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**March 22–25, 2018**

**Warsaw, Poland**

# Polski Przegląd Neurologiczny



**CZASOPISMO EDUKACYJNE POLSKIEGO TOWARZYSTWA NEUROLOGICZNEGO**

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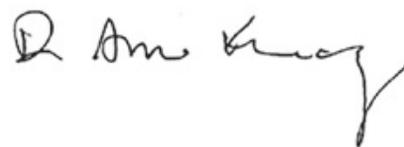
## GUEST EDITORS

### **Controversies in Neurology 2018, Warsaw, Poland**

This year's CONy was once more an exciting event. Again we experienced an exciting four-day conference with top-line faculty discussing and debating many of the pressing questions clinical neurologists face in all fields of neurology. These leading experts helped to illuminate the program made in their subspecialties in recent years, but the stress was, of course, on the unknown and on the issues still under investigation. The program included not only Multiple Sclerosis, Stroke, Dementia, Headache, Movement disorders, Epilepsy and Neuroimmunology, In addition, there were three sessions dedicated to important issues which have a special local relevance Wilson's disease program, and the History of Neurology in Poland.

The present special issue of the Journal of Polish Neurological Society, devoted exclusively to the 12<sup>th</sup> meeting on Controversies in Neurology includes abstracts of invited lectures and free communication presented at the meeting. It is a tribute to this event allowing it to remain immortalized in an international academic journal.

We look forward to more debates and enlightening discussions in CONy 13<sup>th</sup>, which will take place in Madrid, Spain (April 4–7, 2019) (<http://www.comtecmed.com/cony/2018/Default.aspx>).



A.D. Korczyn  
Sackler School of Medicine Tel-Aviv University, Israel

### **Dear Authors and Readers,**

On behalf of prof. Amos Korczyn and myself as the Guest Editors of this supplementary issue of "Polish Neurological Review" journal, I would like to welcome you to the 12<sup>th</sup> World Congress on Controversies in Neurology which is organized this year in Warsaw, Poland. "Polish Neurological Review" is the official educational journal of Polish Neurological Society and the CONy congress is organized under auspices of our society. I hope all your abstracts will be a valuable teaching offer and will also convince participants to visit specific sessions and posters on plenty of highly interesting topics included in the Congress programme.

I wish all of you a great time in Warsaw, both scientific, educational and cultural as well.



J. Slawek  
President of Polish Neurological Society

# **INVITED SPEAKERS ABSTRACTS**

12<sup>th</sup> World Controversies in Neurology  
March 22–25, 2018

Warsaw, Poland

# ALZHEIMER'S DISEASES AND DEMENTIA

## Does cognitive stimulation have value in the treatment of MCI and early AD?

**R. Bullock**

Research, Kingshill Research Centre, UK

Cognitive stimulation is a range of activities aimed at improving cognitive and social functioning. The interventions can be administered in groups or to individuals, so appear to be an effective use of resources. However, the published results to date only deliver low quality evidence at best, mainly from high-income countries. Before definitive recommendations can be made to make cognitive stimulation an available and reimbursed intervention, further studies need to be conducted, particularly in lower income countries. Until that time the value of cognitive stimulation in MCI and AD remains limited.

## The roads to decode the genetic architecture of neurodegenerative diseases

**O. Chiba-Falek**

Neurology, Duke University School of Medicine, USA

Large multi-center genome-wide association studies (GWAS) found associations between multiple genomic loci and neurodegenerative diseases of aging. While GWAS candidate genes were inferred by proximity to the associated SNPs, for many disease-associated loci the precise target genes have yet to be identified. Furthermore, the specific causal genetic variants and the molecular mechanisms through which they exert their pathogenic effects remain largely unknown. The large majority of GWAS associated SNPs are in noncoding, intergenic and intragenic, regions of the genome, suggesting regulatory function. Moreover, expression quantitative trait (eQTL) studies from our lab and others, described the *cis*-association of disease-associated variants with gene expression in brain tissues vulnerable to disease pathology, however, the particular functional variants that directly influence gene expression have yet to be defined and validated. In the post-GWAS era the key question is how to move forward from association to causation in the research arena of the genetic etiologies of age-related neurodegenerative diseases? Our research focuses on mechanistic understanding of noncoding regions in loci associated with neurodegenerative disorders. To decode GWAS-discoveries we apply a multifaceted strategy, combining *in silico*, *in vitro* and *in vivo* approaches. Particularly, we utilize single cells from brain regions affected in Alzheimer's-Parkinson's spectrum diseases to examine neuronal vs. glia disease-specific changes in chromatin accessibility and gene expression, integrate epigenome datasets, and complement these experiments using aging-induced iPSC-derived neuronal models. This talk will feature advancements and challenges in the study of *SNCA* in relation to synucleinopathies, and *TOMM40-APOE* in the context of dementias.

## Predicting clinical improvement after shunting in hydrocephalus — why it is so difficult?

**M. Czosnyka**

Division of Neurosurgery, Dept of Clinical Neurosciences, University of Cambridge, UK

Normal Pressure Hydrocephalus (NPH) is probably an only type of reversible dementia. Starting from 1950', when the first CSF shunts became available, there was a remarkable outbreak of enthusiasm about shunting for hydrocephalus. Different criteria, apart from clinical symptoms and radiography, have been considered. Large ventricles, distorted neural tracks, decrease CBF in white matter around ventricles and other specific loci in a brain, "DESH" picture — all seem to be informative but not very specific. New look with high-resolution MRI seems to open novel horizons; dynamic MRI-CSF flow can be also helpful. From physiological measurement, infusion test with compensatory parameters has equal number of enthusiasts and critics. Measurement of pulse amplitude of ICP or a slope of amplitude-pressure line is advocated as useful in selected centers. Slow vasogenic waves in ICP and pressure-volume compensatory reserve is used rarely. Long-term (72 hours) CSF drainage can be considered as "trial shunting". Role of biochemistry is not very strongly documented, although promising. None of the tests/measurements have alone strong predictive power. Probably combinations of them will be more useful. There is no ideal predictive test in hydrocephalus. Nowadays, we shunt elder patients with more co-morbidity. Therefore typical profile of average NPH patient is more heterogeneous than 40–50 years ago. Excluding co-morbidities with confirming faulty CSF circulation seems to be a plausible strategy. Finding a difference between two states: "too much water" (NPH) and "not enough brain" (atrophy) is challenging, as there is possibly a sizeable area of overlap.

## Should agitation in ad be treated with antipsychotics?

**T. Gabryelewicz**

Department of Neurodegenerative Disorders, Mossakowski Medical Research Centre Polish Academy of Sciences, Poland

Behavioral symptoms such as agitation and aggression are of great importance to family and caregivers as these tend to be the most distressing. When nonpharmacologic management strategies are not sufficient to alleviate patients' behavioral symptoms, pharmacologic treatment may be indicated. The reason for initiating drug therapy must be clearly defined at the outset, and the desired management goals must be identified. Such decisions will need to balance the potential benefits and harms of a particular intervention as compared to other therapeutic options for the individual patient. The use of an antipsychotic medication in patients with AD can be appropriate, particularly in individuals with dangerous agitation, aggression or psychosis, and can minimize the risk of violence, reduce patient distress, improve patient's quality of life, and reduce caregiver burden. There is consistent evidence that these drugs can cause side effects, like drowsiness, rigidity, unusual movements. Studies have linked some of these to a higher risk of death for people with dementia. The FDA has placed a "black box" warning on these drugs describing the risks. In clinical trials, the benefits of antipsychotic medications in AD are modest. Decisions about the treatment of agitation should be an outgrowth of the initial assessment and an understanding of the goals and preferences of the patient and the others involved with the patient. Agitation in AD patients is an ominous sign, frequently leading to nursing home placement. Is it justified to treat patients with neuroleptic drugs in spite of their significant adverse effects?

## Pharmacological treatment of Alzheimer disease in 2028

**E. Giacobini**

Internal medicine, Rehabilitation and Geriatrics, University of Geneva Hospitals, Switzerland

Given the average duration of clinical trials (Phase I to Phase III) of 9–10 years at an average cost of 5–7 billion \$ (SCOTT, 2013) is not too early to consider today the possibility of a pharmacological treatment for 2028. The cause of the disease still escape us and the major investment made so far in developing anti- $\beta$  interventions have not given clinically relevant results, therefore, we are limited to design therapies based on results derived from molecular imaging (PET). This approach moves from traditional neuropathological criteria into a phenotype-targeted therapy which may or may not be casually related. The multistate transition model (C. Jack et al. 2016, 2017) utilizes transition rates to estimate the frequency of each state based on long-term follow up of cognitively unimpaired individuals from 50 to 90 years. The most recent one (C. Jack, 2017) combines three different imaging-based measurements *in vivo*:  $\beta$ -amyloid aggregation, tauopathy, and neurodegeneration, evaluated with repeated PET tested in the same subject. Subtyping based on these criteria makes it possible to design a differentiated therapy targeting specific pathologies in the individual patient. This approach emphasizes the critical need to continue our research in order to find the cause of the disease the best therapy within the next ten years.

