease may be preceded by an infectious disease or, less frequently, by vaccination. Acute hemorrhagic leukoencephalitis (AHLE), also known as Weston-Hurst syndrome, is a rare and severe variant of ADEM first described in 1941. AHLE is characterized by prominent edema and acute hemorrhagic lesions although some subacute cases have also been reported. Mortality rate is up to 70%. Marburg's variant of MS is an acute fulminant form of demyelinating disease. Patients typically present with seizures, headache, vomiting, bilateral optic neuritis, and gait disturbance with hemiparesis or quadriparesis. Symptoms progress rapidly, often stepwise or continuously. The clinical and radiological features of Marburg's MS suggest that this disorder could be an intermediate entity between tumefactive demyelination and ADEM. Schilder's disease is said to be a rare demyelinating disease characterized with bilateral symmetric lesions and seen most frequently in children. Since description of Schilder's disease predates studies of other atypical demyelinating syndromes and of AQP4-IgG and MOG-IgG testing, it remains unclear whether Schilder's disease is distinct from other atypical demyelinating syndromes. Tumefactive demyelination and Baló's concentric sclerosis are most closely associated with prototypical MS.

When to test autonomic nervous system in sleep disorders?

Barbara Barun

Department of Neurology, Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Zagreb, Croatia

There is bidirectional interplay between the autonomic nervous system (ANS) function and sleep regulation. Many patients with ANS impairment have some form of sleep disruption and the majority of patients with untreated sleep disorders will describe symptoms of autonomic impairment. Neuronal networks that help regulate the sleep and waking state are closely located to cell populations that help regulate autonomic function. It is often difficult to measure autonomic fluctuations during sleep due to the disruptive nature of beat-to-beat blood pressure monitors. Spectral analysis of the RR interval is an indirect and noninvasive alternative. As sleep progresses from stage 1 NREM sleep to the deeper stages 2 and 3 NREM sleep, parasympathetic tone increases, resulting in progressive reduction in heart rate, blood pressure and cardiac output. Comparing to NREM sleep, REM sleep is a state of autonomic instability. Sleep deprivation alone can increase sympathetic drive. Patients with insomnia may develop increased diurnal sympathetic drive, leading to clinical presentation of hyperarousal. Obstructive sleep apnea (OSA) may lead to increased sympathetic tone and diminished baroreceptor sensitivity, thus increasing the risk of hypertension, cardiovascular and cerebrovascular disease and atrial fibrillation. Every person with cardiovascular and cerebrovascular disease should be screened for OSA. The autonomic imbalance in narcolepsy patients is likely to be directly related to the loss of hypocretin cells in the hypothalamus. Narcolepsy patients are more likely to be non-dippers, a phenomenon that has been associated with greater cardiovascular risk in other sleep disorders.

Seizure prophylaxis – con

Silvio Bašić

Department of Neurology, Dubrava University Hospital, Referral Centre for Preoperative Assessment of Patients with Pharmacoresistant Epilepsy, Zagreb, Croatia

Prophylactic use of antiepileptic drugs (AEDs) generally is not recommended. AEDs should only be prescribed after the diagnosis of epilepsy has been established, rather than for prevention of seizures in a patient without epilepsy. However, AEDs have been used worldwide as prophylactic drugs, primarily in high-risk intensive care unit patients and in patients with brain tumors. When considering AED prophylaxis, there is a huge question rising regarding its purpose – to prevent acute seizures or epilepsy? There are conflicting data in the literature regarding prophylactic AED treatment, mostly in observational studies. No clinical trial with a high level of evidence for the benefit of AED use in the prevention of acute seizures and especially epilepsy has been reported to date. Thus, AED prophylaxis is more frequent in the settings where other specialties (neurosurgeons, intensive care specialists, anesthesiologists, etc.) are taking care of patients with brain insults, probably due to a lower degree of epileptology knowledge or more probably due to the unjustified fear of possible seizures. Anyway, regarding the setting in which it is often used and difficulties in demonstrating its efficiency, the prophylactic use of AEDs will remain a 'gray zone' for which it will be very difficult to find clear conclusions regarding its general justification.

Autonomic nervous system testing in stroke

Danira Bažadona

Department of Neurology, Zagreb University Hospital Centre, Zagreb, Croatia

Autonomic nervous system (ANS) dysfunction accompanying stroke leads to greater mortality and morbidity rates. ANS dysfunction was shown to be dependent on lesion location, laterality, size and stroke severity. According to some yet quite opposite results, the etiology of stroke may also influence the severity of ANS dysfunction. Heart rate variability (HRV) is one of the ANS function tests mostly used in stroke patients because of its availability and noninvasiveness. HRV reflects interval fluctuations between two sequential heartbeats by measuring the amount of heart rate fluctuation around the mean heart rate. It reflects the balance between the sympathetic and parasympathetic nervous system. Although it is more difficult to administer in moderate and severe stroke patients, a battery of tests for ANS function has been shown useful, the results being in concordance with those obtained by HRV measurement. Decreased HRV is associated with well-known risk factors for stroke. Commonly used ABCD2 score has only moderate predictive value in the evaluation of recurrent ischemic events, so HRV measurement could be a new tool for risk stratification and outcome prognosis of stroke and transient ischemic attack patients. ANS dysfunction in stroke is an often overlooked problem. ANS testing in patients with cerebrovascular diseases could increase the accuracy of risk stratification management and offer new therapeutic strategies for stroke prevention and treatment in the future.

Successful screening tool for Alzheimer's disease: reality or fiction?

Danira Bažadona[1], Fran Borovečki[1,2]

[1]*Department of Neurology, Zagreb University Hospital Centre, Zagreb, Croatia*
[2]*University of Zagreb, School of Medicine, Zagreb, Croatia*

Alzheimer's disease (AD) is a growing public health issue due to aging of the population, presenting a great need for highly sensitive and specific tests that would allow preclinical diagnosis of mild cognitive impairment (MCI) and AD, thus enabling timely intervention. Episodic memory impairment and spatial navigation deficit are often considered to be the first symptoms of cognitive impairment due to neurodegenerative changes in the structures of the medial temporal lobe, particularly due to AD. Several approaches have been developed with the aim of early diagnosis of AD, such as hidden goal test (HGT), beta-amyloid and tau PET or measuring plasma levels of beta amyloid. HGT has been developed and used for detection of spatial navigation deficit in MCI patients. HGT allows for testing of both allocentric and egocentric spatial orientation. The main task in HGT for the subject is to find an invisible goal using its relation to the starting position and/or orientation cues. Research conducted in 33 MCI patients and 91 healthy control subjects showed statistically significant between-group differences in the average error measured in allocentric, egocentric and combined allocentric-egocentric subtests. The high negative predictive values suggested high discriminative capacity and diagnostic potential for HGT as a tool to detect subjects in healthy population who will progress to MCI. HGT has proved to be a good screening tool, but also a good confirmatory diagnostic test. Used in combination with other biomarkers, HGT can improve early identification of MCI patients who will convert to AD.

Autonomic dysfunction and polyneuropathy

Ervina Bilić

Department of Neurology, Referral Centre for Neuromuscular Diseases and Clinical Electromyoneurography, Zagreb University Hospital Centre, University of Zagreb, School of Medicine, Zagreb, Croatia

Autonomic dysfunction may be present in a broad spectrum of neuromuscular diseases, from inherited myopathies, motor neuron diseases (spinal muscular atrophy, amyotrophic lateral sclerosis) to autoimmune diseases primarily affecting neuromuscular junction. However, from the clinical point of view, autonomic function is most important in polyneuropathies, especially in small fiber neuropathies such as diabetic neuropathy or amyloidosis associated neuropathy (transthyretin or any other). Small fiber sensory neuropathy (SFSN) is a disorder in which only the small sensory cutaneous nerves are affected. The majority of patients experience sensory disturbances that start in the feet and progress upwards. These patients have what is called length-dependent SFSN. This type of SFSN is often due to diabetes or impaired glucose metabolism (i.e. early or pre-diabetic state) and may progress to typical diabetic polyneuropathy. However, in a significant percentage of patients, no underlying etiology is found and patients have idiopathic SFSN. A small percentage of patients with SFSN experience subacute onset sensory disturbances diffusely over the whole body, including the trunk and sometimes even the face. These patients have non-length-dependent SFSN and almost all cases are idiopathic. The symptoms of SFSN are primarily sensory in nature and include unusual sensations such as pins-and-needles, pricks, tingling and numbness. Some patients may experience burning pain or coldness and electric shock-like brief painful sensations. Pain in the feet and hands are the most common symptoms of SFSN. However, this condition can also reduce the body's ability to feel pain in a concentrated area and sense temperature. As the disease progresses, people may notice symptoms in their knees, legs and arms. Other symptoms of SFSN include tingling or prickling sensation (paresthesia), hypersensitivity to touch and temperature changes, numbness in the feet, legs or lower stomach, bladder control issues, constipation, sexual dysfunction, excessive or infrequent sweating, skin discoloration, dry eyes and mouth, extremely low blood pressure that may cause fainting, and rapid or irregular heartbeat. Symptoms of SFSN can range from mild to severe. In the early stages, people often experience mild symptoms that may go unnoticed. Over time, symptoms typically worsen and progress to other areas of the body. Sudomotor dysfunction is one of the earliest detectable neurophysiologic abnormalities in distal SFSN. Sweat glands are innervated by small, unmyelinated sympathetic C nerve fibers that are responsible for the sweat response. Degeneration of small C-fibers innervating sweat glands has been observed in diabetes patients. Diagnosis of SFSN is based on history, clinical examination and supporting laboratory investigations. Electromyography and nerve conduction studies are performed to eliminate involvement of motor and large sensory nerve fibers. Skin biopsies are used to confirm loss of cutaneous nerve innervation. Nerve and muscle biopsies are rarely needed. Quantitative sensory testing (QST) is a noninvasive optimal diagnostic approach to patient with SFSN. Abnormalities in sudomotor function in diabetes patients were found to correlate with the presence of autonomic neuropathy. Thus, sudomotor function represents an attractive tool to evaluate the peripheral autonomic system in people with diabetes mellitus.

Neuropathy in oncology – to treat or retreat?

Ervina Bilić

Department of Neurology, Referral Centre for Neuromuscular Diseases and Clinical Electromyoneurography, Zagreb University Hospital Centre, University of Zagreb, School of Medicine, Zagreb, Croatia

Neuropathy is a common finding in a significant proportion of persons suffering from various oncologic diseases. There are several proposed mechanisms that may lead to neuropathy in the field of oncology, e.g., chemotherapy-induced (iatrogenic toxic), paraneoplastic, irradiation-induced, infective due to neurotropic virus reactivation/infection, caused by malnutrition or other joined diseases. In clinical practice, we are faced with great inter-individual differences, even in the same branch of oncology or in the same treatment protocol. The background of such a broad spectrum of possible causes leads to at least few pathophysiologic mechanisms present in each patient (for example, toxic and malnutrition, vitamin deficiency and irradiation, etc.). Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common adverse effects of chemotherapeutic agents, limiting the use of many chemotherapy regimens. The prevalence of this disabling pain condition reaches up to 68% in the short term when receiving chemotherapy. The severe pain of CIPN causes loss of functional abilities and decreases patient quality of life. The additional financial burden and waste of medical resources caused by CIPN cannot be ignored either. The neuropathogenesis of CIPN is still unclear. Multifactorial pathologic processes may be involved, including oxidative stress, apoptosis, altered calcium homeostasis, immune response, glutamate signaling, ectopic activation of MAP-kinases and nociceptors, and neuroinflammation. Accumulating research has indicated that the production of reactive oxygen species is a significant cause of peripheral neuropathy induced by chemotherapy. The main challenge in CIPN is to choose optimal causative and symptomatic treatment, which will not interfere with oncologic treatment efficacy. In toxic neuropathies, one usually finds axonal damage due to cytoskeleton damage or altered apoptotic mechanisms, while in autoimmune neuropathies the typical finding is large fiber demyelinating damage. Immunity also may play an important role in neuropathy development in many oncologic, especially hemato-oncologic diseases such as the graft *versus* host disease (GVHD). Increasing the safety of allogeneic hematopoietic stem cell transplantation (allo-HSCT) has also increased the number of patients at risk of developing chronic GVHD (cGVHD), which is a major late cause of post-transplant non-relapse mortality and morbidity. Mitochondrial and endoplasmic reticulum damage seems to play a role in toxic neuropathy development, since some therapeutic agents may activate the mitochondrial-based apoptotic pathway. It is known that peripheral neuropathy is a well-recognized manifestation of mitochondrial inherited diseases. It is possible that changes in mitochondrial dysfunction may contribute to the appearance of neuropathy in diabetes, as this too is associated with small fiber neuropathy. Chronic GVHD affects up to 50% of patients who are long-term survivors. Neurological manifestations of cGVHD are being increasingly recognized, with peripheral nervous manifestations being by far most common. This involvement can occur at any level of the peripheral nervous system, including the peripheral nerve, the neuromuscular junction, or the muscle and adjacent fascia. Neurological manifestations can usually occur several months to years after allo-HSCT and have to be distinguished from different infectious and metabolic complications, as well as from the side effects of the potentially neurotoxic drugs. Neuropathies in cGVHD can be acute or chronic, mostly resemble Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy or other type of chronic immune-mediated axonal polyneuropathy.

Peripheral nerve in internal medicine

Ivica Bilić

Department of Neurology, Split University Hospital Centre, School of Medicine, University of Split, Split, Croatia

Peripheral neuropathy encompasses a broad range of disorders characterized by damage to nerves after they exit the central nervous system with clinical manifestations including weakness, pain, numbness, tingling, and/or autonomic dysfunction depending on the type of peripheral nerve involved. Peripheral neuropathies are common, occurring in up to 10% of the general population. Symptoms can range from mild to disabling and rarely are life threatening. Usually symptoms develop over weeks or months. Neuropathy can affect one nerve (mononeuropathy), or two or more nerves in different areas (multiple mononeuropathy or mononeuropathy multiplex), but most often affecting many nerves (polyneuropathy). Neuropathies can often be misdiagnosed and very often are underdiagnosed. Peripheral nerve disturbances can be found in various disorders in internal medicine such as diabetes, systemic autoimmune diseases, vascular and blood problems that decrease oxygen supply to peripheral nerves, hormonal imbalances, kidney and liver disorders, nutritional or vitamin imbalances, alcoholism and exposure to toxins, certain cancers and benign tumors, during usage of chemotherapy drugs, and in various infections. Neurological manifestations of various diseases in internal medicine are important to recognize, as they may often be the presenting manifestation leading to diagnosis of a systemic disease or may be associated with increased morbidity, other complications or mortality. Diagnosis of peripheral neuropathy usually includes medical history, physical and neurological examination, body fluid tests and genetic testing. Additional tests can be ordered such as nerve conduction velocity testing, electromyography, nerve biopsy or skin biopsy. Radiology imaging tests (magnetic resonance imaging or computed tomography) are not so much helpful in these conditions as in other neurology topics, and muscle and nerve ultrasound is a somewhat novel diagnostic method the contribution of which in diagnosing peripheral neuropathies is still to be defined. Accurate diagnosis and recognition of peripheral nerve damage in systemic diseases and conditions often require multidisciplinary care and can be essential in minimizing morbidity and decreasing the risk of permanent neurological damage.