## Is amyloid deposition a non-specific manifestation of aging?

**P. Giannakopoulos**

Medical Direction, University Hospitals of Geneva, Switzerland

PET amyloid imaging has been initially considered as the main tool to investigate the beginning of the AD process in cognitively intact individuals. The percentage of PET-amyloid positive controls is of 6% at age 60 but reaches 50% at age 90 in community-based sample pointing to the fact that amyloid deposition (as amyloid plaque formation) is closely related to the aging process. In fact, increased PiB binding has been reported in almost 20–30% of cognitively preserved elders mainly in posterior cingulate cortex, precuneus and prefrontal cortex. Compared with amyloid-negative, amyloid-positive controls showed a moderate decline in verbal and visual episodic memory over 36 months but no changes in non-memory functions. Most importantly, the absence of amyloid in MCI cases is associated with cognitive stability at 36 months. Increased PET-PiB binding is associated with brain atrophy, cortical thinning but also decreased cortical metabolism, aberrant functional connectivity at rest and decreased task-related deactivation of the default mode network. Altogether these data suggest that contrasting with CSF  $A\beta$  and tau changes that sign a biological diathesis to neurodegeneration, amyloid positivity in the human brain are present as a part of the aging process representing a critical step preceding the installation of AD pathophysiology. However, not all cases with elevated PET-PiB bindings evolve to AD and several cases develop dementia not necessarily related to amyloid aggregation. Several recent contributions revealed that neurodegeneration takes place without a temporal link with fibrillar amyloid deposits. Alternative but less frequent pathways exist starting from tau deposition with modest  $A\beta$  pathology.

## Is inflammation a valid target for intervention in AD?

**P. Giannakopoulos**

Medical Direction, University Hospitals of Geneva, Switzerland

Immunological mechanisms in the human brain have been recently shown to be involved in Alzheimer disease (AD) lesion propagation via the activation of microglia and astrocytes that lead to the release of pro and anti-inflammatory mediators. These mechanisms may be triggered by external factors (systemic inflammation, obesity, hypertension, cardiovascular risk factors) but their consequences show an impressive inter-individual variability. The ligand-receptor interaction that controls the expression of microglia is perturbed in AD with increasing activation of this cellular population due to A $\beta$  accumulation that in turn increase A $\beta$  production given the activation of cytokines and intracellular signaling pathway. It remains, however, unclear why A $\beta$  continues to accumulate and why AD pathology progresses despite chronic microglia activation. In the same line, the activation of astrocytes in AD may allow for removing A $\beta$  peptide preventing its accumulation in extracellular space but may also favor the formation of A $\beta$  aggregates via the production of a very large number of proinflammatory cytokines. After the failure of several disease-modifying treatments in AD, focusing on neuroinflammation appears an *ultima ratio* choice. The pertinence of this approach is, however, questionable given the complexity and instability of the inflammatory reactions in the human brain that have been documented by the accumulation of negative data for non-steroidal anti-inflammatory drugs, COX-2 selective compounds, and nutraceuticals. The main obstacle is the number of targets and their double role in human biology: microglial phenotypes are multiple and rapidly changing, most of the cytokines overexpressed in AD have a double role (deleterious but also protective), astrocytes control neuronal homeostasis via their trophic function but may contribute to A $\beta$ -mediated toxicity and tau hyperphosphorylation. Is there a real chance to identify one molecule or a combination of agents that: a. decreases the detrimental effect of neuroinflammation but preserve the normal immune response to lesion formation, and b. decrease A $\beta$  production and tau abnormal phosphorylation without affecting key pathways for neurotrophism and survival? Is it possible to reach this objective in the absence of valid biomarkers and animal models for neuroinflammation, modest results in molecular imaging, and, last but not least, no definite knowledge about the temporal evolution and staging of neuroinflammatory phenomena? One should not forget that amyloid-based clinical trials had an impressive cost but still have been broadly failed despite a simpler biology. Investing on neuroinflammation due to the absence of therapeutic promises may be risky leading to future disappointments.

## Genomic analysis points to pathways of neurodegeneration

**J. Hardy**

Department of Molecular Neuroscience, UCL Institute of Neurology, UK

As we identify many causative and risk genes for neurodegenerative syndromes through positional cloning, exome sequencing, and genome-wide association studies it is becoming clear that these are mapping to specific pathways. In this lecture, I shall discuss this phenomenon and its importance in delineating specific vulnerabilities of specific neuron types. For Alzheimer's disease, I will outline that the current evidence supports the view that the microglial response to membrane damage is critical and that this suggests that Ab disruption of neuronal membranes may be the initiating event. For fronto-temporal dementia, many of the genes involved are components of the endosomal/lysosomal pathway. For Parkinson's disease some genes are also lysosomal or endosome/lysosome components whereas others, particularly in early onset disease, are involved in mitophagy. For FTD/ALS many genes are ubiquitin proteasome genes whereas for pure ALS genes the majority are RNA metabolism genes. For

the ataxias, many genes are involved either in Ca homeostasis (Purkinje cells) or ubiquitin proteasome (granule cells). I will discuss how these vulnerabilities are likely to be related to the functions of the relevant neurons and how understanding these vulnerabilities may help us as we seek treatments.

## **General anesthesia does not increase the risk of dementia**

**L. Honig**

Neurology, Taub Institute, and Sergievsky Center, Columbia University Medical Center, USA

In clinical practice, it is common to have patients present with a history of onset of dementia symptoms after surgery with anesthesia. Most often, in the postoperative period, symptoms of sedation and/or delirium may occur, with confusion, disorientation and often psychosis, such as hallucinations and/or delusions. Following resolution of the postoperative period, family members and associates may note symptoms of dementia such as memory or language problems. Patients and their families often associate the surgery, and in particular, the general anesthesia that commonly is used, as an etiological, causal factor, relating to onset of dementia symptoms. The alternate possibility is that in the postoperative state, whether due to the stress of surgery, sedation or other effects of anesthetics, and sensorium-affecting effects of opioids often used intraoperatively and postoperatively are simply “unmasking” dementia symptoms in persons with the underlying neurodegenerative disease, who are otherwise well-compensated and managing without obvious problems. Furthermore, once a patient has manifested delirium symptoms, there is a heightened sensitivity of family members and associates towards their mental state, and small lapses in memory or cognition are noticed more than they likely would have been prior to the operative period. Despite some animal experiments attempting to show that anesthetics might affect beta-amyloid and tau accumulations, the timing of the symptoms, and the epidemiological evidence all strongly militate against the likelihood of any effect of anesthetics on the risk of dementia. Rather operative periods are simply mileposts, at which dementia symptoms may be first noticed for the reasons described above.

## **Obstructive sleep apnea does not increase the risk of dementia**

**L. Honig**

Neurology, Taub Institute, and Sergievsky Center, Columbia University Medical Center, USA

Obstructive sleep apnea (OSA) is increasingly diagnosed in Europe and North America. This is both due to a likely real increased prevalence of this condition due to increasing obesity in the population, and also due to ascertainment, with increased diagnosis due to the more widespread availability of sleep studies, instrumentation, and laboratories. Given the increasing prevalence of both OSA and Alzheimer’s disease in the aging population, it is unsurprising that some have argued that there might be a connection between the presence of OSA and dementia risk. In part, this is driven by the idea that decreased oxygenation of the blood, might somehow cause either amyloid and tau pathology or independent neurodegeneration. And in part, this is driven by the observation that persons with OSA, provided with nocturnal continuous positive airway pressure (CPAP) may feel subjectively, and in some studies even objectively, more alert and wakeful during the daytime hours. Despite these observations, there is little evidence that nocturnal hypoxic episodes, such as are found with obstructive sleep because either beta-amyloid or tau degenerative changes, nor that they cause other brain changes that would result in reversible dementia. In persons with apparent concomitant Alzheimer’s disease and OSA, controlled trials of CPAP have indeed sometimes shown mild improvements in alertness, attention, and executive function, but have not “cured” or significantly benefited persons of their primary cortical dementia symptoms such as language, memory, and visuospatial dysfunction. Thus, evidence to date does not support an etiologic effect of OSA on the risk of dementia.

## The term Alzheimer's disease should be dropped as it is impeding future research — Con

**D.S. Knopman**

Neurology, Mayo Clinic, USA

The term Alzheimer's disease has unfortunately come to mean many things to different people. However, as a term that has been in the public eye for several decades, it would be needlessly confusing to abandon it. The very identity of the many advocacy groups around the world revolves around the term Alzheimer's disease. Politicians have targeted Alzheimer's disease for additional funding. Changing the name would create confusion. To borrow terminology from the commercial sphere, the "brand identity" of Alzheimer's disease is a major asset for the field. It is a rallying point for fundraising both private and public, and it is a rallying point for advances in public policy. There is no question that the parallel usages of the term Alzheimer's disease as a synonym for amnestic dementia, on the one hand, and a neuropathological diagnosis, on the other hand, can sometimes lead to misrepresentations of mechanisms and misunderstandings of clinical diagnoses. Personally, this writer favors the use of the term Alzheimer's disease to be limited to a pathologically defined disease based on a particular burden of neuritic amyloid plaques and an isocortical distribution of neurofibrillary tangles. That means that persons with mild cognitive impairment or dementia that is believed to be due to Alzheimer's disease would be diagnosed as mild cognitive impairment due to Alzheimer's disease or dementia due to Alzheimer's disease. That terminology would clearly indicate the two key features of the diagnosis, first the syndromic designation (ie MCI or dementia) and second the presumed etiology.

## Can the diagnosis of AD be made solely on biomarker evidence?

**D.S. Knopman**

Mayo Clinic, Rochester MN, USA

This title captures an important issue now facing the field. What is behind the question is a concept that has existential value for the field: "What do we mean by the term 'Alzheimer Disease (AD)'?" (1) Is AD a clinical diagnosis? I would say "No, unlike the term 'dementia,' it is not simply a description of a set of symptoms". Unfortunately, many lay people and many scientists and clinicians outside of the specialist community often use the term "AD" to mean "dementia". That seems like an obviously flawed use of terminology because there are many other conditions including common ones that also cause dementia and even cause amnestic dementia. (2) Is AD a "clinicopathological entity?" Such usage of the term AD has been proposed by some members of the dementia research community, and they use the term "AD" to stand for the combination of a clinical syndrome of amnestic dementia that is reliably or invariably associated with a particular neuropathological substrate of beta-amyloidosis and neurofibrillary tangle deposition. Those who use the term this way have also extended the biological correlates to include biomarkers of beta-amyloidosis and neurodegeneration. While there is some merit to this approach, the research community has clearly demonstrated that the link between amnestic dementia and the AD pathobiology is not nearly as invariant as other diseases (eg, Huntington disease or progressive supranuclear palsy). Thus, there are many individuals with amnestic dementia who lack AD pathobiology and vice versa, many individuals with non-amnestic presentations who have pure AD pathobiology. Thus, I reject the notion of AD as a clinicopathological entity. (3) Is AD a neuropathological designation? I think this is the most legitimate and least ambiguous use of the term "AD" In this view, the term "AD" stands for the combination of beta-amyloidosis and neurofibrillary tangle deposition. Both CSF beta-amyloid and amyloid PET measurements have been validated as reliable proxies for brain amyloidosis; and further that CSF tau and tau PET similarly stand for neurofibrillary

tangle formation. But getting back to the question of this debate: Can the diagnosis of AD be made solely on biomarker evidence?”, this is the background upon which the debate will occur. In particular, with the availability of biomarkers, the field is now able to detect the pathobiology of AD antemortem. So should the field be able to diagnose “AD” on biomarker evidence in both cognitively normal people and persons who are overtly symptomatic?

## **Why have we failed to cure AD?**

**A.D. Korczyn**

Sackler School of Medicine Tel-Aviv University, Ramat-Aviv 69978, Israel

The most popular target in AD clinical trials has been beta-amyloid. However, while this protein has a central role in early onset AD, particularly in those patients carrying mutations in APP, PSEN1 or PSEN2 genes, there is no convincing evidence that it is involved in the pathogenesis of late-onset AD. Additionally, elimination of beta-amyloid has not led to clinical improvement or to arrest disease progression. Therefore, attempts should be directed at other targets, including APOE, inflammation and cardiovascular risk factors.

## **The term “Alzheimer’s disease” should be dropped as it is impeding future research**

**A.D. Korczyn**

Sackler School of Medicine Tel-Aviv University, Ramat-Aviv 69978, Israel

Most early-onset AD (EOAD) cases are familial due to dominant mutations in a few genes. Late onset dementia has a similar pathology to the early onset disease but does not have the same genetic background. In fact, it is a multifactorial disorder. The amyloid deposition in EOAD is due to overproduction, and all those who carry the mutation will accumulate amyloid and develop dementia. In the late-onset disease, amyloid is not overproduced but rather its clearance is reduced. There is no proof that amyloid is toxic in the late disease, and its removal has not led to clinical improvement. Thus calling senile dementia “AD” has been counterproductive.

## **Pathological role of chronic hypoxia in the pathogenesis of Alzheimer’s disease**

**W. Le**

Neurology, 1<sup>st</sup> Affiliated Hospital of Dalian Medical University, China

Alzheimer’s disease (AD) is the most common neurodegenerative disease mainly caused by genetic and environmental perturbation. It is believed that abnormal tau phosphorylation, altered amyloid  $\beta$  ( $A\beta$ ) metabolism and chronic neuroinflammation play important role in the disease pathogenesis. Our previous studies have documented that chronic hypoxia is one of the important environmental factors that may trigger the AD development and aggravate the disease progression. Recently, we have conducted a series of investigations to determine the pathological effects of chronic hypoxia on the onset and development of AD, and we have identified the possible molecular mechanisms underlying the chronic hypoxia-mediated AD pathogenesis. Based on our studies we have found that chronic hypoxia can cause long-lasting inflammation in the brain, and specific tau phosphorylation, mitochondrial disruption and chronic inflammation in the brain. Moreover, we have further documented that

epigenetic modulation of DNA methylation might be the key player in the chronic hypoxia-mediated neurodegeneration in AD. Our findings may represent a new opportunity for the therapeutic intervention of this devastating disease.

## Transmission of misfolded proteins in neurodegenerative disorders: a common mechanism of disease progression

V.M.Y. Lee

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The deposition of  $\beta$ -sheet rich amyloid aggregates formed by disease-specific proteins is a common feature of many neurodegenerative diseases and are believed to cause neuronal dysfunction directly or indirectly. Recent studies have strongly implicated cell-to-cell transmission of misfolded proteins through templated recruitment as a common mechanism for the onset and progression of various neurodegenerative disorders. Emerging evidence also suggests the presence of conformationally diverse “strains” for each type of disease protein, which may be another shared feature of amyloid aggregates, accounting for the tremendous heterogeneity within each category of diseases. In Alzheimer’s disease and other age-related tauopathies, the normally soluble tau protein accumulates as insoluble neurofibrillary tangles whereas in Parkinson’s disease and other related synucleinopathies, the highly soluble  $\alpha$ -synuclein protein are converted to aggregated Lewy bodies in neuron and glia. Finally, in FTLTD-TDP and ALS, TDP-43 forms aggregates in the brain and spinal cord. We have developed mouse models of these neurodegenerative diseases and have used them to test the “transmission” hypothesis and the “strain” hypothesis in order to elucidate mechanisms of progressive spread of this pathology as well as to explore the molecular basis of strain heterogeneity.

## Does general anesthesia increase the risk of dementia?

G. Logroscino

Department of Basic Medicine Neuroscience and Sense Organs — Department of Clinical Research in Neurology of the University of Bari at “Pia Fondazione Card G. Panico” Hospital, University Of Bari Aldo Moro, Italy

There is extreme interest in studying the possible relationship between anesthesia and the onset and progression of cognitive disorders. This is also determined by the increasing number of elderly subjects, in the age of higher risk for cognitive decline and dementia, who undergo surgery. A significant number of patients who are cognitively normal undergoing anaesthesia will develop symptoms of cognitive dysfunction in a limited period of time, generally hours or days. There is general disagreement, however, about the real risk and the prognosis. This is probably due to lack of consistency across the definition of cognitive changes. Post-operative delirium is a good indicator of increased risk of developing cognitive impairment and dementia. Following anesthesia, the decline in cognition is observed in some individuals and this group may be characterized by specific vulnerability for future decline associated with the onset of a specific dementia process. We need to consider that exposure to anesthetics has been shown associated with AD pathology *in vitro*. Clinical studies are less concordant. Consistently, a recent meta-analysis of epidemiological studies showed no clear association in 13 high quality studies but the association was significant when restricted to studies using medical records. Preoperative assessment of cognitive changes may be useful to establish the real risk of the patient undergoing surgery. The cognitive preoperative assessment would allow focused management including specific referral for patients at risk, delirium prevention, specifically optimizing care through more constant observation and monitoring. This could allow more timely treatment options. The debate is still open.

## Can the diagnosis of AD be made solely on biomarker evidence?

**G. Logroscino**

Department of Basic Medicine Neuroscience and Sense Organs — Department of Clinical Research in Neurology of the University of Bari at "Pia Fondazione Card G. Panico" Hospital, University of Bari Aldo Moro, Italy

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the deposition of amyloid plaques and neurofibrillary tangles. Cerebrospinal fluid measures of amyloid-beta, total-tau, and phospho-tau are clinically available and allow detection *in vivo* of both amyloid and tau pathology. With the use of labeled tracers that bind amyloid plaques, the amyloid PET is now clinically available for the detection of amyloid pathology and tracers for tau pathology are becoming available. Structural MR permits to study the progression of neurodegeneration. Therefore, AD is now a clinically and biologically entity with biological fluid and imaging evidences of pathology *in vivo*. We are able to identify an individual with evidence of amyloid deposition with or without evidence of neurodegeneration before the clinical onset of disease or with the presence of minimal clinical signs (preclinical or prodromal AD). Biomarkers *in vivo* have improved both the accuracy of diagnosis, distinction of clinical phenotypes and anticipation of diagnosis. This process is required because the clinical diagnosis is achieved when neurodegeneration may have started several years before and reached a severe stage. Starting optimal therapy at this stage would be ineffective. In conclusion, the diagnosis of AD depends on the definition of disease. If we define the disease based on the underlying pathology, we can reach a diagnosis based only on biomarkers. However, AD is a complex disorder, determined by the different type of pathological lesions and amyloid driven diagnosis may be limited among the elderly.

## Is obstructive sleep apnea an important risk factor for dementia?

**G. Logroscino**

Department of Basic Medicine Neuroscience and Sense Organs — Department of Clinical Research in Neurology of the University of Bari at "Pia Fondazione Card G. Panico" Hospital, University of Bari Aldo Moro, Italy

Obstructive Sleep Apnea Syndrome (OSAS) is characterized by episodes of upper airway obstruction during sleep that results in intermittent hypoxemia and arousal. OSAS causes hypoxia and also decrease the quality of sleep because the sleep is fragmented. Overtime OSAS determine daytime sleepiness, cognitive dysfunctions, and functional decline. The progression of subsequent functional decline may induce over time dementia. The underlying brain damage results from heterogeneous processes including reduced cerebral blood flow, ischemic brain lesions, white and grey matter lesions and loss. The neuropsychology of cognitive impairment in OSAS is still under investigation. The first domains involved include attention, executive functioning, and motor control but on long-term also long-term episodic memory is affected. Several studies involving total sleep loss, sleep reduction and clinically related sleep fragmentation report impaired performance on tasks of frontal lobe function. The mechanisms of OSA-cognitive impairment association are probably not only degenerative. Recent studies show that dementia risk is higher in subjects with OSAS and vascular changes and the severity of cerebrovascular impairment was related to the severity of OSAS. Medications as antipsychotics, narcotics, and anxiolytics could increase the risk of cognitive impairment are subjects with OSAS. CPAP therapy should be therefore considered for OSA both in subjects with MCI and with dementia.