Diagnosis of Alzheimer's disease based on biological characteristics

Marina Boban

Department of Neurology, Referral Center for Cognitive Neurology and Neurophysiology, Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Zagreb, Croatia

At the beginning, Alzheimer's disease (AD) was defined as a clinicopathological entity diagnosed during lifetime as probable or possible AD, while definitive diagnosis was only established at autopsy. Over time, significant progress in the field of biomarkers for AD led to establishing diagnostic recommendations for preclinical, mild cognitive impairment and dementia stages of AD. These recommendations were published in 2011 and were based on the additional use of amyloid and tau biomarkers for establishing the diagnosis of AD. With the growing use of *in vivo* biomarkers and based on neuropathological studies of AD, two distinct entities were recognized indicating the possibility of mismatch between clinical presentations and pathological findings in AD, i.e. a group of atypical AD presentations (with positive AD pathology but atypical, non-amnestic presentations, so called AD chameleons) and a group of AD mimics (with typical AD clinical presentation and no AD pathology). Based on these findings, a unifying update of the 2011 guidelines was presented in 2018 by the National Institute on Aging and Alzheimer's Association as a Research Framework not intended for use in routine clinical practice, but rather for observational and interventional research. In the Research Framework, AD is diagnosed based on the underlying pathologic processes that can be detected by using available biomarkers *in vivo* with omitting clinical symptoms/signs of the disease. Biomarkers (imaging or fluid) in the Research Framework are grouped into those of amyloid-β deposition (CSF Aβ42, or Aβ42/Aβ40 ratio, amyloid PET) [A] or tau deposition (CSF phosphorylated tau, tau PET) [T], and neurodegeneration (anatomic MRI, FDG PET, CSF total tau) [(N)]. This ATN classification shifts the definition of AD in living people from a syndromal/clinical to a biological construct. Additionally, this biomarker-based Research Framework outlines two cognitive schemes for staging of the severity of cognitive impairment, i.e. a scheme using three traditional syndromal categories and a six-stage numeric scheme using ATN biomarkers.

Infectious etiology of demyelinating changes

Marija Bošnjak Pašić[1,2]

[1]*Division of Neuroimmunology of the Central Nervous System, Department of Neurology, Referral Centre for Demyelinating Diseases of the Central Nervous System, Zagreb University Hospital Centre, Zagreb, Croatia*
[2]*School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia*

Correct diagnosis of demyelinating lesions in the central nervous system (CNS) is very important both for therapeutic and prognostic purposes. However, assigning the correct diagnosis is not always easy. The diagnosis is most often assigned based on patient history, clinical picture and paraclinical tests (above all radiological imaging of the brain and spinal cord with magnetic resonance (MRI), analysis of cerebrospinal fluid and other laboratory tests). The most common inflammatory, autoimmune demyelinating disease of the CNS is multiple sclerosis (MS). It is also significant because it is an incapacitating disease of young people. Henceforth, it is important to assign correct diagnosis in order to appropriately treat and to stop or halt its progression. When we speak about differential diagnosis of demyelinating diseases which have to be excluded on assigning the diagnosis of MS, it is important to exclude infectious diseases. The most common chronic infections are *Borrelia burgdorferi* (Lyme disease), *Treponema pallidum* (syphilis), *Brucella melitensis* (brucellosis), *Bartonella henselae* (cat scratch disease), *Mycoplasma pneumoniae*, *Rickettsia conorii* (Mediterranean spotted fever), HIV, human T-lymphotropic virus types 1 and 2, human herpesvirus 6, hepatitis C, JC virus (progressive multifocal leukoencephalopathy), Leptospira serovars (leptospirosis), and Creutzfeldt-Jacob disease. The aim is to show some rare cases from clinical practice which are very important in the differential diagnosis of MS or are a consequence of treatment with certain drugs.

What is a pseudosyncope?

Tereza Gabelić

Department of Neurology, Zagreb University Hospital Centre, Zagreb, Croatia

Pseudosyncope is the occurrence of transient loss of consciousness in the absence of true loss of consciousness. Most cases of pseudosyncope are classified as a conversion disorder, which is assumed to be a physical manifestation of internal stressors. The incidence of pseudosyncope is probably not sufficiently recognized, but it is important to consider it in the differential diagnosis of syncope. As with syncope of other etiologies, it is extremely important to take a detailed medical history from which the clinician collects important data on the symptoms that preceded the loss of consciousness, the duration of loss of consciousness, and the possible neurological signs during the loss of consciousness. People with pseudosyncope are more likely to be young women with an increased number of episodes in the last 6 months, and pseudosyncope itself may be preceded by dizziness, shortness of breath and tingling, which can be a diagnostic challenge since vasovagal syncope may have similar prodromal symptoms. Regarding diagnostic methods, testing of the autonomic nervous system is the gold standard in distinguishing different types of syncope. Understanding the epidemiology, biological basis, and approach to the diagnosis of pseudosyncope is important in order to improve the recognition of this disorder so that patients can be adequately assisted while avoiding lengthy, costly, and potentially dangerous extensive diagnostic procedures. The general approach to treatment includes limiting unnecessary interventions, providing the necessary support to the patient, as well as encouraging functionality in order to preserve the quality of life.

Genomic diagnostics of epilepsies

Kristina Gotovac Jerčić[1], Fran Borovečki[1,2]

[1] *Department of Neurology, Zagreb University Hospital Centre, University of Zagreb School of Medicine, Zagreb, Croatia*
[2] *Department of Functional Genomics, Centre for Translational and Clinical Research, Zagreb University Hospital Centre, University of Zagreb School of Medicine, Zagreb, Croatia*

Rapid progress of genetic diagnostic methods and application of genomic technologies has revealed the genetic basis of many neurological diseases that were traditionally characterized as idiopathic. Epilepsy is the fourth most common neurological disorder characterized by recurrent epileptic seizures. It is now thought that 70%-80% of epilepsy cases have a genetic cause, whilst the remaining 20%-30% are due to acquired conditions such as brain trauma, stroke and tumors. Previous diagnostic methods enabled analysis of single genetic mutations, making determination of the causal mutation time consuming, expensive, and very often not detectable. The precise differential diagnosis of epilepsies is challenging due to their genetic heterogeneity, phenotypic similarities and overlapping symptoms. The most commonly used molecular diagnostic technique applied in the diagnosis of complex diseases is next generation sequencing (NGS). We have applied our custom designed epilepsy panel that consists of 142 genes and exome sequencing in patients with epilepsy, which enables identification of causative variants in patients in whom standard diagnostic procedures failed to identify a clear genetic cause of disease. These results offer further proof that NGS approaches represent powerful tools for establishing a definitive diagnosis and can improve treatment efficacy.

When to test autonomic nervous system in a patient with multiple sclerosis?

Mario Habek

Department of Neurology, Referral Centre for Autonomic Nervous System Disorders, Zagreb University Hospital Centre, Zagreb, Croatia

Multiple sclerosis (MS) is the leading cause of neurological disability in young adults. Although it is recognized that autonomic nervous system (ANS) is frequently involved in MS and there is evidence from the laboratory and clinical standpoint that it may be implicated in the pathophysiology of MS, there is still no clear answer when to test the ANS in a patient with MS. In this presentation, we will try to answer this question.

In a patient with first clinical event suggestive of MS – clinically isolated syndrome (CIS): with the increasing number of highly efficacious disease modifying therapies available for the treatment of MS, it has become even more relevant to early identify patients who will have significant disease activity and/or progression in the nearer or later future. Studies on large cohorts of pwCIS have shown that demographic and topographic characteristics are low-impact prognostic factors, the presence of oligoclonal bands is a medium-impact prognostic factor, and the number of lesions on brain magnetic resonance is a high-impact prognostic factor for development of future disease activity and disability progression. Beside these well-known factors, ANS has recently been identified as an important contributor to the development of disease activity in MS. Autonomic symptom burden and low levels of serum epinephrine have been associated with the development of first relapse after CIS.

In a patient with suspected progressive form of MS, differentiating between relapsing and progressive forms of MS can sometimes be a troublesome task for the clinician. Studies have shown that there is a significant difference in the autonomic function between these two disease phenotypes, with progressive MS having a higher burden of autonomic dysfunction compared to relapsing forms, which is particularly evident for sweating dysfunction. Furthermore, MS phenotype corrected for age, sex and disease duration was a statistically significant predictor of the degree of autonomic dysfunction.

In patients with MS starting S1P receptor modulators, it has been shown that MS related ANS dysfunction may be associated with a fingolimod and/or siponimod related decrease in heart rate (HR) at treatment initiation. Several studies on fingolimod investigated predictors of this decrease in HR after treatment initiation. The common finding in all of them is that parasympathetic nervous system dysfunction is predictive of either fingolimod induced bradycardia or the requirement of extended monitoring, which is an indirect measure of HR abnormalities. Similarly, heart rate variability parameters reflective of parasympathetic nervous system function were identified as predictors of HR decrease.

Calcitonin-gene related peptide and migraine

Davor Jančuljak

Department of Neurology, Osijek University Hospital Centre, Osijek, Croatia

Calcitonin-gene related peptide (CGRP) is a widespread neuropeptide in the central and peripheral nervous systems. There are several receptors on which the CGRP molecule acts; for the pathophysiology of migraine, its binding to the CGRP receptors in the trigeminovascular system is the most important event. Evidence supporting the key role of CGRP in the pathophysiology of migraine is based primarily on several findings from clinical trials. Serum and saliva CGRP concentrations are increased during migraine attacks. Triptans reduce CGRP levels, which coincides with the migraine pain relief phase. Intravenous administration of CGRP may cause a delayed moderate to severe migraine condition, suggesting that CGRP may play a role in the onset of pain in people prone to migraines. Finally, selective CGRP receptor antagonists can effectively alleviate both pain and associated migraine symptoms. CGRP plays a key role in neurogenic inflammation, mast cell degranulation, vasodilation, sensory signaling activation, and peripheral sensitization. The CGRP neuropeptide is abundantly present in trigeminal ganglion neurons and is released from peripheral nerves as it is secreted within the trigeminal ganglion. The release of CGRP from peripheral branches (C fibers) triggers a cascade of events involving increased nitric oxide synthesis and trigeminal nerve hypersensitivity. The secreted CGRP in the trigeminal ganglion interacts with neighboring neurons and satellite glial cells. Neurons in the trigeminal ganglion with A delta fibers have CGRP receptors where excessive CGRP release in a migraine attack stimulates neurons in a state of pain maintenance and leads to peripheral sensitization, causing later central sensitization in the nucleus caudalis spinalis n. trigemini.

Cognitive training – new therapeutic approach to patients with mild cognitive impairment

Nataša Klepac

Department of Neurology, Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Zagreb, Croatia

Cognitive training (CT) has attained attention as a non-pharmacological approach to maintain cognition in older adults. CT involves guided drill-and-practice on standardized tasks designed to load on specific cognitive processes, typically without explicit teaching of memory or problem-solving strategies. CT can target multiple domains and usually adapts task difficulty to individual performance. Recent randomized control trials and meta-analyses of experimental studies indicate positive effects of CT on the cognitive function of healthy older adults but also patients that demonstrate impaired cognitive functions for several reasons. Furthermore, a large-scale randomized control trial with older adults, independent at entry, indicated that CT delayed their cognitive and functional decline over a five-year follow-up. This supports CT as a potentially efficient method to postpone cognitive decline in persons with mild cognitive impairment (MCI) and CT as a therapeutic option able to prevent or delay cognitive or functional decline. Training in the elderly with MCI had greater effect in the younger old and more cognitively preserved individuals. In MCI, CT is efficacious on global cognition, memory, working memory and attention, and helps improve psychosocial functioning, including depressive symptoms. The effect of CT was corroborated by a moderate effect size on common clinical measures of global cognition (mainly the Mini-Mental State Examination). Moderate effect sizes on memory are encouraging, as amnestic MCI profiles are at a higher risk of dementia conversion. Participants in CT groups improved significantly over the intervention period but there are still insufficient data to determine whether training gains can be maintained over long-term without further training. Cognitive interventions can contribute to promoting health and independence among patients with MCI. Further investigations in large samples with long follow-up period are now warranted to verify the role of cognitive interventions as a reliable tool to prevent cognitive functions and wellbeing.

Peripheral nerve trauma – a challenge in electromyoneurography laboratory

Biserka Kovač

Department of Neurology, Vukovar National Memorial Hospital, Vukovar, Croatia

Peripheral nerve injuries include a variety of conditions in which one or more peripheral nerves are damaged leading to neurological deficits distally to the level of lesion. Peripheral nerve injuries may occur as isolated neurological conditions or, more commonly, in association with soft tissue, vascular and bone damage. In patients with polytrauma, associated peripheral nerve injures can often be overlooked. The diagnosis is based on clinical assessment and electrodiagnostic examination by electromyoneurography (EMNG). Interpreting EMNG findings and explaining the electrophysiological pattern is not an easy task, as it depends on the time that has elapsed from the peripheral nerve trauma to the time when the examination is performed and on the understanding the pathophysiological and pathomorphological processes that have occurred and continue on the damaged nerve at the time of examination. The main task of the neurologist performing EMNG is to determine the location and degree of damage to peripheral nerve using detection electromyography (EMG) and conductivity studies of peripheral motor and sensory fibers. Slowing of the conduction velocity or block of conduction through the injured segment of a peripheral nerve without denervation potentials at rest indicates injury to the myelin sheath of the nerve. It could be a predictor of good prognosis, but it can also occur in complete nerve sections or in secondary axon damage, as well as in mixed injuries (axon and myelin) at different sites of the same axon or at individual axons of the same nerve. All of the above leads to difficulties in interpreting the EMNG findings. Clinical and electrophysiological monitoring of patients with peripheral nerve trauma is highly required. In patients in whom recovery does not occur even after 3-6 months, it is necessary to decide on surgical intervention with graft insertion to bridge the injury site. Regardless of the applied method of treating peripheral nerve trauma, EMNG can objectify nerve recovery very well in line with clear improvement in clinical neurological findings.

How to speed up analysis of ANS biosignals?