## Is amyloid deposition a non-specific manifestation of aging?

L. Middleton

Neuroepidemiology and Ageing (NEA) Research, School of Public Health, Imperial College, London

High amyloid brain load, mainly in amyloid plaques (APs), together with a high intra-cerebral load of intracellular tau-enriched neurofilament tangles (NFTs) and brain atrophy, as the pathological landmarks of Alzheimer's disease (AD). Indeed, the 2011 (and currently being revised) NIA/AA diagnostic criteria for research purposes postulate that the presence of biomarker-based evidence of the above neuro-pathological findings are key criteria for the diagnosis of AD. Of note, most of the current drug discovery and development programmes of the pharmaceutical industry are targeting amyloid cascade key components as the amyloid hypothesis is thought to represent the core aetiological pathway of this otherwise multi-factorial disease. However, increasingly emerging longitudinal and case-control studies suggest that up to 30% of clinically probable AD patients have below-threshold amyloid load. On the other hand, high amyloid load, as documented by amyloid positron emission tomography (PET) or in cerebrospinal fluid (CSF) studies is found in ~40–50% of patients with mild cognitive impairment (MCI) and 15–30% in cognitively healthy volunteers of a similar age group. These figures increase with increasing age and several studies in older old individuals show increased amyloid load with increasing age. Furthermore, population-based neuro-pathological studies confirm the presence of high levels of post mortem APs and NFTs in the brains of individuals with no history of significant cognitive decline, in particular, those who are APOE4 carriers. These findings and discrepancies prompted the hypothesis of this debate. Our two speakers, both well-known experts in the field, will outline the *pro* and *con* arguments, leading to a wider discussion among the audience on this very important issue.

## Can the diagnosis of AD be made solely on biomarker evidence?

L. Middleton

Neuroepidemiology and Ageing (NEA) Research, School of Public Health, Imperial College, London

Alzheimer's disease (AD) is a devastating and relentlessly progressive neurodegenerative late onset disease, which is reaching epidemic proportions world-wide, due to the unprecedented increase of longevity. AD is defined by the progressive deterioration of memory, executive function and other cognitive domains that result in a progressive inability of patients to function within the society and their own family. All therapeutic trials of novel disease modifying therapies have failed, reflecting our significant gaps of knowledge of the precise biological mechanisms underpinning the disease aetiology. Furthermore, there is an emerging consensus that increasing and accumulating disease pathology precedes by (perhaps) decades the clinical onset. Thus, an optimal intervention aimed at arresting or reversing AD seems to be in the pre-clinical stages, prior to the disease clinical onset. However, we do know that, even in the oldest old, the risk of AD does not exceed 40%, thus 60% of individuals may never develop significant cognitive decline. Identifying high-risk-for AD individuals remains a major challenge in drug development and in secondary prevention strategies. More recently, it has been suggested that the biomarker — based evidence of an abnormally high brain amyloid and tau load (pathophysiological AD biomarkers), together presence of findings suggestive of neurodegeneration, such as hippocampal atrophy, FDG-PET abnormalities or high tau can constitute sufficient basis for the diagnosis of AD, even in the absence of any cognitive decline. Thus, there is increasing popularity for biomarker-based disease diagnosis in the pre-clinical stage; similar to the pre-clinical diagnosis of forms of cancer. However, there are several lines of argument against this concept. Firstly, the pathological significance of the biomarker-based profile in AD is not comparable to that of cancer diagnosis based

on pathology. Secondly, the specificity and sensitivity of the proposed AD-biomarker profile remain to be validated. Thirdly, we know that ~30% of clinically probable AD cases do not carry this profile and that a significant number of cognitively healthy older individuals who do have this biomarker profile are disease free and may well never develop AD. Unlike cancer, AD is primarily a clinical distinct entity whose pathological and biological underpinning mechanisms are not, as yet, known with some precision; our understanding of AD is, probably 20 years behind other common diseases, such as cancer. Finally, it would be ethically and medically improper, in the light of our current knowledge, to suggest to a cognitively healthy individual that she/he has AD; probably the disease that they dread the most, as they grow old. This is different from suggesting high risk, although such statement must also be supported by strong and unequivocal scientific evidence.

## Is inflammation a valid target for intervention in Alzheimer's disease? Pro

**A. Nordberg**

Neurobiology, Care Sciences and Society (NVS), Karolinska Institutet, Sweden

Emerging evidences are underlying the importance of neuroinflammation in Alzheimer's disease (AD) and other neurodegenerative disorders leading to dementia. Most interestingly neuroinflammation appears to have an active role in the pathogenesis of different proteinopathies which strongly motivate to more deeply understand the involvement and time course of early inflammatory processes and their possible causal role in AD disease progression to unravel the relationship and coupling between astrogliosis and different proteinopathies, synaptic functions and cognition. The rapid development of *in vivo* molecular imaging techniques including positron emission tomography (PET) provides unique possibilities for early detection of pathophysiological processes and understand the time course and interaction between different processes in the brain leading to cognitive impairment. Inflammatory processes including astrogliosis and microglia activation well known from post-mortem studies can now be studied *in vivo* by PET. The prominent initially high and then declining astrogliosis in AD during disease progression, contrasting with the increasing beta-amyloid plaque load, suggest that astrocyte activation is implicated in the initiation of AD pathology. Astrocytosis thereby seem to occur earlier in disease time course than tau deposition and cerebral glucose hypometabolism. Astrocytosis may thus not be a reflection of solely dysfunctional non-neuronal cells in AD but a consequence of phenotypic astrocytic changes initiated at very early disease stage contributing to the development of AD disease pathology and at such a tentative target for new therapeutic interventions.

## Is TBI a risk for dementia? Pro

**D. Perl**

Pathology (Neuropathology), Uniformed Services University of the Health Sciences, USA

Many epidemiologic studies have investigated whether prior head trauma represents a risk factor for the subsequent development of dementia. Here, we will not consider the risk of dementia among contact sports participants and will address the potential risks for dementia following a single prior episode of moderate to severe head trauma. The majority of such studies have identified that a prior incident of moderate-severe head trauma is associated with an enhanced risk for the subsequent development of dementia. It has been assumed that this risk resulted in the subsequent development of Alzheimer's disease in exposed patients. Few studies have investigated the neuropathology or clinical phenomenology of such cases in order to confirm this assumption. Sayed, et al. (2013), using the NACC database, showed a statistically higher tendency for behavioral changes and parkinsonian features among patients enrolled with dementia following TBI when compared to dementia patients without

a prior history of TBI, suggesting that a clinical phenotype separate from that of typical Alzheimer's disease might emerge following TBI. Neuropathology studies of such cases are rare. Crane, et al (2016) studied 7,130 participants of the three large longitudinal studies that were screened for a history of TBI with loss of consciousness. They showed that TBI with loss of consciousness was associated with an increase in Lewy body formation, the progression of parkinsonian features and an increased risk for incident Parkinson disease but not Alzheimer's disease-related pathology. Finally, I will present the findings from a well-documented representative case which highlights many of these issues.

## **The term “Alzheimer`s disease” should be dropped as it is impeding future research**

**R. Pernecky**

Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-Universität München, Germany

The prevalence of dementia and its healthcare and socio-economic impact are exploding worldwide and drug development success rates need to be improved urgently; the traditional linear model of pharmaceutical R&D has become outdated and virtually all new drugs have failed since the cholinesterase inhibitors were introduced to the markets two decades ago. Drug development has been more successful in other fields of medicine such as infectious diseases and cancer, in which translational models are applied, linking population-based cohorts and genetic data with potential drug targets and study endpoints. This powerful translational approach is fuelled by technology platforms such as neuroimaging, -omics and fluid biomarkers. The dementia field requires a significant cultural change to discover and develop effective disease-modifying treatment options and advanced knowledge about the relevant disease mechanisms must be translated to improved diagnostic, prognostic and preventative approaches. The present debate focusses on the usefulness of the term “Alzheimer's disease” and it is discussed if it is still required and helpful in research or if it should be dropped to accelerate scientific progress.

## **How can robotic technology help in long-term care of dementia patients?**

**K. Rejdak**

Neurology, Medical University of Lublin, Poland

A person with amnesic mild cognitive impairment (MCI) and early stages of Alzheimer's disease (AD) has difficulties in instrumental activities of daily living, which depend on memory and executive functioning. With the progress of the disease, the help needed for the execution of daily tasks normally increases, leading to a burden on the shoulders of informal caregivers, and in many cases to institutionalization. The number of elderly adults and the incidence of cognitive impairment among them are increasing. As a result, the resources allocated to assisting elderly people will not prove sufficient in the foreseeable future. Robotic assistants could be a way to help people remain safe in their own homes, ensuring their independence in everyday life. In this context, several social robots, which are human or pet-like robots such as NAO, Paro, KASPAR, PaPeRo, AIBO, and iCat aim at providing social support, engagement, and independence for people with special needs? Thus, people with cognitive impairment constitute a group, which may particularly benefit from healthcare robots. The project: Robotic Assistant for MCI Patients at home (RAMCIP) is an EU Horizon 2020 funded project. RAMCIP aims to research and develop real robotic solutions for assistive robotics for the elderly and those suffering from Mild Cognitive Impairments and dementia. This is a key step to developing a wide range of assistive technologies. We have adopted existing technologies from the robotics community, fused those with user-centered design activities and practical validation, with the aim to create a step-change in robotics for assisted living.

## Trend of antipsychotic prescription at the time of dementia diagnosis

D. Religa<sup>1, 2</sup>, S. Bukhari<sup>1</sup>, E. Schwertner<sup>1</sup>, J. Secnik<sup>1</sup>, B. Winblad<sup>1, 2</sup>, M. Eriksdotter<sup>1, 2</sup>

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**Introduction:** Within the last 10 years, multiple studies and recommendations have been made to limit the use of antipsychotic use in patients with dementia. To date, there was no original data presented in Sweden on trend regarding antipsychotic drug use in this patient group. The aim of this study was to evaluate the change of antipsychotic drug use in relation to implemented guidelines in Primary and Specialist care.

**Material and methods:** This was a cross-sectional cohort study using. Data was collected at the time of dementia diagnosis using Swedish Dementia Quality Registry (SveDem) between May 2007 and December 2015. 55 215 patients were selected for the study. Multivariate logistic regression was used to calculate odds ratio (OR) and 95% confidence intervals (CI) for having antipsychotics prescribed in different time periods.

**Results:** Antipsychotics use changed from 10.1% in 2007–2008 to 5.2% in 2014–2015. In an adjusted model with 2007–2008 as reference; 2014–2015 had a decreased risk of AP use for All [OR 0.49 (0.38–0.64)], Primary care [OR 0.51 (0.34–0.76)] and Specialist care [OR 0.52 (0.389–0.70)].

**Conclusions:** Compared to 2007–2008, there was a decrease in risk of AP use at the time of dementia diagnosis the following years. We conclude that both specialist units and primary/communal care units decreased their risk of AP use compared to 2007–2008 and there is no significant difference between them in our adjusted model.

## General anesthesia and the risk of dementia

I. Santana

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Neurology, Faculty of Medicine of the University of Coimbra, Portugal

Many patients that undergo surgical procedures and general anesthesia develop postoperative delirium (POD) with an increased long-term risk of death (10–20%), cognitive impairment up to five years after surgery and eventually dementia. Rates of POD range from 9 to 87%, depending on the type of surgery, settings of care and particularly patient's age and characteristics. The connection between POD and a further development postoperative cognitive dysfunction (POCD) is controversial, ranging from 10% to 20% at 6 months, maybe because there are mutual predisposing risk factors that increase transitory or definitively brain vulnerability to cognitive decline. Well-known underlying risk factors for both syndromes are age  $\geq$  65 years of age, previous cognitive decline and sensorial deprivation. Intra and perioperative insults and procedures already identified include perfusion deficits and hypoxic events, particularly during heart or vascular surgery, systemic inflammation, pain, sleep disturbances and consequent use of medications with anticholinergic actions. Nonetheless, evidence-based recommendations are lacking regarding the specific anesthesia agents to use, general versus regional anesthesia, systemic arterial pressure monitoring, and management or disallowed medication and analgesia. Conversely, a cognitive reserve which is promoted by educational/cultural attainment and cognitive/physical activity is highlighted as an underlying preventive player and another link between POD, exacerbation of cognitive decline and dementia. Evaluation of both, cognition and neurocognitive reserve may be a key in understanding which modifiable factors can preserve cognitive function in later life after surgery, providing a target for preventive interventions and stratification of patients according to their risk to POCD.

## Is traumatic brain injury a risk for dementia?

**B. Tousi**

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The concept of association between neurodegenerative disease and head trauma dates back to 1928 with a description of “punch drunk” in former boxers (Martland, JAMA 1928) and the term traumatic encephalopathy was introduced later (Parker, J Neurol Psychopathol 1935). Since then, this diagnosis has been reported with different contact sports. Previous studies on the association between traumatic brain injury and neurodegenerative diseases have controversial findings. Some studies have found that blows to the head can raise a person’s likelihood of dementia, as can highly physical sports. The recent study of American football players has shown that CTE is a tauopathy with a unique distribution as a result of repetitive traumatic brain injuries. 696 of the 19,936 people, with severe head injuries, went on to develop dementia, while only 326 of the 20,703 people with milder injuries did the same. The risk of dementia was highest in people who sustained severe, traumatic head injuries between the ages of 41 and 50. This large study adds to prior published work indicating that a history of traumatic brain injury significantly increases the risk of non-Alzheimer’s dementia, which may be down to the effects of chronic brain inflammation caused by head trauma. In working-aged persons, a history of moderate-to-severe TBI is associated with an increased risk for future dementia but not for Parkinson disease or amyotrophic lateral sclerosis. In a retrospective population-based follow-up study using the Finnish Care Register, moderate to severe TBI was associated with an increased risk for Neurodegenerative disease, with a higher hazard ratio (HR) of 1.8 (95% CI 1.6–2.1) compared to mild TBI (Raj, et al, Plos medicine 2017). Data is limited in suggesting evidence of an association between mild TBI (with loss of consciousness) and dementia. There are limitations in CTE studies such as being retrospective or convenient samples. In a study of high school football players who were followed at age 65, there was no difference in cognitive abilities between football players and the control group (Deshpande, et al. 2017). The pathological findings are not suggestive of an Alzheimer’s type of dementia. More longitudinal studies needed to study further this correlation.

## New insights into transmission of tau pathologies and interactions of plaques with tangles

**J. Trojanowski**

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We developed novel tauopathy models in nontransgenic (non-Tg) mice by injecting pathological tau extracted from postmortem brains of AD (AD-tau), progressive supranuclear palsy (PSP-tau), and corticobasal degeneration (CBD-tau) patients into different brain regions of non-Tg mice. This revealed differences in tau strain potency between AD-tau, CBD-tau, and PSP-tau as well as differences in cell-type specificity of tau strain transmission such that only PSP-tau and CBD-tau strains induced astroglial and oligodendroglial tau inclusions. Further, we demonstrated that the neuronal connectome, but not the tau strain, determined the neuronal spread of tau pathology. Finally, CBD-tau- and PSP-tau-injected mice showed spatiotemporal transmission of glial tau pathology, suggesting glial tau transmission contributes to the progression of tauopathies. Thus, different tau strains determine seeding potency and cell-type specificity of tau aggregation that may underlie diverse human tauopathies. We also examined the link between AD tangles and A $\beta$  plaques by injecting human AD-tau into A $\beta$  plaque-bearing mouse models that do not overexpress tau. This led to the formation of three major types of AD tau pathologies: dystrophic plaque associated neurites (NP tau), neurofibrillary tangles (NFTs) and neuropil threads (NTs) which had different temporal onsets and functional consequences on neural activity and behavior. We speculate A $\beta$  plaques create a unique environment that facilitates the rapid

amplification of proteopathic AD-tau seeds initially appearing as NP tau followed by the formation and spread of NFTs and NTs, likely through secondary seeding events. This study provides insights into a new multistep mechanism underlying A $\beta$  plaque-associated tau pathogenesis.

## Does general anesthesia increase the risk of dementia?

**M. Tsolaki**

3<sup>rd</sup> Department of Neurology, Aristotle University of Thessaloniki, Makedonia, Greece

Predisposing factors to identify preventive strategies for Alzheimer's disease (AD) has become increasingly important last years. Surgery and anesthesia have been proposed to increase the incidence of post-operative cognitive decline (POCD) and AD. Mechanisms: Animal studies indicate that volatile anesthetics may augment the pathological processes of AD by affecting amyloid  $\beta$  processing. Neuro-inflammation plays a pivotal role in POCD. Prevention: BIS-guided anesthesia reduced anesthetic exposure and decreased the risk of POCD. Hypertonic saline can improve post-operative delirium (POD). The PPAR $\gamma$  agonist pioglitazone attenuated the surgery-induced inflammatory changes and rescued the associated POCD. Berberine rescued POCD in twenty-month-old male C57BL/6 mice. Administration of NADPH oxidase inhibitor apocynin (APO) could rescue POCD. Depth of anesthesia: Small clinical trials have demonstrated increased POD and POCD in patients who were relatively deeply anesthetized. Kind of anesthesia: Available randomized controlled trials suggest that there is no significant difference in the incidence of POD or POCD when general anesthesia and regional anesthesia are compared. Type of surgery: POCD is associated with non-cardiac surgery and even sedation for non-invasive procedures such as coronary angiography. Recently the focus of POCD has shifted from the type of surgery or anesthetics to patient susceptibility. Besides old age, mild cognitive impairment has been shown to increase the risk of developing POCD and AD. The use of CSF or PET to diagnose AD many years before symptoms appear may identify susceptible individuals. Recent meta-analysis, however, suggests: Further well-designed studies are warranted to better characterize the relationship of interest.

## The syndrome of normal pressure hydrocephalus: a case for splitter and lumpers

**U. Wuellner**

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When normal pressure hydrocephalus (NPH) was initially conceptualized by Hakim, Adams and Fisher in 1965, they lumpily described 3 patients with ventriculomegaly and cognitive impairment improving after ventriculoarterial (VA) shunting (J Neurol Sci and NEJM). The three split up in at least two categories: a 16-year-old-boy and a man in his forties', both with traumatic brain injury, one with subdural hematoma, the other with skull-fracture and severe contusion. The third patient presented with cognitive impairment, gait disturbance, and urine incontinence. While this case seems to correspond to what today is considered the Hakim-triad, an elevated CSF cell count was recorded. Neither CT-scans nor MRI were available but pneumoencephalography only and the many causes of reduced CSF flow over the convexity could not be imagined. Adams in his textbook stated that the syndrome of NPH may follow various conditions including SAH, chronic meningitis etc., but — according to the observations in their initial paper — “in at least one-third of our cases is presumably due to an asymptomatic fibrosing meningitis”. Leinonen and Alafuzoff, who analyzed post-mortem findings in 10 patients with presumed iNPH, however, found no evidence of such but severe vascular pathology in four (considered as causative) and amyloid- $\beta$  (A $\beta$ ) aggregates in three. Thus, neuropathological characteristics of iNPH as a distinct disease still need to be discovered and we are left with Adams'

statement that the most consistent improvement is attained in those NPH patients in whom a cause had been established.