Magdalena Krbot Skorić

Department of Neurology, Referral Centre for Autonomic Nervous System Disorders, Zagreb University Hospital Centre, Zagreb, Croatia; School of Electrical Engineering and Computing, University of Zagreb, Zagreb, Croatia

Autonomic nervous system (ANS) regulates important systems in the human body such as heart rate, digestion, respiratory system, etc. Its dysfunction is related to different disorders and information on dysfunction is presented in the ANS biosignals. Due to the increased number of different types of ANS testing techniques and data acquisition, digital signal processing (DSP) techniques are a useful tool for gathering information on the functional state of the ANS. With the development of testing methods, the amount of acquired data increases significantly. The majority of data are processed manually, which usually is a time-consuming process and its results depend on subjective assessment, hence being prone to human error. Because of this, there is a need to objectify the processes of signal analysis, which could be performed with automation of ANS biosignal analysis. Examples emphasizing this problem are DSP methods for analysis of heart rate variability (HRV) and baroreflex sensitivity (BRS) indices. HRV analysis is frequently used, it has well defined protocols and mathematical definitions, and because of that is suitable for machine learning, risk prediction modeling and artificial intelligence methods. BRS indices provide information on baroreflex vagal and adrenergic components. Automated calculation of BRS indices enhances the speed and precision, as the same criteria are applied for pre-processing and feature extractions. Automation of the ANS biosignals processing considerably reduces subjective assessment and the likelihood of human error, the process is time-saving, and enables analysis of a large amount of data.

Vascular lesions in the differential diagnosis of demyelinating diseases

Ivan Martinez

Department of Neurology, Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Zagreb, Croatia

Multiple sclerosis (MS) is a complex disease and its clinical and radiological heterogeneity often makes its diagnosis challenging. In our daily work, we are frequently asked to consult on patients with incidentally observed abnormalities on brain magnetic resonance imaging (MRI) that may be suggestive of MS. Misinterpretation of such MRI findings is a frequent contributor to misdiagnosis of MS. Lesion location, morphology and number are important considerations when assessing MRI for fulfillment of MS criteria, particularly in patients of older age at presentation, with atypical syndromes and red flags atypical for MS. Lesions typically observed in MS are larger than 3 mm^2, ovoid, well circumscribed, and homogeneous in signal character, distributed mainly in the periventricular, cortical, juxtacortical, infratentorial and spinal cord regions. Nonspecific white matter changes tend to be punctate in character, nonovoid, and frequently located within subcortical regions. In the cases presented, I want to emphasize the importance of vascular brain lesions in the differential diagnosis of MS. Most of the incidentally found white matter lesions will have a vascular origin. Vascular causes of white matter disease are arteriosclerosis, emboli, vasculitis, systemic diseases and diabetes. Ischemic white matter lesions present as lacunar infarcts, watershed infarcts or diffuse hyperintense lesions within the deep white matter. Lacunar infarcts are due to arteriolar sclerosis of small penetrating medullary arteries. Watershed infarctions are the result of atherosclerosis of larger vessels, for instance carotid obstruction, or of hypoperfusion. Atherosclerotic brain changes are seen in 50% of patients older than 50 years. They are found in normotensive patients, but are more common in hypertensives.

Functional movement disorders

Vladimir Miletić

Department of Neurology, Zagreb University Hospital Centre, Zagreb, Croatia

Functional neurological disorders (FNDs) are among the most common neurological causes of disability. Functional movement disorders (FMDs) are part of the FND spectrum, and are defined as abnormal involuntary movements that are incongruent with known neurological conditions and have no organic neuroanatomical background. Throughout the history of modern medicine, various terms have been used to describe conditions without organic etiology, such as 'conversion', 'hysteria', 'somatization' and 'psychogenic disorders'. Today, the term 'functional', which is less offensive and stigmatizing and more acceptable to patients, is used to describe these disorders. This enabled a new shift in thinking about FND and departure from the previously present focus on psychological factors as the main precipitating determinants for the development of FND. According to the results of epidemiological studies, almost 16% of patients referred to a neurologist have FND. The incidence of FND is estimated at 4-12/100000 inhabitants *per* year, and the prevalence is 50/100000 inhabitants. In their clinical presentation, FMDs can mimic all organic movement disorders, so clinical distinction is prone to error due to the exceptional clinical overlap of symptoms. Therefore, the evaluation of patients with possible FMDs requires skills and knowledge about the clinical features of various movement disorders, detailed and targeted taking history data, and conducting neurological examination to identify 'positive' clinical signs. The diagnosis of FMDs should not be made by excluding organic disease, but should be based on 'positive' criteria, such as identification of the characteristic clinical signs incongruent with known organic disorders. The first step in treating FMDs is to convince the patient of the diagnosis process itself and the importance of accepting it. For now, there is no consensus on the optimal treatment strategy. The aim of the presentation is to provide basic insights into the clinical picture of FMDs and 'positive' clinical signs.

When to perform autonomic nervous system testing in patients with movement disorders?

Vladimir Miletić

Department of Neurology, Zagreb University Hospital Centre, Zagreb, Croatia

The autonomic nervous system (ANS) regulates multiple essential bodily functions (cardiovascular, thermal, gastrointestinal, urinary, sexual, exocrine) maintaining internal physiologic homeostasis under changing internal and external conditions. The activity of the ANS is predominantly but not exclusively reflexive in nature. The importance of the ANS results from the fact that every organ in the human body is connected to the ANS and consequently regulated by it. The ANS consists of three subdivisions, sympathetic, parasympathetic, and enteric nervous systems. For synchronous and 'orchestral' action of the ANS, proper functioning of the central component/control consisting of insular and anterior cingulate cortex, amygdala, hypothalamus, nucleus solitarius, periaqueductal gray matter and ventrolateral reticular formation is required. Autonomic dysfunction can involve central and peripheral components, and is clinically manifested by a variety of symptoms. It can be caused by either primary neurodegenerative disorders or secondary autonomic disorders such as those that are due to diabetes, trauma, vascular and inflammatory conditions. Disabling symptoms and signs of autonomic dysfunction, such as orthostatic and postprandial hypotension, bowel and bladder disturbances, and erectile failure are frequently observed in neurodegenerative diseases characterized by abnormal accumulation of α-synuclein, such as multiple system atrophy, Parkinson's disease, Lewy body dementia, and pure autonomic failure. It is estimated that almost 90% of patients with Parkinson's disease have one or more symptoms of autonomic dysfunction. Some of the autonomic symptoms may precede motor symptoms for years, thus having potential relevance as putative clinical predictors of the disease. It is traditional belief that contrary to α-synucleinopathies, autonomic dysfunction in neurodegenerative disorders characterized by abnormal accumulation of tau protein is rarely of clinical significance. However, recent studies indicate a significant autonomic dysfunction associated with tauopathies, which is particularly evident in patients with progressive supranuclear palsy. Autonomic dysfunction is a common and serious problem in patients with various movement disorders, having marked influence on the quality of life, and therefore should not be neglected. The aim of the presentation is to highlight the most common symptoms of autonomic dysfunction in patients with movement disorders, and to provide basic knowledge about understanding the results of ANS testing.

Challenges in neurosurgical treatment of epilepsy

Goran Mrak[1], Jakob Nemir[1], Niko Njirić[1], Željka Petelin Gadže[2], Vlatko Šulentić[2], Sibila Nanković[2], Zdravka Poljaković[2], Andreja Bujan Kovač[2], Petra Nimac Kozina[2], Biljana Đapić Ivančić[2], Magdalena Krbot Skorić[2], Marko Radoš[3], Milan Radoš[4], David Ozretić[3], Ivan Jovanović[3], Ratimir Petrović[5], Anja Tea Golubić[5]

[1] *Department of Neurosurgery, Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Zagreb, Croatia; Affiliated Partner of ERN EURACAN*
[2] *Department of Neurology, Referral Centre for Epilepsy of the Ministry of Health of the Republic of Croatia, Affiliated Partner of the ERN EpiCARE, Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Zagreb, Croatia*
[3] *Department of Diagnostic and Interventional Neuroradiology, Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Zagreb, Croatia*
[4] *Croatian Institute for Brain Research, School of Medicine, University of Zagreb, Zagreb, Croatia*
[5] *Department of Nuclear Medicine and Radiation Protection, Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Zagreb, Croatia*

Epilepsy is one of the most common neurological disorders and despite modern medical therapy, seizures are not adequately controlled in 25% of patients and they suffer severe morbidity, disability and social isolation. Over years, surgical treatment of epilepsy has become more sophisticated and accessible in the majority of modern countries. The objective of this review is to report on a series of patients with intractable epilepsy who underwent invasive monitoring and surgery or surgery alone when presurgical noninvasive workout showed clear surgical focus. The main challenge is whether to do a set of presurgical workout or rely on semiology and basic diagnostic procedures (electroencephalogram and 3T magnetic resonance imaging, MRI). Complex MRI positive epilepsy requires further method such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) procedures, and even invasive monitoring. Through several case reports, we will discuss the decision-making process for certain patients. Presurgical workup determines the epileptic zone, the removal of which can lead to seizure freedom with an additional goal to spare the regions that mediate the key neurological functions. Modern imaging and electrophysiological methods reveal more subtle changes within the brain, and without 3T MRI with postprocessing software, PET, SPECT and invasive monitoring, tailored epilepsy surgery will never develop further. Our comprehensive team consists of dedicated neurologists, neuropsychologists, neuroradiologists and neurosurgeons. Hippocampal sclerosis is the most common cause of complex partial epilepsy of the temporal origin. Surgical resection is often the only way to gain seizure freedom in patients due to very common pharmacoresistance associated with that kind of pathology. In our series of over 100 selective amygdalohippocampectomies, seizure freedom was achieved in 85% of cases. Malformations of cortical development are a heterogeneous group of disorders characterized by abnormal cerebral cortical cytoarchitecture. Surgical excision or disconnection are the procedures which commonly end up with seizure freedom if they are not within the functional cortex. Callosotomy is very efficient in patients with drop attack, and we found it very useful when vagus nerve stimulation fails in epilepsy control. In conclusion, current types of surgical resections after invasive monitoring and extensive presurgical workout produce excellent treatment results with a high rate of seizure freedom in up to 60%-80% of cases, and a very low rate of permanent morbidity. In our series of patients, mortality rate was 0% and morbidity rate 4%.

Seizure prophylaxis – pro

Sibila Nanković

Zagreb University Hospital Centre, Department of Neurology,
Referral Centre for Epilepsy of the Ministry of Health of the Republic of Croatia, Zagreb, Croatia

The routine use of seizure prophylaxis after acute brain injury is controversial. Seizure prophylaxis should be considered in high-risk intensive care unit (ICU) patients such as those with acute neurological injury (head trauma, subarachnoid hemorrhage, intracranial hemorrhage) or those undergoing surgery for brain tumors. Critically ill patients with acute brain injury are at a risk of nonconvulsive seizure. To prevent prolonged seizures/status and further complications, electroencephalography monitoring should be considered in ICU patients if there is any suspicion of nonconvulsive seizures. Antiepileptic drugs (AEDs) used for seizure prophylaxis should be chosen on the basis of individual patient characteristics, including concomitant medications and comorbidities in order to avoid drug interactions and severe adverse effects. Some AEDs can be loaded intravenously to rapidly achieve therapeutic concentrations. It is important to limit seizure prophylaxis therapy to those at highest risk, and to choose appropriate drugs and duration of therapy.

Pharmacoresistant epilepsy: possibilities of treatment

Željka Petelin Gadže[1], Vlatko Šulentić[1], Sibila Nanković[1], Zdravka Poljaković[1], Andreja Bujan Kovač[1], Petra Nimac Kozina[1], Biljana Đapić Ivančić[1], Magdalena Krbot Skorić[1], Barbara Sitaš[1], Goran Mrak[2], Andrej Desnica[2], Jakob Nemir[2], Marko Radoš[3], Milan Radoš[4], David Ozretić[3], Ivan Jovanović[3], Ratimir Petrović[5], Anja Tea Golubić[5]

[1] *Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Department of Neurology, Referral Centre of the Ministry of Health of the Republic of Croatia for Epilepsy, Affiliated Partner of the ERN EpiCARE, Zagreb, Croatia*
[2] *Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Department of Neurosurgery, Zagreb, Croatia, Affiliated Partner of the ERN EURACAN*
[3] *Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Department of Diagnostic and Interventional Neuroradiology, Zagreb, Croatia*
[4] *Croatian Institute for Brain Research, School of Medicine, University of Zagreb, Zagreb, Croatia*
[5] *Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Department of Nuclear Medicine and Radiation Protection, Zagreb, Croatia*

Epilepsy is a common neurological disease affecting 1% of the population, which in many instances turns out to be a life-long chronic burden with consequences that can sometimes be quite severe, e.g., excessive bodily injury, neuropsychological and psychiatric impairment, social disability, higher mortality rates, and overall reduced quality of life. The gold standard of epilepsy treatment is permanent therapy with antiepileptic drugs (AEDs) based on the concept of prophylactic suppression of seizure activity. Around one-third of patients have pharmacoresistant epilepsy and interestingly, the proportion of these patients has not considerably changed with the introduction of newer AEDs since the early 1990s. According to the definition of the International League Against Epilepsy, AED resistance is defined as "failure of adequate trials of two tolerated, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve seizure freedom". Current treatment options for these patients include surgical removal of the seizure focus, and alternative approaches such as neurostimulation (vagus nerve stimulation, responsive neurostimulation, deep brain stimulation), ketogenic diet, as well as lifestyle changes. In these patients, nonpharmacological treatment options should be considered early rather than late, but only resective epilepsy surgery can be curative. Epilepsy surgery is an evidence-based treatment option for patients with pharmacoresistant focal epilepsy, with the rate of seizure-free surgical outcomes ranging from 70% to 80% in well-selected cases. Several randomized controlled trials have demonstrated that surgical treatment is safe and effective for pharmacoresistant epilepsy, yet this therapy is still underutilized. There are examples of epileptic syndromes and diagnoses for which epilepsy surgery may be suggested only by noninvasive presurgical diagnostics (mesial temporal lobe epilepsy associated with hippocampal sclerosis, circumscribed epileptogenic lesions (not near eloquent areas), benign neoplasms, vascular malformations, epileptic encephalopathies and multifocal disease (for corpus callosotomy), etc.). In other cases, surgery may be suggested only after additional invasive presurgical diagnostics (temporal lobe epilepsy with discordant electroclinical data, normal magnetic resonance imaging, extratemporal circumscribed epileptogenic lesions close to eloquent area, malformations of cortical development, and dual pathologies). Data from epilepsy surgery studies show that people with shorter epilepsy duration are more likely to be seizure-free at follow-up. In addition, longer epilepsy duration is the only modifiable predictor of impaired adaptive and cognitive development, thus supporting early surgical intervention. Therefore, patients who might benefit from epilepsy surgery should be referred for presurgical assessment without delay. Early surgical intervention for appropriately chosen patients with pharmacoresistant epilepsy offers the best opportunity to avoid lifetime disability and premature death.

Specific *versus* nonspecific preventive treatment of migraine

Damir Petravić

Department of Neurology, Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Zagreb, Croatia

Recognition of the caltitonin gene-related peptide (CGRP) as a key player in the pathogenesis of migraine, highly prevalent primary headache, has resulted in development of specific preventive treatments, i.e. small molecule CGRP antagonists and large molecule monoclonal antibodies targeting CGRP or CGRP receptor. CGRP monoclonal antibodies are highly selective, have an extended biological half-life, are administered monthly or quarterly by subcutaneous injection or intravenous infusion, and require minimal or no dose titration. These large molecules appear ideally suited for migraine prevention. According to phase III studies, CGRP monoclonal antibodies are effective, safe and well tolerated for the preventive treatment of both episodic and chronic migraine. Long-term effectiveness and safety determination will require broad exposure in heterogeneous migraine patient populations in clinical practice. CGRP monoclonal antibodies have distinct advantages over currently available oral nonspecific preventive drugs, which will be discussed.