## **The sensitivity and predictability of the clinical criteria of NPH for the response to shunting**

**C. Wikkelso**

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The clinical criteria are described in several iNPH guidelines like the International guidelines (A. Marmarou 2005) and recently the Japanese Guidelines (E. Mori 2012). The criteria are operational and not standardized or validated. There are no pathophysiological specific markers for diagnosing iNPH. The sensitivity and predictability of the criteria are sparsely investigated and by nature very difficult to evaluate. Parts of the criteria; like age, unknown cause, Evans Index (EI) 0.3 are obligatory and relatively simple to apply. However, none of these have any relevance if symptoms and signs of iNPH are lacking (EI 0.3 are seen in 20.6% of healthy individuals older than 70 years). Operating on patients with symptoms and signs compatible with iNPH will improve up to 84% (European Multi-Centre Study, P. Klinge 2012). In single centre studies, the improvement rate is often lower even if supplementary methods are used. Using supplementary methods can be positive predictive for criteria for surgery, but will also exclude many patients from successful treatment (P. Klinge 2012). There are few studies addressing the phenotype of iNPH and its sensitivity and predictability. Data on 429 iNPH patients showed a broad-based gait in 75%, shuffling gait in 65% and freezing of gait in 30%; pathological Romberg test in 53% and retropulsion in 46%; impaired bladder control in 85%. Sixty-eight % of the patients improved after surgery highlighting the low sensitivity and predictability of symptoms and signs (S. Agerskov submitted).

# EPILEPSY

## Can psychogenic seizures be reliably diagnosed by observing behavior or should continuous EEG always be required? — No

**E. Beghi**

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Psychogenic non-epileptic seizures (PNES) are neither paroxysmal behavioral changes resembling epileptic seizures without organic cause nor ictal, peri-ictal and inter-ictal EEG changes that characterize epilepsy. The gold standard for diagnosis is the recording of a typical event with video-EEG to confirm the absence of electrographic changes on the ictal tracing. The high prevalence of PNES in settings where drug-resistant epilepsies are common reflects the difficult diagnostic approach when the ascertainment is based only on the semiology of seizures and inter-ictal EEG findings. Several video-documented signs are implicated (including preserved awareness, eye flutter and modification by others) but none of them, individually taken, has high sensitivity. The inter-rater reliability of neurologists and psychiatrists (the two specialists most commonly involved in the management of seizures) is sub-optimal when the diagnosis of PNES is based on the assessment of video-recordings alone. The reliability of the diagnostic approach is even poorer when PNES have non-motor behavioral changes. Witnesses' reports are even less useful for the diagnosis of PNES because only two signs have been identified as diagnostic predictors (side-to-side head movements and eyes closed) but the sensitivity was low for both. There are no data on the diagnostic yield of video-supported induction of PNES. In a recent consensus conference on the diagnosis of PNES (unpublished), experts concluded that no single sign can confirm or exclude the diagnosis of PNES. The contribution of continuous video-EEG monitoring can be also unhelpful because a typical event cannot be invariably captured and the inter-rater reliability is only moderate.

## AED treatment issues in the elderly

**E. Ben-Menachem**

Neurology, Institution of Clinical Neuroscience, Sahlgrenska Academy, University of Göteborg, Sweden

The results of clinical trials of antiseizure drugs (AEDs) and the experience of treating the younger adult cannot be extrapolated to the elderly. Older persons with epilepsy invariably have more somatic comorbidities and different etiologies than younger patients. Most often (50%) the etiology is cerebrovascular disease. Tumors and dementia are also thought to be major contributing etiologies in the elderly. Therefore, it is important to consider when choosing and dosing an AED, the physiological and metabolic changes that can occur with the aging process. The therapeutic window for treatment is often much smaller in older, more fragile patients. Factors such as enzyme induction and kidney function are considerations that must be included in every choice of an AED in this group. Treatment options and evidence for efficacy and effectiveness of the available AEDs will be discussed in the perspective of the aging patient.

## Is there an advantage to continue trying new AEDs indefinitely in refractory patients? — No

**E. Ben-Menachem**

Sahlgrenska University Hospital, Sahlgrenska University Hospital, Sweden

This debate concerns the question if patients should be offered to try new antiepileptic drugs (AED) indefinitely. There are many reasons why continuing with AEDs without offering other alternatives can prevent the patient from achieving seizure freedom or at least a reduction in seizure frequency and severity. It is generally accepted that patients, after trying one or two appropriate AEDs, should be evaluated for epilepsy surgery possibilities. It is important not to delay this evaluation. Additional trials of AEDs can result in improvement but the statistics imply that this is most often not the case. By primarily concentrating on switching AEDs, there can be a delay in efforts to improve the situation in other ways as through diet or neuromodulation. Other activities include improving the social environment and consideration of side effects of AEDs.

## Do antiepileptic drugs increase the risk of depression or suicidality? — Yes

**I. Blatt**

Department of Neurology, Sheba Medical Center, Israel

Psychiatric adverse effects (PAEs), including depression, are reported in 15–20% of patients with epilepsy on antiepileptic drugs (AEDs). In 2008 the FDA issued a warning of increased risk for suicidal ideation and behavior during treatment with AEDs, based on findings of a meta-analysis of 199 trials of 11 AEDs. An expert consensus statement by an ILAE task force concluded that some (but not all) AEDs can be associated with PAEs which can lead to suicidal ideation and behavior. The actual suicidal risk was considered very low but remained to be established. PAE risk varies considerably with different AEDs; GABAergic effects play an important part in depression. Barbiturates, vigabatrin, tiagabine, topiramate, levetiracetam, zonisamide, and felbamate seem to be associated with higher risks compared with other AEDs. In a retrospective study, 16% of 1394 outpatients on a second-generation AED experienced PAEs. The average rate for a single AED was 8.4%; 6.1% resulted in dosage change and 4.3% led to AED discontinuation. There were fewer PAEs with gabapentin and lamotrigine, and more with levetiracetam and tiagabine. Low rates of PAEs were seen with vigabatrin, felbamate, oxcarbazepine; intermediate rates with topiramate and zonisamide. Non-AED predictors, most significantly prior psychiatric history, affected the rates of AED-related PAEs, but when these were controlled for, relative PAE rates for the different AEDs remained similar. Patients with clinically relevant risk factors are relatively more vulnerable to AED PAEs, but the main finding reported in multiple studies remains robust: AEDs increase depression and suicidality risk.

## Can we rely upon fMRI to localize language and memory when planning epilepsy surgery? — No

**I. Blatt**

Department of Neurology, Sheba Medical Center, Israel

Epilepsy surgery success can be compromised by postoperative memory decline, particularly verbal memory decline after dominant temporal lobe resections. It is therefore essential to reliably evaluate

memory functions pre-operatively, identify pre-surgical memory deficits and predict post-operative memory outcomes. Neuropsychological testing and intra-carotid amobarbital procedure are helpful but have their shortcomings. Direct cortical stimulation is very helpful when necessary. fMRI is a promising non-invasive imaging procedure of brain activity but has pitfalls and limitations. Memory-fMRI has is still not sufficiently reliable for pre-operative individual patient counseling and decision making. fMRI is not a direct measure of cortical neuronal activity, but an indirect tool which images the time course of BOLD signal changes, analyzing a vascular response of neuronal activity. Although several fMRI paradigms have been developed to assess memory functions, they are predictive of post-operative memory outcome at the group level, comparing groups of patients to groups of controls. To be clinically relevant memory fMRI needs to be predictive on a single-subject basis. Memory-fMRI paradigm development is challenging and has not yet produced robust activation which can be reliable in single patients. Normal functioning patients may show poor memory fMRI activation. Post-surgical memory-fMRI changes have been observed without verbal memory function decreases. The reproducibility of memory-fMRI results has been assessed in Alzheimer's disease but not in epilepsy patients. Other technical problems include tissue-air interfaces and draining veins in the mesial temporal regions that interfere with the BOLD signal. Memory-fMRI is still not ready to be relied upon when planning epilepsy surgery.

## **Is there an advantage to continue trying new antiepileptic drugs indefinitely in refractory epilepsy? — Pro**

**M. Brodie**

Epilepsy Unit, Scottish Epilepsy Initiative, UK

It is well known that most patients who attain seizure freedom do so with their first or second antiepileptic drug (AED) schedule. There are, however, some people who tolerate AEDs poorly and it may take some time to find an acceptable regimen for them. Others will respond to the addition of a particular drug with a distinct mechanism of action after failing treatment with a range of other options due to lack of efficacy. Some patients will become seizure free with a combination of 2 or 3 AEDs mostly with different mechanisms of action. In our own recently published outcome study in 1795 newly diagnosed patients followed for up to 30 years, 24%, 15%, 14%, 7% and 7% attained seizure freedom for at least one year on an unchanged 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup> and 7<sup>th</sup> schedule, respectively. I will also present some individual cases, who have responded unexpectedly well to the addition of a specific AED with a distinct mechanism of action, after more than 10 other drug schedules have failed due to adverse effects and/or lack of efficacy. Continuing to aim for seizure freedom or settling for the best tolerated and/or most effective regimen often depends on the attitude of the patient and his or her acceptance of a few seizures each month. Nevertheless, while always trying to be honest, I rarely tell my patients that seizure freedom will never be attained. After all, hope springs eternal!