Critically ill and septic patient in neurological intensive care unit – how important is the right nutritional approach?

Zdravka Poljaković

Department of Neurology, Zagreb University Hospital Centre and School of Medicine, University of Zagreb, Zagreb, Croatia

Although weight changes are not easy to evaluate in the intensive care unit, most of the patients suffer malnutrition and loss of body mass, including loss of muscle and sarcopenia. Consequential frailty is strongly correlated with age, disability and comorbidity, septic state being the most important one. Certain parameters, especially C-reactive protein and albumin, reflect the inflammatory status and have some implication to the estimation of nutritional status. The parameters that can help assess nutritional status should be evaluated on daily basis, and supportive therapy added accordingly. Early appropriate nutritional support can favorably influence final outcome of the patient, as malnutrition directly increases mortality rates in these patients. In this lecture, we discuss the way and timeliness of optimal nutrition for the critically ill neurological patient in septic condition.

Lacosamide in status epilepticus – do we use it too late?

Zdravka Poljaković

Department of Neurology, Zagreb University Hospital Centre and School of Medicine, University of Zagreb, Zagreb, Croatia

Apart from standard antiepileptic parenteral drugs, there are ever more reports and studies on the use of lacosamide in status epilepticus. Oral and intravenous formulations of lacosamide have already been approved as adjunctive therapy in the treatment of partial-onset seizures in adults and adolescents. In status epilepticus, intravenous lacosamide tended to be used mainly in nonconvulsive status epilepticus as second- or third-line treatment. The proportion of patients with no seizures when intravenous lacosamide was the last drug administered was 76.5% on average. Current evidence on the use of intravenous lacosamide in acute seizures and status epilepticus is restricted to retrospective case reports and case series (class IV), which urges further prospective studies to inform clinicians. However, as lacosamide is one of only three intravenous antiepileptic drugs in Croatia, we report our experience with lacosamide in status epilepticus and discuss the rationale for applying lacosamide as the first-choice intravenous antiepileptic in established status epilepticus in particular patients and status subgroups.

Treatment guidelines for status epilepticus – theory and practical approach

Zdravka Poljaković

Department of Neurology, Zagreb University Hospital Centre and School of Medicine, University of Zagreb, Zagreb, Croatia

Status epilepticus is one of the most important neurological emergencies, with a mortality rate of up to 20%. The most important therapeutic goal is fast, effective, and well-tolerated cessation of status epilepticus. Current treatment guidelines include intravenous antiepileptics such as phenytoin/fosphenytoin, phenobarbital and valproate as standard treatment after failure of first-line therapy, namely, benzodiazepines. Recently, two newer antiepileptic drugs (levetiracetam and lacosamide) have been added to this list of antiepileptics. Further treatment in case of refractory status epilepticus includes parenteral anesthetics and intubation. Super-refractory status epilepticus is a life-threatening condition with high mortality and morbidity of up to 80%. Early treatment with highly effective antiepileptic parenteral drug with minor or no adverse events could reverse the negative outcome of this state. In this report, we review international guidelines for the treatment of status epilepticus, Croatian standard of care in status epilepticus and report our experience with established, refractory and super-refractory status epilepticus in our patient cohort and with parenteral antiepileptic drugs available. Due to regulatory facts in Croatia, the choice of first-line drug in epileptic status may slightly differ from classical guidelines and approach. However, the use of certain first-line antiepileptic drug is the most important step in the treatment of established status epilepticus and the right choice might determine the outcome of the patient. Therefore, practical implementation of the guidelines is analyzed and discussed in this lecture in comparison with knowledge about common antiepileptic drugs recommended in the international guidelines for status epilepticus treatment.

Air pollution and stroke

Borislav Radić

Department of Neurology, Zagreb University Hospital Centre, Zagreb, Croatia

Exposure to air pollution is now well recognized by scientists, media and the population as a major public health issue. It ranks within the top five risk factors for mortality in emerging countries. Forty *per* cent of all deaths could be induced by outdoor air pollution and 89% of deaths attributed to ambient air pollution are observed in low- and medium-income countries as a result of rapid industrialization. Robust data confirm the high risk of morbidity and mortality due to particulate matter measuring less than 2.5 μm (PM 2.5) for myocardial infarction and congestive heart failure, lung disease and cancer, and diabetes, and nitrogen dioxide (NO2) for fetal growth in multiple pregnancy. However, the association between air pollution and stroke overall and by subtypes, is less clear. Recent works within the Global Burden of Disease study, which evaluated data from 1990 to 2013 in 188 developed and developing countries, demonstrated for the first time that air pollution contributed 30% to the burden of stroke. This new vascular risk factor can be considered as a potentially modifiable risk factor for stroke that is a major public health problem, being the first cause of motor handicap and the second cause of cognitive disorder and death worldwide. The aim of this review is to clarify biological and clinical features of the association between air pollution and the risk and mortality of stroke.

EEG analysis and SPECT imaging in Alzheimer's disease, vascular dementia and mild cognitive impairment

Borislav Radić

Department of Neurology, Zagreb University Hospital Centre, Zagreb, Croatia

Dementia encompasses a wide range of symptoms associated with decline in memory or other cognitive skills and severe enough to reduce a person's ability to perform everyday activities. Alzheimer's disease (AD) nowadays represents a leading public-health problem given the rising age of the population, being the most common of all dementias with a steadily increasing incidence and prevalence. Vascular dementia (VaD) is the second most common cause of dementia in elderly people. Mild cognitive impairment (MCI) is an intermediate stage between the expected cognitive decline of normal aging and the more serious decline of dementia. Clinical electroencephalography (EEG) is a relatively simple and inexpensive diagnostic tool with a high sensitivity for diffuse organic brain damage of various causes, but with low specificity for the type of dementia. Brain perfusion single-photon emission computed tomography (SPECT) imaging is a functional nuclear imaging technique performed to evaluate regional cerebral perfusion. Retrospective analysis included a group of patients diagnosed with AD, VaD and MCI. The study group consisted of 50 patients, 29 female and 21 male. The results of our study indicated that in the group of patients with AD, EEG changes were present in all patients. These changes were mostly in the form of theta waves, focal abnormalities and spike-and-wave complexes in frontotemporal regions, with the reduction amplitude of alpha waves. In most patients, SPECT revealed hypoperfusion in temporoparietal regions with occasional unilateral abnormalities in frontotemporal region. EEG changes in patients with VaD were predominantly in the form of theta waves, while SPECT showed mostly 'patchy' abnormalities. EEG readings were normal or showed minimal changes in the group of patients with MCI, while SPECT imaging revealed mostly normal cerebral blood flow. In conclusion, EEG and SPECT are diagnostic methods that show specific changes, especially in AD. EEG can be used to monitor therapeutic effect and progression of AD, as well as the possible transition from MCI to early stage AD.

Stereotactic techniques in epilepsy surgery

Peter C. Reinacher[1,2]

[1]*Stereotactic and Functional Neurosurgery, Medical Center – University of Freiburg, Freiburg, Germany*
[2]*Fraunhofer Institute for Laser Technology, Aachen, Germany*

There are different stereotactic techniques that can help improve epilepsy diagnostics and treatment. The workflow of stereotactic implantation of intracerebral electrodes for stereo-EEG is demonstrated combining the advantages of frameless and frame-based techniques. These include advanced visualization using automatic anatomical segmentation, 3D visualization and planning the SEEG implantation and the following resection strategy in an augmented reality setup and high precision and accuracy using a stereotactic frame. Furthermore, several strategies developed to increase safety in aviation by improving situational awareness are transferred to the stereotactic operation. To demonstrate stereotactic treatment options in epilepsy, we report our experience with radiofrequency thermocoagulation (SRT) for disconnection of hypothalamic hamartomas. Between July 2015 and November 2019, we treated 19 consecutive patients (6 female, 13 male, age 1-55 years, median 7 years) with epileptogenic hypothalamic hamartomas (13 Delalande II, 3 Delalande III, 3 Delalande IV) with SRT. At follow-up (median 12 months), freedom from gelastic seizures (GS) was achieved in 94% (15/16) and freedom from nGS in 83% (15/18) of patients. All but two patients showed recovery or considerable improvement of their epilepsy (Engel class 1: 74%, Engel class 2: 11%, Engel class 3: 5%, and Engel class 4: 11%).

Peripheral nerve ultrasound

Barbara Sitaš

Department of Neurology, Referral Centre for Neuromuscular Diseases and Clinical Electromyoneurography, Zagreb University Hospital Centre, Zagreb, Croatia

Neuromuscular ultrasound is a rapidly evolving, widely available tool to assess muscle and nerve morphology. Needle electromyography and nerve conduction studies (NCS) give us information on muscle and nerve function. Combining these two, we get a more comprehensive approach when evaluating a neuromuscular patient. Ultrasound (US) is a portable, painless, noninvasive method without ionizing radiation. For assessing peripheral nerves, a high frequency (12+ MHz) linear array transducer is used. Normal nerve has a so called 'honey-comb' appearance in cross-sectional (axial) view. Nerve needs to be assessed along its length for possible pathology. Most nerves are easily traced proximally to their origin with a few exceptions. Cross-sectional area is one of the most valuable measurements. In practice, US is particularly beneficial in diagnosis, management and follow up of entrapment neuropathies, nerve trauma and some polyneuropathies. In entrapment neuropathies (e.g., carpal tunnel syndrome), focal nerve enlargement due to edema and inflammation, nerve flattening, hypoechogenicity, loss of nerve mobility and increased intraneural vascularity can be observed. In nerve trauma, US can provide useful information that can help plan therapeutic approach since it can assess morphology and be used immediately after trauma, unlike NCS which are best used with a few-week delay. US can identify transected nerves (distinguish between axonotmesis and neurotmesis), pseudoaneurysm, neuroma, bony compression, etc. When considering generalized neuropathies, US has been especially beneficial when assessing chronic immune-mediated polyneuropathies.

Advantages of valproate in the treatment of patients with epilepsy

Davor Sporiš

Department of Neurology, Dubrava University Hospital, Zagreb, Croatia
Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia
Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

Modern approach in the treatment of patients with epilepsy is individualized and includes the specific characteristics of the drug, as well as the specifics of individual patient. Sodium valproate is a standard antiepileptic drug that acts as an inhibitor of the UDP-glucuronosyl transferase (UGT) enzyme system with broad-spectrum antiepileptic activity and multiple mechanisms of action. It is favorable for rational polytherapy especially with lamotrigine. According to the Croatian guidelines for pharmacological treatment of epilepsy, it is indicated as the first choice in the treatment of generalized tonic-clonic, tonic and atonic seizures, absence and myoclonic seizures, juvenile myoclonic epilepsy, and juvenile absence epilepsy. Furthermore, it is the first choice of treatment in Dravet syndrome, Doose syndrome and Lennox-Gastaut syndrome. It is recommended in patients with psychiatric comorbidity and brain tumors, and has less pronounced cognitive side effects. Dosing once a day is excellent for patient therapy compliance. The side effects (except for women with epilepsy of generative age) are relatively rare and include thrombocytopenia, weight gain, loss of hair, gastrointestinal symptoms and encephalopathy with hyperammonemia. Serious hepatic failure has been reported in a few patients, as well as pancreatitis.

Depression: causative process or risk factor in Parkinson's disease?

Helena Šarac

Department of Neurology, Division of Neurodegenerative Disorders and Neurogenetics, Zagreb University Hospital Centre, Zagreb, Croatia

Parkinson's disease (PD) is a neurodegenerative disorder characterized by selective degeneration of dopaminergic neurons in the substantia nigra. The major motor symptoms associated with PD are frequently accompanied by non-motor symptoms including mood, anxiety, depression, sleep disorder and cognitive impairment. PD is characterized by a long preclinical phase, which frequently includes depression. Stress enhances serotonergic and/or noradrenergic activity in prefrontal cortex, striatum, and hippocampus. Increased dopamine and 5-HT availability may transiently increase motor symptoms and have the capability to harm neurons along the nigrostriatal pathway during the preclinical stage of PD. Neuronal degeneration in the raphe nuclei leads to reductions of 5-HTT and 5-HT in the striatum and prefrontal cortex. The altered 5-HT transmission may also be the result of weak neuromodulation by dopamine neurons. 5-HT neurons have the ability to store and release dopamine from antiparkinsonian drugs. 5-HT loss and non-motor symptoms associated with PD may then result from the synergistic action of the serotonergic and dopaminergic systems. MAO-inhibitors including selective serotonin reuptake inhibitors (SSRIs) have the potential to increase dopamine in the striatum to improve motor symptoms of PD. A new treatment approach for PD may therefore consist of inhibiting 5-HT transporters to increase antiparkinsonian effects of SSRI. The possibility that depression is a harbinger of PD and that treating depression may help in the management of PD is therefore of great importance. Synergistic action of the serotonergic and dopaminergic systems is important for causation and delivering a comprehensive treatment for these two disorders.

Defining epileptogenic networks

Vlatko Šulentić[1], Željka Petelin Gadže[1], Sibila Nanković[1], Zdravka Poljaković[1], Andreja Bujan Kovač[1], Petra Nimac Kozina[1], Biljana Đapić Ivančić[1], Magdalena Krbot Skorić[1], Goran Mrak[2], Andrej Desnica[2], Jakob Nemir[2], Sergej Marasanov[2], Marko Radoš[3], Milan Radoš[4], David Ozretić[3], Ivan Jovanović[3], Ratimir Petrović[5], Anja Tea Golubić[5]

[1] *Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Department of Neurology, Referral Centre of the Ministry of Health of the Republic of Croatia for Epilepsy, Affiliated Partner of the ERN EpiCARE, Zagreb, Croatia*
[2] *Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Department of Neurosurgery, Zagreb, Croatia, Affiliated Partner of ERN EURACAN*
[3] *Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Department of Diagnostic and Interventional Neuroradiology, Zagreb, Croatia*
[4] *Croatian Institute for Brain Research, School of Medicine, University of Zagreb, Zagreb, Croatia*
[5] *Zagreb University Hospital Centre, School of Medicine, University of Zagreb, Department of Nuclear Medicine and Radiation Protection, Zagreb, Croatia*

Defining epileptogenic networks is essential in the presurgical treatment of patients with pharmacoresistant epilepsy. Epileptogenic networks are defined by the brain region involved in the production and propagation of epileptic activities. The concept of epileptogenic networks is widely accepted as a more effective model of explaining the complex dynamics between epileptic seizures and epileptic anomalies within the brain. This dynamics is also a reason for discrepancies between semiology and pharmacoresistance of epilepsy, as well as epilepsy surgery failure. The process of emergence of epileptogenic networks is complex and determined by various factors. Still, a certain pattern does exist as a result of functional and anatomical connections within the brain. If semiology of seizures is clearly identifiable and well-known, it can provide useful data on epilepsy onset and spread. This is supposed to be a starting point for further treatment. After semiology has been defined, further methods for defining networks are needed. Apart from video electroencephalography (EEG) and brain magnetic resonance imaging (MRI), further diagnostics would include neuropsychological testing, brain positron emission tomography (PET) and single-photon emission computed tomography (SPECT), functional MRI, magnetoencephalography (MEG), as well as post-processing of brain MRI images with the Morphometric Analysis Program. Final confirmation of existence of epileptogenic networks is only possible by use of invasive EEG monitoring. After data have been collected by use of all of these methods, it is possible to partially define epileptogenic networks and explore options for further treatment, which is most likely to be a surgical one. Yet, expectations of the outcome may be only partially fulfilled, as epileptogenic networks are complex and very often overlapping with eloquent cortex and prone to changes during long-standing course of epilepsy.

Sepsis as a hypercoagulable state

Svjetlana Šupe

Zagreb University Hospital Centre, Department of Neurology, Intensive Care Unit, Zagreb, Croatia

Sepsis is an uncontrolled inflammatory and procoagulable response to infection mediated by the activation of the immune system. According to the 2016 guidelines, sepsis is defined as (a) life-threatening organ dysfunction owing to a dysregulated host response to infection, and (b) onset marked by the beginning of any organ dysfunction remote from the site of infection. Sepsis is identified as a novel stroke risk factor, increasing the risk of stroke within a relatively short period of time, but is also associated with long-term risk of stroke and death. The possible mechanisms linking sepsis to stroke could be atrial fibrillation, hemodynamic instability, coagulopathy, systemic inflammatory response syndrome and prolonged inflammation. An increased risk of stroke after sepsis has been observed in people under 45 years of age. Multiple factors activate coagulation during sepsis and normal endogenous anticoagulants that inhibit different parts of the coagulation cascade are down-regulated and damaged in this condition. Imbalance between coagulation and fibrinolysis leads to a hypercoagulable state and organ dysfunction in sepsis. Sepsis-induced coagulopathy progresses to disseminated intravascular coagulation (DIC) characterized by widespread microvascular thrombosis and even bleeding complications. Three major factors contribute to DIC, i.e. coagulation activation, platelet aggregation and endothelial damage. Once sepsis is identified in intensive care unit patients, early and aggressive appropriate management is a priority, including infection control, hemodynamic stabilization and modulation of septic response. Timing of DIC recognition and application of therapy is crucial for outcome. The fundamental strategy for sepsis-associated DIC management is treatment with antithrombotic drugs, primarily anticoagulants but antiplatelet drugs may also reduce organ failure and mortality.

Dilemmas in parkinsonism – 10 tips for distinguishing

Srđana Telarović

University of Zagreb, School of Medicine and Department of Neurology, Zagreb University Hospital Centre, Zagreb, Croatia

Parkinsonism is an umbrella term that refers to a group of different conditions characterized by movement disorders. Given the similarities with idiopathic Parkinson's disease (PD), it is important to make a distinction between PD and parkinsonism, and to correctly identify the underlying condition from the parkinsonism group. Among the signs of parkinsonism, tremor is the leading cause of diagnostic and therapeutic dilemmas. Tremor is the most common hyperkinesis in humans, with its occurrence often impressive not only to patients but also to physicians. Due to the variety of etiologic factors, diseases, conditions, substances, drugs and circumstances that can cause it, tremor represents a common diagnostic and subsequently therapeutic challenge. Contrary to the popular belief that any tremor is an imperative sign of PD and that tremor within this disease is most common of all types of tremor, this hyperkinesis is often a sign of other conditions that do not necessarily originate from primary neurological disorders. Therefore, familiarity with the variety of causes and presentations, as well as with other extrapyramidal symptoms and signs, is of extreme importance in the differential diagnostic procedure. Although the findings from laboratory, imaging, genetic and other diagnostic tests may contribute, targeted medical history and clinical examination play the dominant role in definitive diagnosis. The specifics of defining characteristics and indicators of different tremors and other signs of parkinsonism require knowledge of a specialized, targeted clinical examination and evaluation. Only with such a focused approach it is possible to overcome the common diagnostic traps faced in this challenging field. Furthermore, with correct and timely diagnosis and, consequently, appropriate therapy it is possible to avoid the (unfortunately not rare) use of incorrect therapy, especially of dedicated antiparkinsonian agents with potentially harmful side effects. Altogether, education on this topic aims to improve the recognition and differentiation of different entities in the context of parkinsonism, thus to ensure successful treatment and ultimately contribute to the patient quality of life.

Anatomic variations in hand and foot innervation

Davorka Vranješ

Referral Centre for Neuromuscular Diseases and Clinical Electromyoneurography, Zagreb, Croatia

Anatomic variations in the course of peripheral nerves and innervation of the hand and foot are not uncommon in the general population but mostly remain unrecognized. Although most of them are asymptomatic and do not affect diagnostic findings, in some cases they may complicate the diagnosis of compression neuropathies, peripheral lesions and neuropathy. Anastomosis between the median nerve and ulnar nerve is a relatively common anatomic variant in the innervation of the hand. Martin-Gruber anastomosis (MGA) is a connection from the median and ulnar nerve on the forearm. It is the most common anastomosis that occurs between these two nerves. This connection carries motor axons which innervate some of the intrinsic muscles that are usually innervated by the ulnar nerve. Marinacci anastomosis (so-called reverse MGA) is an anastomosis in which the anastomotic branch originates proximally in the ulnar nerve and unites distally with the median nerve. Riche-Cannieu anastomosis (RCA) is the communication between the recurrent branch of the median nerve and the deep branch of the ulnar nerve in the hand. Clinical presentation of RCA can be in three forms. All hand muscles can be innervated by the ulnar nerve (all ulnar hand) or motor innervation can be dominantly provided by the ulnar nerve, and lastly some of the median innervated muscles can be innervated by the ulnar nerve. Berrettini anastomosis is the most common neural connection often considered a normal anatomic structure. It exists as a junction between the common digital nerves of ulnar and median nerves, most often from the fourth to third common digital nerve. The rare anatomic variations in the innervation of the hand are bifurcation of median nerve proximal in the carpal tunnel, wrist or forearm; trifurcation of the ulnar nerve proximal or in Guyon's canal; and also the sensory branch to the dorsum may be absent. There are descriptions in the literature of an anatomic variation in which the lateral antebrachial cutaneous nerve (branch of the musculocutaneous nerve) innervates the radial border of the dorsum of the hand and thumb in addition to, or replacing, the superficial radial nerve. A common anatomic variant in the innervation of the foot is the accessory peroneal nerve. It generally arises from the superficial peroneal nerve as it runs under the peroneal brevis muscle, traveling distally to the foot to the lateral malleolus. It subsequently branches to innervate ligaments, joints, and the extensor digitorum brevis muscle. Its prevalence as a normal anatomic variant has been reported to be 17% to 28% in anatomic studies. This variation may be important in case of the existence of compressive neuropathy of the peroneal nerve at the neck of the fibula for preserving function of the extensor digitorum brevis muscle. The superficial peroneal nerve and its cutaneous branches may have different anatomic variations in the course and distribution, posing a risk of iatrogenic damage. Anatomic variations of tibial nerve and its branches, medial plantar nerve and lateral plantar nerve, are rarely described. A rare case of tibial nerve trifurcation within the tarsal tunnel has been described recently. Sural nerve (SN) is a sensory nerve in the lower extremity which branches to supply the skin on the distal posterolateral third of the lower limb. Typically, the medial sural cutaneous branch of the tibial nerve (MSCN) and the peroneal communicating nerve unite to form the SN. Anatomic variations in the formation and course of SN are relatively common in the population. The most common variation is junction of the two source nerves. Anatomic studies have shown that about 30% of SN have direct continuation of MSCN, and other less common variations have been described. Clinically, SN is also widely used for diagnostic and therapeutic purposes (nerve transplantation), so detailed knowledge of anatomic variants of the SN is important for the implementation of these and other procedures.

Myelin oligodendrocyte glycoprotein antibody disease (MOG-AD)

Ivana Zadro

Zagreb University Hospital Centre, Department of Neurology,
Referral Centre for Demyelinating Diseases of the Central Nervous System, Zagreb, Croatia

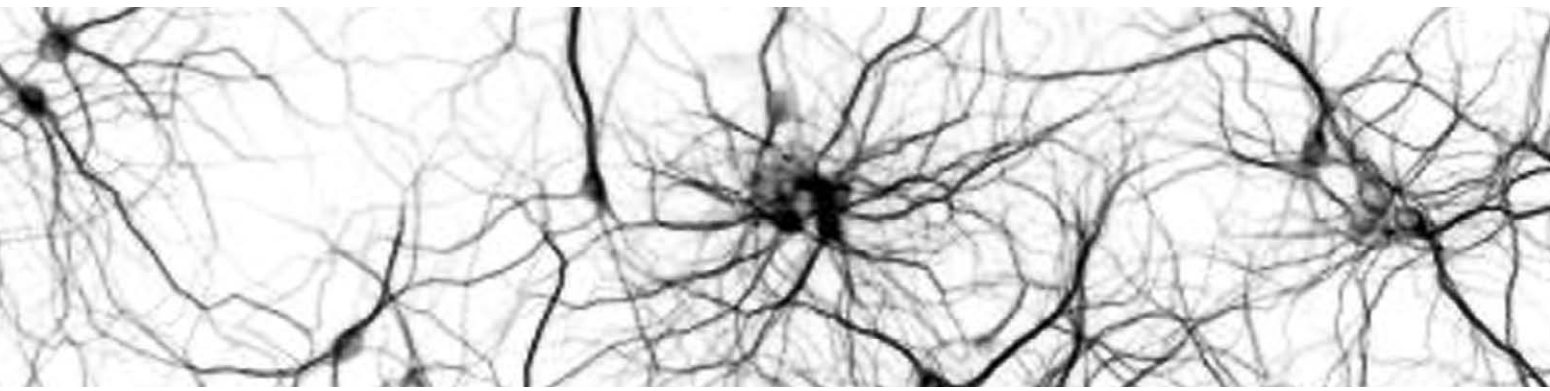
Myelin oligodendrocyte glycoprotein antibody disease (MOG-AD) is an idiopathic, inflammatory, demyelinating disease of the central nervous system (CNS) with a range of phenotypic presentations including acute disseminated encephalomyelitis (ADEM), neuromyelitis spectrum disorder (NMOSD) and cortical encephalitis. MOG is a glycoprotein uniquely expressed in oligodendrocytes in the CNS. MOG-AD is characterized by a monophasic or relapsing course of neurological dysfunction, and occurs in the presence of serum MOG antibodies detected using specific cell-based assays (indirect fluorescence test or fluorescence-activated cell sorting). One of the most common presentations is similar to NMOSD with recurrent optic neuritis, longitudinally extensive transverse myelitis, or both, and the other is that of ADEM with typical symptoms of encephalitis including decreased consciousness, seizures, headache, and behavioral changes. Other presentations include cortical encephalitis with epileptic seizures, sometimes with abnormal behavior or focal symptoms, brainstem syndrome and short segment transverse myelitis. Magnetic resonance imaging (MRI) characteristics can help in differentiating MOG-AD from other neuroinflammatory disorders, including multiple sclerosis and neuromyelitis optica. There is no known unique radiographic pattern for MOG, but leptomeningeal enhancement, thalamic lesions, pontine lesions, cerebellar peduncle lesions, deep white matter lesions, tumefactive, poorly defined lesions, and cortical lesions were more common in MOG-AD than in NMOSD or non-MOG antibody cases. Cerebrospinal fluid can have lymphocytic pleocytosis, normal or mildly elevated protein, and rare oligoclonal bands. Randomized control trials are limited, but observational open-label experience suggests a role of high-dose steroids and plasma exchange in the treatment of acute attacks, and of immunosuppressive therapies such as steroids, oral immunosuppressants and rituximab as maintenance treatment.

Depakine Chrono in pregnancy and breastfeeding

Iris Zavoreo

Department of Neurology, Division of Epilepsy, Neuromuscular Disorders and Clinical Electrophysiology, Sestre milosrdnice University Hospital Centre, Zagreb, Croatia

Prospective registries and meta-analyses have better defined the risk of major congenital malformations (MCMs) in offspring exposed to particular antiepileptic drugs (AEDs) at different dose levels. Valproate is the drug with the highest risk, whereas the prevalence of MCMs is lowest with lamotrigine, levetiracetam and oxcarbazepine. For valproate, phenobarbital, phenytoin, carbamazepine and lamotrigine, the risk of MCMs is dose-dependent. Prenatal exposure to valproate has been confirmed to cause an increased risk of cognitive impairments and autistic traits. In a population-based study, the risk of AED-induced autistic traits was attenuated by periconceptional folate supplementation. Knowledge about the passage of various antiepileptic drugs into breast milk and its consequences for the infant is limited. Faced with this uncertainty, breastfeeding is often discouraged for these patients. Phenobarbital, primidone, carbamazepine, valproate and levetiracetam are probably compatible with breastfeeding. In practice, a risk-benefit analysis should be performed for each mother under antiepileptic treatment wishing to breastfeed her child, so that individual risk factors can adequately be taken into account when counseling the patient.



Indeks / Index

Indeks / Index

Oslonite se na dokazanu učinkovitost i sigurnost lijeka AUBAGIO® kako bi utišali oluju[1-5*]

***AUBAGIO® je oralni lijek za RRMS, koji se uzima jedanput dnevno. Pokazao je značajno i dosljedno smanjenje stope relapsa i trajnog pogoršanja onesposobljenosti, kao i smanjenje brojnih vrijednosti aktivnosti bolesti utvrđenih s MR. U načelu se dobro podnosi, a ukupna incidencija nuspojava opaženih u bolesnika liječenih lijekom AUBAGIO® bila je slična onoj u bolesnika koji su primali placebo.[1-3]**

RRMS = relapsno-remitirajuća multipla skleroza; MR = magnetska rezonanca

Referencije: 1. Sažetak opisa svojstava lijeka Aubagio (teriflunomid), www.ema.europa.eu. **2.** O'Connor P, Wolinsky JS, Confavreux C, et al; for the TEMSO Trial Group. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011;365(14):1293-1303. **3.** Confavreux C, O'Connor P, Comi G, et al; for the TOWER Trial Group. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13(3):247-256. **4.** O'Connor P, Comi G, Freedman MS, et al; for the Teriflunomide Multiple Sclerosis Oral (TEMSO) Trial Group and the MRI-AC in Houston, Texas. Long-term safety and efficacy of teriflunomide: nine-year follow-up of the randomized TEMSO study. Neurology. 2016;86(10):920-930. 5. Comi G, Freedman MS, Kappos L, et al. Pooled safety and tolerability data from four placebo-controlled teriflunomide studies and extensions. Mult Scler Relat Disord. 2016;5:97-104.