## **When using combination antiepileptic drug therapy, we should preferentially prescribe drugs with different mechanisms of action-pro**

**M. Brodie**

Epilepsy Unit, Scottish Epilepsy Initiative, UK

Despite the availability of a range of novel antiepileptic drugs (AEDs) with different mechanisms of action, outcomes for adolescents and adults with the common epilepsies have been unchanged over the past 20 years. Nevertheless, it is possible to make some patients seizure free with suitable combinations of 2 or 3 AEDs. Since we do not understand the pathophysiology of pharmacoresistant

epilepsy, it makes sense to target a range of pharmacological mechanisms in the hope of finding the right schedule for each individual patient. The only combination that has proven synergism is sodium valproate with lamotrigine, which are mechanistically dissimilar. We are aware now that fast and slow sodium channel blockers can be regarded as working differently on the sodium channel i.e. is not mechanistically identical. In our outcome audit exploring seizure freedom with combination therapy, the top 10 successful duotherapies all contained AEDs with different mechanisms of action, including phenobarbital (a GABAergic drug) and phenytoin (a sodium channel blocker), which was third on the list. The positive conclusion to this debate is particularly self-evident since the majority of available AEDs possess different mechanisms of action!

## **When using combination antiepileptic drug therapy, should be preferentially prescribe drugs with different mechanisms of action? — Con**

**M. Holtkamp**

Neurology, Epilepsy-Center Berlin-Brandenburg, Charité — Universitätsmedizin Berlin, Germany

From a mechanistic point of view, it seems possible that antiepileptic drugs with the same mechanism of action, e.g. the sodium-channel-blockers (SCB) lamotrigine and oxcarbazepine, do not have an additive effect in regard to efficacy but synergistically produce more typical adverse effects compared to the combination of a SCB with a non-SCB. One study analyzed the pooled data of some randomized controlled trials on the SCB lacosamide and exactly produced the results mentioned above (Sake et al. 2010 CNS Drugs). However, in that study, patients with SCB seemed to have more severe epilepsy with higher current and lifetime numbers of antiepileptic drugs. Thus, a more unfavorable response to additionally administered lacosamide in this patient group is not surprising. Other studies failed to demonstrate any outcome differences when comparing combinations of two SCB to combinations of a SCB with antiepileptic drug acting via a different mechanism of action. Personal experiences have shown that in most patients e.g. lamotrigine can be combined with another SCB without clinically relevant adverse events as long as the doses and serum concentrations are within moderate ranges.

## **Do antiepileptic drugs increase the risk of depression or suicidality or are we just witnessing the natural history of mood disorders in epilepsy when depression occurs?**

**M. Holtkamp**

Department of Neurology, Epilepsy-Center Berlin-Brandenburg, Germany

Newer antiepileptic drugs (AED), e.g. those launched after 1990, are not more efficacious compared to standard AED, but it seems that they are generally better tolerated. The latter aspect may justify the high prices health care systems have to pay within the first decade when new compounds are protected by patent and low-cost generics are not available. Interestingly, depression and may be some other psychiatric disorders inversely have been more often reported with newer AEDs such as brivaracetam, levetiracetam, perampanel, and zonisamide, while standard AED such as carbamazepine and valproate are even administered in psychiatric patients as mood stabilizers, effects which are also observed in some epilepsy patients affected by depression. However, we cannot exclude that in the last decades physicians have become more sensitive to detect and to report depression in epilepsy patients. Thus, in older days when there were few alternatives to carbamazepine, the lower rates of mood disorders may be explained by underreporting. In that case, depression indeed may be majorly attributed to the natural course of epilepsy and less so to AED.

## Can psychogenic seizures be reliably diagnosed by observing behavior or should continuous EEG always be required?

J. Jedrzejczak

Department of Neurology and Epileptology, Medical Center of Postgraduate Education, Poland

With the growth of intensive EEG-video monitoring, it became apparent that psychogenic nonepileptic seizures (PNES) are more common than was previously believed. Epileptic seizures and psychogenic seizures often coexist in the same patient. Diagnosis traditionally relied on identification of bizarre or atypical paroxysmal behavioral changes, especially in patients with known psychological or psychiatric disorder. The ictal activity itself may present with discontinuous, uncoordinated activity with erratic progression. Pelvic thrusting thrashing or flailing movements, jerking movement tremors and the lack of gradual slowing in the rate of clonic activity are more common in PNES. However, no single feature of PNES has proved to be pathognomonic, although recent studies found that diagnosis is associated with a distinct cluster of signs. It is true that in the differential diagnosis of seizures, the combination of Video EEG monitoring (VEM) with the history of patients and witnesses offers a diagnostic “gold-standard”. However, VEM not infrequently fails to capture the events and it will not differentiate certain types of frontal lobe epileptic seizures (ES) from PNES. Moreover, in some cases there is limited availability of VEM. The aim of presentation is to discuss if, when, and to what extent visual information and alternative PNES screening tools allow experienced epileptologists to predict the diagnosis of psychogenic nonepileptic seizures without the aid of EEG. To look at the pros and cons of clinical diagnosis of psychogenic nonepileptic seizures based on holistic approach.

## Should we preferentially use vagus nerve stimulation early in patients with both seizures and depression? — our experience

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**Background:** Vagus nerve stimulation (VNS) is a viable treatment option in drug-resistant epilepsy and depression. In patients with drug-resistant epilepsy polytherapy is necessary that emphasizes greater incidence of side effects which further impair quality of life, on the physical, psychosocial and neurocognitive level. Our study aimed to examine the quality of life in patients with drug-resistant epilepsy who had undergone VNS implantation.

**Material and methods:** The study included 27 patients with drug-resistant epilepsy with implanted VNS — case group (14 M, 13 F; mean age  $34.7 \pm 28.3$  years) and 18 controls — patients with drug-resistant epilepsy without implanted VNS (10 M, 8 F; mean age  $45.2 \pm 30.8$  years). The quality of life was examined using the questionnaires “Quality of life in epilepsy” (QOLIE-31 validated Croatian 1.0 version) and “Beck Depression Inventory I” (BDI I validated Croatian version). For statistical analysis nonparametric Mann-Whitney test for independent samples was used. The study was approved by the Ethical Committee of the University Hospital Centre Zagreb.

**Results and conclusion:** The Mann-Whitney test showed significant difference in the QoLIE-31 score between the case and the control group ( $p = 0.041$ ). In the case group we have noticed that younger

patients had lower score of QoLIE-31 and higher score of BDI-I than the older ones. Our results show positive influence on the quality of life and mood improvement following VNS implantation in patients with drug-resistant epilepsy. VNS can be an effective treatment when used early in patients with both seizures and depression.

## Can we rely upon fMRI to localize verbal memory when planning epilepsy surgery?

**W. Theodore**

Epilepsy Section, NIH, USA

Several studies have shown that fMRI can identify brain regions important for verbal memory in patients with epilepsy being considered for surgery. There is a significant correlation between laterality indices when the intracarotid sodium amytal test and fMRI are compared in the same patient. Moreover, asymmetric activation left mesial temporal or language network activation during verbal encoding predicts verbal memory decline after left temporal lobectomy. A model including left fMRI activation during delayed recognition, side of seizure onset, and preoperative verbal memory score correctly predicted worse verbal memory in 90% (Dupont, et al 2010). These data suggest that fMRI is at least as accurate as the intracarotid sodium amytal test (Wada) for preoperative memory mapping. The Wada is invasive, suffers from many procedural vagaries, and has been shown to have limited predictive value for post-operative deficits. Only 10 cases of global amnesia have been reported over more than 50 years after epilepsy surgery, and all had independent preoperative evidence for contralateral dysfunction or atypical language dominance. The Wada has been declining in use, and many centers, perhaps a majority, no longer perform it at all. fMRI can replace it.

## Can psychogenic non-epileptic seizures be diagnosed by assessing behavior without concomitant EEG recording?

**M. Tripathi**

Neurology, Professor, India

Psychogenic nonepileptic seizures are not uncommon. Any center involved in the management of episodic events which occur in epilepsy would be seeing about 5–25% of persons with nonepileptic events. About 5–15% would be PNES. The diagnosis of PNES is based on red flags obtained in the history of such patients. There are several clinical clues on history and examination. Over the years several biomarkers for the diagnosis have also been researched into. These could be serum prolactin, BDNF, non-EEG markers of the autonomic nervous system and the gold standard which is the EEG being non-ictal when the clinical event is happening. The gold standard has always been the unequivocal documentation of the habitual events having the clinical phenomenology of PNES and no ictal patterns on the simultaneous EEG. About 5–10% of patients with epilepsy will have a combination of pseudoseizures with true seizures. These can be documented only with simultaneous video EEG. Just depending on manifest behavior could help circumvent costly and labor-intensive video EEG monitoring in the epilepsy monitoring unit. Based on the clinical history and video of the patient during the event a reasonably confident diagnosis can be made. Practically most often doing a good clinical history and video observation with neuropsychological scales is enough to make a diagnosis of pseudoseizures.

# HEADACHE

## Head injury can precipitate the onset of migraine

**M. Ashina**

Neurology, Danish Headache Center, Rigshospitalet Glostrup, Denmark

Post-traumatic headache (PTH) is one of the most common secondary headache disorders. It occurs for the first time in close temporal relation to trauma or injury to the head and/or neck. PTH shares many clinical symptoms of primary headaches, including migraine. Having any of migraine-like symptoms does not necessarily mean head injury precipitate the onset of migraine. Recent imaging data showed that PTH and migraine are associated with differences in brain structure. This suggests differences in their underlying pathophysiology.