SKRAĆENI SAŽETAK OPISA SVOJSTAVA LIJEKA – 1. NAZIV LIJEKA I SASTAV: Aubagio 14 mg filmom obložene tablete. Jedna filmom obložena tableta sadrži 14 mg teriflunomida. **2. TERAPIJSKE INDIKACIJE:** Za liječenje odraslih bolesnika s relapsno-remitirajućom multiplom sklerozom (MS). **3. DOZIRANJE I NAČIN PRIMJENE:** Preporučena doza teriflunomida je 14 mg jedanput na dan. Tablete se moraju progutati cijele s malo vode. *Starija populacija* AUBAGIO se mora primjenjivati uz oprez u bolesnika u dobi od 65 godina i starijih zbog nedostatnih podataka o sigurnosti i djelotvornosti. *Oštećenje bubrežne funkcije* Nije potrebno prilagođavati dozu u bolesnika s blagim, umjerenim ili teškim oštećenjem bubrežne funkcije koji se ne liječe dijalizom. Bolesnici s teškim oštećenjem bubrežne funkcije koji se liječe dijalizom nisu ispitivani. Teriflunomid je kontraindiciran u toj populaciji. *Oštećenje jetrene funkcije* Nije potrebno prilagođavati dozu u bolesnika s blagim i umjerenim oštećenjem jetrene funkcije. Teriflunomid je kontraindiciran u bolesnika s teškim oštećenjem jetrene funkcije. *Pedijatrijska populacija* Sigurnost i djelotvornost teriflunomida u djece i adolescenata u dobi od 10 do manje od 18 godina nisu još ustanovljene. Nema relevantne primjene teriflunomida u djece od rođenja do manje od 10 godina starosti za liječenje multiple skleroze. **4. KONTRAINDIKACIJE:** Preosjetljivost na djelatnu tvar ili neku od pomoćnih tvari. Bolesnici s teškim oštećenjem jetrene funkcije (Child-Pugh stadij C). Trudnice ili žene reproduktivne dobi koje ne upotrebljavaju pouzdanu kontracepciju tijekom liječenja teriflunomidom i nakon liječenja sve dok su koncentracije lijeka u plazmi iznad 0,02 mg/l. Prije početka liječenja mora se isključiti trudnoća. Dojilje. Bolesnici s teškim imunodeficijentnim stanjima, npr. AIDS-om. Bolesnici sa značajno oštećenom funkcijom koštane srži ili značajnom anemijom, leukopenijom, neutropenijom ili trombocitopenijom. Bolesnici s teškom aktivnom infekcijom, do njezina izlječenja. Bolesnici s teškim oštećenjem bubrega na dijalizi. Bolesnici s teškom hipoproteinemijom, npr. u nefrotskom sindromu. **5. POSEBNA UPOZORENJA I MJERE OPREZA PRI UPORABI:** *Prije liječenja* teriflunomidom treba provjeriti: krvni tlak, alanin aminotransferazu (ALT/SGPT), kompletnu krvnu sliku, uključujući diferencijalnu sliku leukocita i broj trombocita. Tijekom liječenja teriflunomidom treba kontrolirati: krvni tlak, alanin aminotransferazu/serumsku glutamat-piruvat transaminazu (ALT/SGPT), kompletnu krvnu sliku na temelju kliničkih znakova i simptoma (npr. infekcija). **6. INTERAKCIJE S DRUGIM LIJEKOVIMA I DRUGI OBLICI INTERAKCIJA:** Farmakokinetičko djelovanje drugih tvari na teriflunomid *Snažni induktori citokroma P450 (CYP) i prijenosnika:* istodobna primjena ponovljenih doza (600 mg jedanput na dan tijekom 22 dana) rifampicina (induktora CYP2B6, 2C8, 2C9, 2C19, 3A) kao i induktora efluksnih prijenosnika P-glikoproteina [P-gp] i proteina koji uzrokuje rezistenciju raka dojke na lijekove s teriflunomidom (70 mg u jednokratnoj dozi) smanjila je izloženost teriflunomidu za približno 40%. Rifampicin i drugi poznati snažni induktori citokroma i prijenosnika, kao što su karbamazepin, fenobarbital, fenitoin i gospina trava, moraju se primjenjivati uz oprez tijekom liječenja teriflunomidom. *Kolestiramin ili aktivni ugljen* Osim ako je ubrzana eliminacija poželjna, ne preporučuje se bolesnike koji primaju teriflunomid liječiti kolestiraminom ili aktivnim ugljenom jer oni uzrokuju brzo i značajno smanjenja koncentracije lijeka u plazmi. Farmakokinetičke interakcije teriflunomida na druge tvari *Učinak teriflunomida na supstrat izoenzima CYP2C8:* lijekovi koji se metaboliziraju putem CYP2C8, poput repaglinida, paklitaksela, pioglitazona ili roziglitazona, moraju se primjenjivati uz oprez tijekom liječenja teriflunomidom. *Učinak teriflunomida na oralne kontraceptive: 0,03 mg etinilestradiola i 0,15 mg levonorgestrela* lako se ne očekuje da bi ova interakcija s teriflunomidom mogla negativno utjecati na djelotvornost oralnih kontraceptiva, treba razmisliti o vrsti ili dozi oralnih kontraceptiva koji se upotrebljavaju u kombinaciji s teriflunomidom. *Učinak teriflunomida na supstrat izoenzima CYP1A2: kofein* Lijekovi koji se metaboliziraju putem CYP1A2 (poput duloksetina, alosetrona, teofilina i tizanidina) moraju se primjenjivati uz oprez tijekom liječenja teriflunomidom, jer on može smanjiti njihovu djelotvornost. *Učinak teriflunomida na varfarin* Preporučuje se pomna kontrola i praćenje INR-a kada se varfarin primjenjuje istodobno s teriflunomidom. *Učinak teriflunomida na supstrate organskog anionskog transportera 3 (OAT3):* Potreban oprez kada se teriflunomid primjenjuje istodobno sa supstratima OAT3, kao što su cefaklor, benzilpenicilin, ciprofloksacin, indometacin, ketoprofen, furosemid, cimetidin, metotreksat i zidovudin. *Učinak teriflunomida na BCRP i/ili supstrate organskog anionskog transportnog polipeptida B1 i B3 (OATP1B1/B3):* Kada se primjenjuje istodobno s teriflunomidom, preporučuje se smanjenje doze rosuvastatina za 50%. Također je potreban oprez kada se teriflunomid primjenjuje istodobno s drugim supstratima BCRP-a (npr. metotreksatom, topotekanom, sulfasalazinom, daunorubicinom, doksorubicinom) i lijekovima iz skupine organskih anionskih transportnih polipeptida, osobito inhibitorima HMG-CoA reduktaze (npr. simvastatinom, atorvastatinom, pravastatinom, metotreksatom, nateglinidom, repaglinidom, rifampicinom). Bolesnike treba pažljivo motriti kako bi se uočili mogući znakovi i simptomi prekomjerne izloženosti lijekovima, a u obzir treba uzeti i smanjenje doza tih lijekova. **7. PLODNOST, TRUDNOĆA I DOJENJE:** *Primjena u muškaraca* Rizik od embriofetalne toksičnosti uslijed liječenja muškaraca teriflunomidom smatra se niskim. *Trudnoća* Postoje malobrojni podaci o primjeni teriflunomida u trudnica. Ispitivanja na životinjama pokazala su reproduktivnu toksičnost. Teriflunomid može prouzročiti ozbiljne prirođene mane ako se primjenjuje tijekom trudnoće. Teriflunomid je kontraindiciran tijekom trudnoće. Žene reproduktivne dobi moraju koristiti djelotvornu kontracepciju tijekom liječenja i nakon liječenja, sve dok je razina teriflunomida u plazmi iznad 0,02 mg/l. Tijekom tog razdoblja žena treba s nadležnim liječnikom razgovarati o planovima za prekid kontracepcije ili promjenu metode kontracepcije. Ako je test na trudnoću pozitivan, liječnik i bolesnica moraju razgovarati o rizicima za trudnoću. Moguće je da se brzim snižavanjem razine teriflunomida u krvi primjenom postupka ubrzane eliminacije pri prvom kašnjenju menstruacije može smanjiti rizik za plod. U žena koje primaju teriflunomid i koje žele zatrudnjeti treba prekinuti primjenu lijeka, a preporučuje se i primjena postupka ubrzane eliminacije kako bi se što prije postigla koncentracija manja od 0,02 mg/l. Dojenje Teriflunomid je kontraindiciran tijekom dojenja. Plodnost Rezultati ispitivanja na životinjama nisu pokazali utjecaj na plodnost. Premda nedostaju podaci u ljudi, ne očekuje se učinak na plodnost u muškaraca i žena. **8. UTJECAJ NA SPOSOBNOST UPRAVLJANJA VOZILIMA I RADA NA STROJEVIMA:** AUBAGIO ne utječe ili zanemarivo utječe na sposobnost upravljanja vozilima i rada na strojevima. U slučaju nuspojava poput omaglice bolesnici se moraju uzdržati od upravljanja vozilima i rada na strojevima. **9. NUSPOJAVE:** *Vrlo česte* nuspojave prijavljene kod primjene lijeka AUBAGIO u placebom kontroliranim ispitivanjima su bile glavobolja, proljev, mučnina, alopecija i povišene vrijednosti ALTa. Česte su nuspojave bile gripa, infekcija gornjih dišnih putova, infekcija mokraćnih putova, bronhitis, sinusitis, faringitis, cistitis, virusni gastroenteritis, oralni herpes, infekcija zuba, laringitis, atletsko stopalo, neutropenija, anemija, blage alergijske reakcije, anksioznost, parestezija, ishijas, sindrom karpalnog kanala, palpitacije, hipertenzija, bol u gornjem dijelu abdomena, povraćanje, zubobolja, osip, akne mišićno-koštana bol, mijalgija, artralgija, polakizurija, menoragija, bol, astenija, povišene vrijednosti GGT-a, povišene vrijednosti aspartat aminotransferaze, smanjenje tjelesne težine, smanjenje broja neutrofila i leukocita, povišena kreatin-fosfokinaza u krvi. *Manje česte* nuspojave su blaga trombocitopenija, hiperestezija, neuralgija, periferna neuropatija, poremećaji noktiju, posttraumatska bol. **10. PREDOZIRANJE:** Nema iskustva s predoziranjem niti trovanjem teriflunomidom u ljudi. Teriflunomid u dozi od 70 mg na dan primjenjivan je tijekom najviše 14 dana u zdravih ispitanika. Nuspojave su bile sukladne sigurnosnom profilu teriflunomida u bolesnika s multiplom sklerozom. **11. FARMAKODINAMIČKA SVOJSTVA:** Farmakoterapijska skupina: Imunosupresivi, selektivni imunosupresivi, ATK oznaka: L04AA31. **12. NOSITELJ ODOBRENJA:** sanofi-aventis groupe, 54 rue La Boétie, F-75008 Paris, Francuska. **13. BROJ(EVI) ODOBRENJA ZA STAVLJANJE GOTOVOG LIJEKA U PROMET:** EU/1/13/838/001-005. **14. NAČIN I MJESTO IZDAVANJA: Na recept, u ljekarni.** Detaljnije informacije o ovom lijeku dostupne su na web stranici Europske agencije za lijekove http://www.ema.europa.eu/.

Ovo je skraćeni Sažetak opisa svojstava lijeka te sukladno Pravilniku o načinu oglašavanja o lijekovima (Narodne Novine broj 43/15) molimo prije propisivanja lijeka Aubagio pročitajte zadnji odobreni Sažetak opisa svojstava lijeka i Uputu o lijeku.

SANOFI GENZYME

SAMO ZA ZDRAVSTVENE RADNIKE
Prije propisivanja, pročitajte cijeli Sažetak opisa svojstava lijeka.
Detaljnije informacije su dostupne na:
Sanofi-aventis Croatia d.o.o. | Heinzelova 70 | 10000 Zagreb | Hrvatska | GZHS.AUBA.19.10.0523 (11/19)

Jedanput dnevno AUBAGIO® (teriflunomid) 14mg filmom obložene tablete

PRUŽITE JOJ RUKU I TESTIRAJTE NA POMPEOVU BOLEST.

CK - enzim kreatin kinaza
ALT - enzim alanin aminotransferaza
AST - enzim aspartat aminotransferaza

POMPEOVA bolest

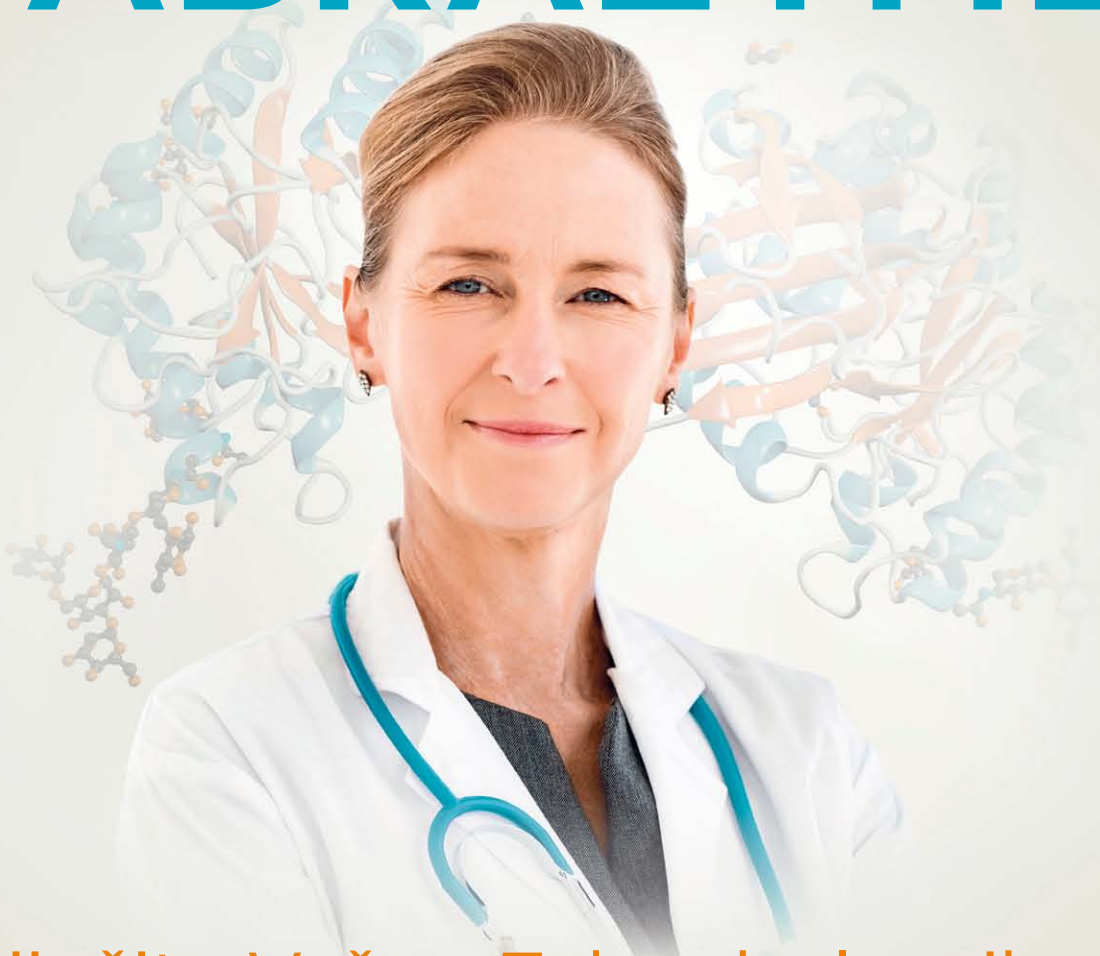
SANOFI GENZYME
www.sanofigenzyme.com

Reference: 1. Chan et al. The emerging phenotype of late-onset Pompe disease: A systematic literature review, Molecular Genetics and Metabolism 120 (2017) 163–172

SAMO ZA ZDRAVSTVENE RADNIKE

sanofi-aventis Croatia d.o.o. | Heinzelova 70 | 10000 Zagreb | Hrvatska | Tel: +385 (0) 1 6003 470 | Fax: +385 (0) 1 6003 480 | GZHS.MYOZ.18.11.0538 (05/19)

OSLONITE SE NA FABRAZYME



Liječite Vašeg Fabry bolesnika lijekom Fabrazyme

1 mg/kg

jedanput svaka 2 tjedna

Terapijska indikacija[1]

Fabrazyme je indiciran kao dugoročna enzimska nadomjesna terapija u bolesnika s potvrđenom dijagnozom Fabryjeve bolesti (nedostatak α-galaktozidaze A).

Fabrazyme je indiciran u odraslih, djece i adolescenata u dobi od 8 i više godina.

Fabrazyme®
agalzidaza beta
1 mg/kg jedanput svaka dva tjedna

[1] Sažetak opisa svojstava lijeka Fabrazyme

SANOFI GENZYME

SKRAĆENI SAŽETAK OPISA SVOJSTAVA LIJEKA

SKRAĆENI SAŽETAK OPISA SVOJSTAVA LIJEKA – 1.NAZIV LIJEKA I SASTAV: **Fabrazyme 5 mg i Fabrazyme 35 mg** prašak za koncentrat za otopinu za infuziju. Jedna bočica lijeka Fabrazyme sadrži nominalnu vrijednost od 5 mg, odnosno 35 mg agalzidaze beta. Nakon rekonstitucije s 1,1 ml, odnosno 7,2 ml vode za injekcije jedna bočica lijeka Fabrazyme sadrži 5 mg/ml (35 mg/7 ml) agalzidaze beta. Rekonstituirana otopina mora se dodatno razrijediti. **2.TERAPIJSKE INDIKACIJE:** Fabrazyme je indiciran kao dugoročna enzimska nadomjesna terapija u bolesnika s potvrđenom dijagnozom Fabryjeve bolesti (nedostatak α-galaktozidaze A). Fabrazyme je indiciran u odraslih, djece i adolescenata u dobi od 8 i više godina. **3.DOZIRANJE I NAČIN PRIMJENE:** Liječenje lijekom Fabrazyme mora nadzirati liječnik s iskustvom u liječenju bolesnika s Fabryjevom bolešću ili drugim nasljednim metaboličkim bolestima. Doziranje Preporučena doza lijeka Fabrazyme je 1 mg/kg tjelesne težine primijenjeno jedanput svaka 2 tjedna u obliku intravenske infuzije. Početna brzina infuzije ne smije biti veća od 0,25 mg/min (15 mg/sat) kako bi se mogućnost pojave reakcija povezanih s infuzijom svela na najmanju moguću mjeru. Nakon što se u bolesnika utvrdi podnošljivost, brzina infuzije može se u sljedećim infuzijama postupno povećavati. U bolesnika koji dobro podnose infuzije može se razmotriti mogućnost primjene infuzije lijeka Fabrazyme kod kuće. Odluka da se bolesnika prebaci na primjenu infuzije kod kuće smije se donijeti tek nakon procjene i preporuke nadležnog liječnika. Bolesnici kod kojih se u toku primanja infuzije pojave nuspojave moraju odmah prekinuti infuziju i potražiti pomoć zdravstvenog djelatnika. Nije potrebno prilagođavati dozu u bolesnika sa zatajivanjem bubrega. Nisu provedena ispitivanja u bolesnika sa zatajivanjem jetre. U bolesnika starijih od 65 godina sigurnost i djelotvornost lijeka Fabrazyme nisu utvrđene pa trenutno za te bolesnike nije moguće preporučiti režim doziranja. Sigurnost i djelotvornost lijeka Fabrazyme u djece u dobi od 0 do 7 godina još nisu ustanovljene. Nije moguće preporučiti režim doziranja za djecu u dobi od 5 do 7 godina. Nema dostupnih podataka za djecu u dobi od 0 do 4 godine. U djece u dobi od 8 do 16 godina nije potrebno prilagođavati dozu. **4.KONTRAINDIKACIJE:** Po život opasna preosjetljivost (anafilaktička reakcija) na djelatnu tvar ili neku od pomoćnih tvari. **5.POSEBNA UPOZORENJA I MJERE OPREZA PRI UPORABI:** Imunogenost Budući da je agalzidaza beta (r-hαGAL) rekombinantni protein, očekuje se razvoj IgG protutijela u bolesnika u kojih je rezidualna enzimska aktivnost niska ili ne postoji. U većine su se bolesnika razvila IgG protutijela na r-hαGAL, obično unutar 3 mjeseca nakon prve infuzije lijeka Fabrazyme. S vremenom se u većine seropozitivnih bolesnika u kliničkim ispitivanjima primijetio ili trend pada vrijednosti titara (40% bolesnika), navikavanje na lijek (14% bolesnika) ili plato vrijednosti titra (35% bolesnika). Reakcije povezane s infuzijom U bolesnika s protutijelima na r-hαGAL postoji veća vjerojatnost od pojave reakcija povezanih s infuzijom koje se definiraju kao bilo koja povezana nuspojava koja se pojavi na dan infuzije. U tih bolesnika kod ponovne primjene agalzidaze beta liječenje treba provoditi uz oprez. Treba redovito provjeravati status protutijela. Preosjetljivost Kao i kod svakog drugog intravenskog proteinskog lijeka, moguće su alergijske reakcije preosjetljivosti. Učinak liječenja lijekom Fabrazyme na bubrege može biti ograničen u bolesnika s uznapredovalom bubrežnom bolešću. **6.INTERAKCIJE S DRUGIM LIJEKOVIMA I DRUGI OBLICI INTERAKCIJA:** Fabrazyme se ne smije primjenjivati s klorokinom, amiodaronom, benokvinom ili gentamicinom zbog teoretskog rizika od inhibicije unutarstanične aktivnosti α-galaktozidaze A. **7.PLODNOST, TRUDNOĆA I DOJENJE:** Trudnoća Nema odgovarajućih podataka o primjeni agalzidaze beta u trudnica. Istraživanja na životinjama ne ukazuju na izravne niti neizravne štetne učinke na razvoj zametka/ploda. Fabrazyme se ne smije primjenjivati tijekom trudnoće, osim ako nije neophodno. Dojenje Agalzidaza beta može se izlučivati u mlijeko. Budući da nema podataka o učincima izlaganja novorođenčadi agalzidazi beta putem majčinog mlijeka, preporučuje se prekinuti dojenje tijekom primjene lijeka Fabrazyme. Plodnost Nisu provedena ispitivanja kojima bi se procijenili mogući učinci lijeka Fabrazyme na smanjenje plodnosti. **8.UTJECAJ NA SPOSOBNOST UPRAVLJANJA VOZILIMA I RADA NA STROJEVIMA:** Fabrazyme može malo utjecati na sposobnost upravljanja vozilima i rada na strojevima na dan primjene lijeka zbog moguće pojave omaglice, somnolencije, vrtoglavice i sinkope. **9.NUSPOJAVE:** Nuspojave prijavljene u kliničkim ispitivanjima u kojima je sudjelovalo ukupno 168 bolesnika (154 muškaraca i 14 žena) liječenih lijekom Fabrazyme u dozi od 1 mg/kg svaka 2 tjedna u rasponu od najmanje jedne infuzije do liječenja u trajanju od najviše 5 godina klasificirane su prema učestalosti. Vrlo često: glavobolja, parestezija, mučnina, povraćanje, zimica, pireksija, osjećaj hladnoće. Često: nazofaringitis, omaglica, somnolencija, hipoestezija, osjećaj žarenja, letargija, sinkopa, pojačano suzenje, tinitus, vrtoglavica, tahikardija, palpitacije, bradikardija, crvenilo praćeno osjećajem užarenosti, hipertenzija, bljedilo, hipotenzija, navala vrućine, dispneja, kongestija nosa, stezanje u grlu, piskanje pri disanju, kašalj, egzacerbacija dispneje, bol u abdomenu, bol u gornjem dijelu abdomena, nelagoda u abdomenu, nelagoda u želucu, oralna hipoestezija, proljev, pruritus, urtikarija, osip, eritem, generalizirani pruritus, angioneurotski edem, oticanje lica, makulopapularni osip, bol u udovima, mialgija, bol u leđima, grčevi u mišićima, artralgija, stezanje u mišićima, mišićno-koštana ukočenost, umor, nelagoda u prsištu, osjećaj vrućine, periferni edem, bol, astenija, bol u prsištu, oticanje lica, hipertermija. Manje često: rinitis, hiperestezija, tremor, pruritus oka, hiperemija oka, oticanje ušne školjke, bol u uhu, sinusna bradikardija, periferna hladnoća, bronhospazam, faringolaringealna bol, rinoreja, tahipneja, kongestija gornjeg dišnog sustava, dispepsija, disfagija, retikularni livedo, eritematozni osip, pruritički osip, promjena boje kože, osjećaj nelagode na koži, mišićno-koštana bol, osjećaj vrućine i hladnoće, bolest nalik gripi, bol na mjestu primjene infuzije, reakcija na mjestu primjene infuzije, tromboza na mjestu injekcije, malaksalost, edem. U 67% bolesnika pojavila se najmanje jedna reakcija povezana s infuzijom. **10.PREDOZIRANJE:** U kliničkim ispitivanjima primjenjivane su doze do 3 mg/kg tjelesne težine. **11.FARMAKODINAMIČKA SVOJSTVA:** Farmakoterapijska skupina: Ostali lijekovi za probavni sustav i metabolizam, enzimi. ATK oznaka: A16AB04. **12.NOSITELJ ODOBRENJA:** Genzyme Europe B.V., Paasheuvelweg 25, 1105 BP Amsterdam, Nizozemska **13.BROJ ODOBRENJA ZA STAVLJANJE LIJEKA U PROMET:** EU/1/01/188/001-006 **14. NAČIN I MJESTO IZDAVANJA:** Na recept, u ljekarni.

DATUM REVIZIJE: 17.4.2020.

Detaljnije informacije o ovom lijeku dostupne su na web stranici Europske agencije za lijekove http://www.ema.europa.eu.

Ovo je skraćeni Sažetak opisa svojstava lijeka te sukladno Pravilniku o načinu oglašavanja lijekovima (Narodne Novine broj 43/15) molimo prije propisivanja lijeka Fabrazyme pročitajte zadnji odobreni Sažetak opisa svojstava lijeka i Uputu o lijeku.

SAMO ZA ZDRAVSTVENE RADNIKE

SANOFI GENZYME

sanofi-aventis Croatia d.o.o. | Heinzelova 70 | 10000 Zagreb | Croatia | MAT-HR-2000199- 1.0 - 08/2020

OVO JE PRIMARNI CILJ LEMTRADE

Utjecaj na važne trenutke u životu

▼Ovaj je lijek pod dodatnim praćenjem. Time se omogućuje brzo otkrivanje novih sigurnosnih informacija. Od zdravstvenih radnika se traži da prijave svaku sumnju na nuspojavu za ovaj lijek. Upute za prijavljivanje dostupne su na www.halmed.hr.

5 godina dosljedne učinkovitosti i sigurnosnog profila[2]

Poboljšanje onesposobljenosti	Snaga smanjenja progresije i potencijal poboljšanja onesposobljenosti[2]
Očuvanje volumena mozga	Očuvanje volumena mozga smanjenjem moždane atrofije[2,3]
Relapsi	Dugoročno bez relapsa (85% bolesnika bilo je bez relapsa u 5. godini)[2]
Mehanizam djelovanja	Selekcija, deplecija i repopulacija T i B limfocita može promijeniti ravnotežu imunog sustava i smanjiti aktivnost bolesti[4]
Doziranje	2 ciklusa liječenja u 12 mjeseci. Ako je potrebno mogu se primijeniti do 2 dodatna ciklusa liječenja[1]

Reference:
1. Sažetak opisa svojstava lijeka Lemtrada, www.ema.europa.eu, siječanj 2020. **2.** Coles AJ, Cohen JA, Fox EJ, et al. Alemtuzumab CARE-MS II 5-year follow-up. *Neurology*. 2017;89:1-10. **3.** Miller DH, Barkhof F, Frank JA, et al. Measurement of atrophy in multiple sclerosis: pathological basis, methodological aspects and clinical relevance. *Brain*. 2002;125:1676-1695. **4.** Ruck T, Bittner S, Wiendl H, et al. Alemtuzumab in multiple sclerosis: mechanism of action and beyond. *Int J Mol Sci*. 2015;16:16414-16439.

SANOFI GENZYME

LEMTRADA® alemtuzumab 12mg IV

SAMO ZA ZDRAVSTVENE RADNIKE
sanofi-aventis Croatia d.o.o. | Heinzelova 70 | 10000 Zagreb | Hrvatska | GZHS.LEMT.20.01.0031a (04/20)

LEMTRADA®
alemtuzumab 12mg IV

▼Ovaj je lijek pod dodatnim praćenjem. Time se omogućuje brzo otkrivanje novih sigurnosnih informacija. Od zdravstvenih radnika se traži da prijave svaku sumnju na nuspojavu za ovaj lijek. Upute za prijavljivanje dostupne su na www.halmed.hr.

SKRAĆENI SAŽETAK OPISA SVOJSTAVA LIJEKA – 1. NAZIV LIJEKA I SASTAV: Lemtrada 12 mg koncentrat za otopinu za infuziju. Jedna bočica sadrži 12 mg alemtuzumaba u 1,2 ml (10 mg/ml). Alemtuzumab je monoklonsko protutijelo koje se proizvodi u suspenziji stanične kulture sisavaca (jajnici kineskog hrčka) u hranjivom mediju tehnologijom rekombinantne DNK. **2. TERAPIJSKE INDIKACIJE:**Lemtrada je indicirana kao monoterapija koja modificira tijek bolesti kod visoko aktivne relapsno remitentne multiple skleroze (RRMS) kod odraslih bolesnika kod kojih je bolest visoko aktivna unatoč cjelovitom i odgovarajućem liječenju barem jednom terapijom koja modificira tijek bolesti ili kod odraslih bolesnika s brzim razvojem teške RRMS što se definira pojavom 2 ili više relapsa koji onesposobljuju bolesnika tijekom jedne godine te pojavom jedne ili više lezija naglašenih gadolinijevim kontrastnim sredstvom vidljivih na snimci mozga magnetskom rezonancijom ili značajnim povećanjem broja T2 lezija u usporedbi s prethodnom, nedavno učinjenom magnetskom rezonancijom **3. DOZIRANJE I NAČIN PRIMJENE:** Preporučena doza alemtuzumaba je 12 mg/dan, a primjenjuje se intravenskom infuzijom u 2 ciklusa liječenja te ako je potrebno mogu se primijeniti do 2 dodatna ciklusa liječenja. Početno liječenje. Prvi ciklus - 12 mg/dan tijekom 5 uzastopnih dana (ukupna doza 60 mg); drugi ciklus - 12 mg/dan tijekom 3 uzastopna dana (ukupna doza 36 mg) primijenjeno 12 mjeseci nakon prvog ciklusa liječenja. Mogu se razmotriti najviše dva dodatna ciklusa liječenja ako je potrebno (treći ili četvrti ciklus) - 12 mg/dan tijekom 3 uzastopna dana (ukupna doza od 36 mg) primijenjeno najmanje 12 mjeseci nakon prethodnog ciklusa liječenja. Propuštene doze ne smiju se primijeniti istoga dana kada i doza predviđena po rasporedu. *Praćenje bolesnika.* Potrebno je praćenje bolesnika radi utvrđivanja sigurnosti od početka prvog ciklusa liječenja do najmanje 48 mjeseci nakon posljednje infuzije drugog ciklusa liječenja. Ako se primjenjuje treći ili četvrti ciklus: praćenje sigurnosti nastavlja se do najmanje 48 mjeseci nakon posljednje infuzije. *Premedikacija.* Bolesnici moraju tijekom svakog od prva 3 dana bilo kojeg ciklusa liječenja primiti premedikaciju kortikosteroidima neposredno prije primjene lijeka LEMTRADA. Osim toga, može se razmotriti i premedikacija antihistaminicima i/ili antipireticima. U svih se bolesnika mora primijeniti peroralna profilaksa za infekciju herpesom, koja počinje prvog dana svakog ciklusa liječenja i traje još najmanje mjesec dana nakon liječenja lijekom LEMTRADA. *Starije osobe.* Klinička ispitivanja nisu obuhvatila bolesnike starije od 61 godine. Nije utvrđeno reagiraju li stariji bolesnici drukčije od mlađih bolesnika. *Oštećenje bubrežne ili jetrene funkcije.* LEMTRADA nije ispitivana u bolesnika s oštećenjem bubrežne ili jetrene funkcije. *Pedijatrijska populacija.* Sigurnost i djelotvornost lijeka LEMTRADA u djece s MS-om u dobi od 0 do 18 godina još nisu ustanovljene. Nema relevantne primjene alemtuzumaba kod djece u dobi od rođenja do manje od 10 godina za liječenje multiple skleroze. *Način primjene.* LEMTRADA se prije infuzije mora razrijediti. Razrijeđena otopina primjenjuje se intravenskom infuzijom tijekom razdoblja od približno 4 sata. **4. KONTRAINDIKACIJE:** Preosjetljivost na djelatnu tvar ili neku od pomoćnih tvari. Infekcija virusom humane imunodeficijencije (HIV). Bolesnici s teškom aktivnom infekcijom sve do potpunog izlječenja. Bolesnici s nekontroliranom hipertenzijom. Bolesnici s arterijskom disekcijom cervikocefaličnih arterija moždanim udarom, anginom pektoris ili infarktom miokarda u povijesti bolesti. Bolesnici s poznatom koagulopatijom, na terapiji antitrombocitnim lijekovima ili antikoagulansima. Bolesnici s istodobnim drugim autoimunim bolestima (osim MSa). **5. POSEBNA UPOZORENJA I MJERE OPREZA PRI UPORABI:** Ne preporučuje se za bolesnike kod kojih bolest nije aktivna ili za one koji su stabilni na trenutnoj terapiji. Bolesnicima koji se liječe lijekom LEMTRADA mora se dati uputa o lijeku, Kartica za bolesnika i Vodič za bolesnika. Bolesnici prije liječenja moraju biti informirani o rizicima i koristima te o nužnosti da pristanu na praćenje od početka liječenja do najmanje 48 mjeseci nakon posljednje infuzije u drugom ciklusu liječenja lijekom LEMTRADA. Ako se primjenjuje dodatni ciklus, praćenje sigurnosti se treba nastaviti do najmanje 48 mjeseci nakon posljednje infuzije. Kako bi se smanjio rizik od infekcije bolesnici koji primaju lijek LEMTRADA trebali bi izbjegavati uzimanje sirovog ili nedovoljno kuhanog mesa, mekanih sireva i nepasteriziranih mliječnih proizvoda dva tjedna prije, tijekom i barem mjesec dana nakon infuzije lijeka LEMTRADA. *Autoimunost*. Liječenje može dovesti do stvaranja protutijela na vlastiti organizam i povećati rizik od razvoja autoimuno posredovanih stanja koja mogu biti ozbiljna i opasna po život, uključujući poremećaje štitnjače, imunu trombocitopenijsku purpuru (ITP), nefropatije (npr. bolest s protutijelima na glomerularnu bazalnu membranu), autoimuni hepatitis i stečenu hemofiliju. U razdoblju nakon stavljanja lijeka u promet, zabilježeni su slučajevi bolesnika kod kojih su se razvili višestruki autoimuni poremećaji nakon liječenja lijekom LEMTRADA. Kod bolesnika koji razviju autoimunost treba procijeniti postojanje drugih stanja posredovanih autoimunošću.*Preporučene laboratorijske pretrage za praćenje bolesnika*. Najmanje do 48 mjeseci nakon posljednjeg ciklusa liječenja lijekom LEMTRADA, treba periodički provoditi kliničke preglede i laboratorijske pretrage, kako bi se pratila pojava ranih znakova autoimune bolesti: kompletna krvna slika s diferencijalnom krvnom slikom, serumske transaminaze razine kreatinina u serumu i mikroskopska analiza mokraće (prije početka liječenja i u mjesečnim intervalima nakon toga), pretraga funkcije štitnjače, kao što je razina hormona koji stimulira rad štitnjače (prije početka liječenja i svaka 3 mjeseca nakon toga). Za potpune informacije o posebnim upozorenjima i mjerama opreza pri uporabi pogledajte cjeloviti Sažetak svojstava lijeka Lemtrada. **6. INTERAKCIJE S DRUGIM LIJEKOVIMA I DRUGI OBLICI INTERAKCIJA:** Nisu provedena službena ispitivanja interakcija drugih lijekova s lijekom LEMTRADA kod primjene preporučene doze u bolesnika s multiplom sklerozom. **7. PLODNOST, TRUDNOĆA I DOJENJE:** Žene u reproduktivnoj dobi moraju primjenjivati djelotvornu kontracepciju tijekom liječenja lijekom LEMTRADA i do 4 mjeseca nakon svakog ciklusa liječenja. *Trudnoća*. Ograničeni su podaci o primjeni alemtuzumaba u trudnica. LEMTRADA se smije primjenjivati tijekom trudnoće samo ako potencijalna korist opravdava mogući rizik za plod. Alemtuzumab može prijeći placentarnu barijeru i tako potencijalno predstavljati rizik za plod. Ispitivanja na životinjama pokazala su reproduktivnu toksičnost. Nije poznato može li alemtuzumab uzrokovati oštećenje ploda kada se primjenjuje u trudnica niti utječe li na sposobnost reprodukcije. Bolest štitnjače predstavlja poseban rizik za trudnice. Ako se hipotireoza tijekom trudnoće ne liječi, postoji povećan rizik od spontanog pobačaja i štetnih učinaka na plod, kao što su mentalna retardacija i patuljast rast. U majki s Gravesovom bolešću, majčina protutijela koja stimuliraju receptore hormona štitnjače mogu se prenijeti na plod u razvoju i uzrokovati prolaznu neonatalnu Gravesovu bolest. Dojenje. Nije poznato izlučuje li se alemtuzumab u majčino mlijeko u ljudi. Ne može se isključiti rizik za dojenu novorođenčad/dojenčad. Stoga dojenje treba prekinuti tijekom svakog ciklusa liječenja lijekom LEMTRADA i 4 mjeseca nakon posljednje infuzije u sklopu svakog ciklusa liječenja. *Plodnost:* Nema odgovarajućih kliničkih sigurnosnih podataka o učinku lijeka Lemtrada na plodnost **8. UTJECAJ NA SPOSOBNOST UPRAVLJANJA VOZILIMA I RADA SA STROJEVIMA:** LEMTRADA malo utječe na sposobnost upravljanja vozilima i rada sa strojevima. Neke od reakcija povezanih s infuzijom (npr. omaglica) mogle bi privremeno utjecati na bolesnikovu sposobnost upravljanja vozilima ili rada sa strojevima, pa je potreban oprez do prestanka istih. **9. NUSPOJAVE:** Najčešće nuspojave lijeka LEMTRADA (u ≥ 20% bolesnika) bile su osip, glavobolja, pireksija i infekcije dišnih puteva. *Vrlo česte (≥ 1/10):* Infekcija gornjih dišnih putova, infekcija mokraćnih putova, infekcije herpes virusom, limfopenija, leukopenija, uključujući neutropeniju, Basedowljeva bolest, hipertireoza, hipotireoza, glavobolja*, tahikardija*, crvenilo praćeno osjećajem vrućine*, mučnina*, urtikarija*, osip*, pruritus*, generalizirani osip* pireksija*, umor*, zimica*. *Česte (≥ 1/100 i < 1/10)*: Infekcije herpes zosterom, infekcije donjih dišnih putova, gastroenteritis, oralna kandidijaza, vulvovaginalna kandidijaza, gripa, upala uha, pneumonija, vaginalna infekcija, infekcija zuba, papilomi na koži, limfadenopatija, imuna trombocitopenijska purpura, trombocitopenija, anemija, smanjene vrijednosti hematokrita, leukocitoza, sindrom otpuštanja citokina*, preosjetljivost uključujući anafilaksiju*, autoimuni tireoiditis uključujući subakutni tireoiditis, guša, pozitivna protutijela na štitnjaču, nesanica*, anksioznost, depresija, relaps multiple skleroze, omaglica*, hipoestezija, parestezija, tremor, disgeuzija*, migrena*, konjunktivitis, endokrina oftalmopatija, zamagljen vid, vrtoglavica, bradikardija*, palpitacije*, hipotenzija*, hipertenzija*, dispneja*, kašalj, epistaksa, štucanje, bol u ustima i ždrijelu, astma, bol u abdomenu, povraćanje, proljev, dispepsija*, stomatitis, povišene vrijednosti AST, povišene vrijednosti ALT, eritem*, ekhimoza, alopecija, hiperhidroza, akne, kožne lezije, dermatitis, mialgija, slabost mišića, artralgija, bol u leđima, bol u udovima, grčenje mišića, bol u vratu, mišićno-koštana bol, proteinurija, hematurija, menoragija, neredovite mjesečnice, nelagoda u prsištu*, bol*, periferni edem, astenija, bolest nalik gripi, malaksalost, bol na mjestu infuzije, povišena vrijednost kreatinina u krvi, kontuzija, reakcija povezana s infuzijom. *Manje česte (≥ 1/1000 i < 1/100)*: Onihomikoza, gingivitis, gljivična infekcija kože, tonsilitis, akutni sinusitis, celulitis, pneumonitis, tuberkuloza, citomegalovirusna infekcija, pancitopenija, hemolitička anemija, stečena hemofilija A, smanjeni apetit, poremećaj osjeta, hiperestezija, tenzijska glavobolja, diplopija, bol u uhu, fibrilacija atrija*, stezanje u grlu*, nadražena grla, konstipacija, gastroezofagealna refluksna bolest, krvarenja iz desni, suha usta, disfagija, poremećaj probavnog sustava, hematokezija, kolecistitis uključujući akalkulozni kolecistitis i akutni akalkulozni kolecistitis, mjehurići, noćno znojenje, oticanje lica, ekcem, mišićno-koštana ukočenost, nelagoda u udovima, nefrolitijaza, ketonurija, nefropatije uključujući i anti-GBM bolest, cervikalna displazija, amenoreja, smanjenje tjelesne težine, povećanje tjelesne težine, smanjen broj crvenih krvnih stanica, pozitivan test na bakterije, povišena vrijednost glukoze u krvi, povećan srednji volumen stanice. *Pojmovi označeni * obuhvaćaju nuspojave prijavljene kao reakcije povezane s infuzijom.* Za ostale nuspojave pogledajte cjeloviti Sažetak opisa svojstava lijeka. **10. PREDOZIRANJE:** U kontroliranim kliničkim ispitivanjima dva bolesnika primila su do 60 mg lijeka LEMTRADA (tj. ukupnu dozu za početni ciklus liječenja) u jednoj infuziji te su se u njih javile ozbiljne reakcije (glavobolja, osip i hipotenzija ili sinusna tahikardija). Doze lijeka LEMTRADA veće od onih ispitivanih u kliničkim ispitivanjima mogu pojačati intenzitet i/ili produljiti trajanje reakcija povezanih s infuzijom ili njihove učinke na imunološki sustav. **11. FARMAKODINAMIČKA SVOJSTVA:** Farmakoterapijska skupina: imunosupresivi, selektivni imunosupresivi. ATK oznaka: L04AA34. Alemtuzumab je humanizirano monoklonsko protutijelo dobiveno tehnologijom rekombinantne DNK, usmjereno na glikoprotein CD52 molekularne težine 21-28 kD. Smanjenje razine cirkulirajućih B i T stanica primjenom lijeka LEMTRADA, te njihova kasnija repopulacija, mogu smanjiti mogućnost relapsa, što u konačnici usporava napredovanje bolesti. **12. NOSITELJ ODOBRENJA:** Sanofi Belgium, Leonardo Da Vincilaan 19, B-1831 Diegem, Belgija . **13. BROJ ODOBRENJA ZA STAVLJANJE LIJEKA U PROMET:** EU/1/13/869/001**. 14. NAČIN I MJESTO IZDAVANJA:** Na recept, u ljekarni.

Detaljnije informacije o ovom lijeku dostupne su na internetskoj stranici Europske agencije za lijekove www.ema.europa.eu

Ovo je Skraćeni sažetak opisa svojstava lijeka. Sukladno Pravilniku o načinu oglašavanja o lijekovima (Narodne novine broj 43/15) molimo prije propisivanja lijeka LEMTRADA pročitajte zadnji odobreni Sažetak opisa svojstava lijeka i Uputu o lijeku.

SANOFI GENZYME

Bilješke / Notes