## Behavioral therapy is more effective, better tolerated, and safer than preventive medications for migraine

**S. Baskin**

Behavioral Medicine, New England Institute for Neurology and Headache, USA

Diary studies have shown significant correlations between levels of daily stress as a trigger for migraine attacks. Stress-related factors may also progress episodic migraine to a more chronic state. Other risk factors for progression include frequency of attacks, obesity, psychiatric comorbidities, medication overuse and sleep issues; all modifiable by behavioral interventions. Cognitive behavioral sleep therapies have been shown to reverse chronic migraine back to episodic migraine. Poor medication adherence can result in ineffective treatment of acute attacks, medication overuse headache (MOH), and greater risk of preventive medication side effects. Comprehensive behavioral treatments for migraine and MOH commonly incorporate motivation enhancement strategies to maximize preventive medication adherence and optimize acute care. Relaxation training, biofeedback training, and cognitive behavioral therapy have a good evidence base and are recommended in numerous treatment guidelines for the prevention of migraine. Behavioral therapy outcomes equal outcomes with preventive medication alone with less adverse events and there is some evidence that outcomes are enduring. Combination behavioral and medication treatment can enhance outcomes. Cognitive behavior therapy targeted for migraine with comorbid depression has shown promise on measures of headache, depression, anxiety, and quality of life compared to routine primary care. The thesis of this presentation is that headache medicine is mostly behavioral therapy. Effective clinicians perform a comprehensive behavioral assessment and optimize acute and preventive care utilizing headache diaries and behavioral change strategies. It is my position that all these strategies follow principles of behavior that are the most significant change agents in the management of migraine.

## Insufficient sleep in tension-type headache: a population-based study

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**Background:** Insufficient sleep is a common problem in general population and is prevalent among migraineurs. Although tension-type headache (TTH) is the most common type headache, information regarding the association between TTH and insufficient sleep is limited.

**Objectives:** To investigate the prevalence and impact of insufficient sleep among individuals with TTH.

**Material and methods:** We selected a stratified random population sample of Koreans aged 19 to 69 years and evaluated them with a 60-item semi-structured interview regarding headache and sleep. A difference of one hour or more between sleep need and average sleep time indicated insufficient sleep.

**Results:** Of 2,695 participants, 727 (27.0%) and 570 (21.2%) were classified as having insufficient sleep and TTH, respectively. The prevalence of insufficient sleep among individuals with TTH (28.8%) was significantly higher compared to that among individuals with non-headache (20.4%,  $p = 0.001$ ). TTH participants with insufficient sleep had higher visual analogue scale scores for headache intensity ( $4.7 \pm 1.8$  vs.  $4.3 \pm 1.9$ ,  $p = 0.018$ ), and impact of headache (Headache Impact Test-6,  $44.9 \pm 7.0$  vs.  $43.6 \pm 6.1$ ,  $p = 0.001$ ). Multivariable analyses revealed that aged 50 s, insomnia, poor sleep quality, short sleep time and poor sleep quality were significant factors of insufficient sleep among individuals with TTH.

**Conclusions:** A significant proportion of participant with TTH experienced insufficient sleep. Insufficient sleep was associated with an exacerbation of symptom of TTH.

## Non-invasive vagus nerve stimulation in primary headaches

O. Daniel

Headache Center, Laniado Medical Center, Israel

Clinical observations and results from recent studies support the use of non-invasive vagus nerve stimulation (nVNS) for treating primary headaches. The most common types of Primary Headache Disorders are Migraine and Cluster Headache. According to evidence-based recommendations, the only primary symptomatic treatments for CH attacks are subcutaneous sumatriptan and inhaled oxygen. Approved Labeling for sumatriptan in CH indicates a maximum of two doses per day, which may be inadequate for many patients, including those with frequent Attacks, and may lead to Medication Overuse Headache with multiple daily dosing. This treatment is also associated with injection site reactions (e.g., pain, swelling) and neurologic symptoms (e.g., dizziness, tiredness) and has cardiovascular contraindications. Hence, the limited therapeutic options for the acute treatment of CH reflect an Unmet Medical Need. Many well-controlled trials support nVNS efficacy in the acute treatment of Episodic Cluster Headache and Migraine with or without Aura.

## Head injury can precipitate the onset of migraine

**O. Daniel**

Headache Center, Laniado Medical Center, Israel

Headaches are variably estimated as occurring in 25 to 78 percent of persons following mild TBI. Paradoxically, headache prevalence, duration, and severity are greater in those with a mild head injury compared with those with more severe trauma. According to the International Headache Society (IHS) criteria, the onset of headache should be within seven days after the injury. Recurring attacks of migraine with and without aura can result from mild head injury. The impact can also cause acute migraine episodes, often in adolescents with a family history of migraine. Originally termed “Footballer’s Migraine” to describe young men playing soccer who had multiple migraines with aura attacks triggered only by impact, similar attacks can be triggered by mild head injury in any sport. Moreover, among US soldiers with post-traumatic headaches mainly associated with blast trauma, most were of the migraine-type. Biochemical and epidemiologic studies suggest that trauma may be the main etiologic factor of migraine in some cases. Differentiating the different types of post-traumatic migraine has diagnostic, therapeutic, and legal implications.

## PFO in neurological diseases (migraine, stroke) to close or not to close... — Pro...

**I. Domitrz**

Department of Neurology 2<sup>nd</sup> Faculty of Medicine, Warsaw Medical University, Poland

The frequency of PFO in general population varies from 6 to 30%, in the majority epidemiological studies 20–25%. Several studies have investigated the prevalence of patent foramen ovale in patients with migraine. Such data finding out significantly higher prevalence of PFO in patients with migraine with aura suggest that there may be a possible a relationship between migraine with aura and PFO. The PFO is generally considered to be associated with first-ever and recurrent cryptogenic ischemic stroke in young patients without any other risk factors for stroke. The prevalence of PFO was significantly higher in such patients. It is widely accepted that migraine with aura can directly cause an ischemic stroke. Some studies confirmed the decrease of the prevalence of attacks of migraine with aura after percutaneous closure of PFO. Because in many PFO associated conditions it can be difficult to determine the degree to which the PFO is a causative factor in the disease process, it should be recommend a comprehensive diagnostic evaluation to exclude other obvious etiologies of PFO associated conditions before implicating the PFO and proceeding with closure. However, in the properly selected patient population, there is growing clinical experience and experimental evidence suggesting that closure of PFO is a safe and effective treatment modality. Confirmation of a relationship between PFO and stroke or PFO and migraine may lead to another effective treatment such as percutaneous PFO closure and/or antiplatelet/anticoagulant treatment, as a routine procedure.

## Monoclonal anti-bodies towards CGRP and CGRP receptor will be first-line treatment for the prevention of migraine

**L. Edvinsson**

Dept Medicine, Inst Clinical Sciences, Lund University, Sweden

CGRP is a very potent vasodilator with distribution in all vascular regions with similar localization of CGRP receptors, however the detailed functional is incompletely known. CGRP has been shown to be released in primary headaches and blocking this peptide or its receptor reduces symptoms. The available prophylactic treatments rest on therapies that were originally not designed for migraine treatment. The molecular mechanisms of CGRP distribution, release and coupling to the pathophysiology is being elucidated. Blocking CGRP is useful both rapid and long-term in attack prevention. Can it be particularly useful in different subtypes of migraine? This has received novel interest because amazingly the phase II/III trials were positive without AEs. It is worth pointing out that (i) no patients developed hypertension related to the treatment during the trials. (ii) Males (age about 65 y) were exercised on treadmill until the development of angina pectoris. They received the CGRP receptor anti-body Erenumab or its vehicle; interestingly there was no difference. (iii) It has been postulated that blocking the trigeminovascular reflex might exacerbate any cerebral ischemia or a stroke during CGRP blockade. Available trials have not supported this hypothesis BUT the CGRP trials have so far mainly been on subjects of middle age and thus not in a population of high risk for stroke or AMI. (iv) Studies on the CGRP anti-bodies show lack of passage of the blood-brain barrier hence this limits CNS side-effects.

## Monoclonal antibodies to CGRP will become first-line treatment for the prevention of migraine

**H. Göbel**

Kiel Migraine and Headache Center, [www.schmerzlinik.de](http://www.schmerzlinik.de), Germany

CGRP plays a crucial role in the pathophysiology of migraine. Adding so-called monoclonal antibodies, the effect of these inflammatory substances can be stopped for several weeks and the probability of migraine attacks can be significantly reduced. Currently, 4 antibodies are being developed and tested in numerous studies. Erenumab (AMG 334), Galcanezumab (LY2951742), Fremanezumab (TEV-48125), Eptinezumab (ALD403), /ul the new immunotherapy, in contrast to all other available preventive medicines, has been specifically developed for migraine prevention for the first time. The onset of action is fast and initially to be expected within a few days. With the previously available conventional preventive medication, this can often only be achieved after weeks or even months. Side effects of the current migraine preventives such as weight gain, mood changes, tiredness, reduced drive or drowsiness do not occur. The degree of efficacy varied significantly between the treated study participants. Should the currently available data be confirmed, more patients in future will be able to reduce their burden of migraine and return to a normal life. In this debate, it should be discussed, for which patients the new therapy options are useful. It must also be discussed whether it should become a first-line treatment, or whether it should only be used when the current therapy options have proven to be ineffective.

## **Behavioural therapy is more effective, better tolerated and safer than preventive medication for migraine — No**

**H. Hamburger**

Department of Neurology, Amsterdam Sleep Centre, The Netherlands

Many patients suffering from migraine have frequent attacks ranging from 1 to 4 per month. Preventive medication is given when the frequency is high, acute care medications do not work, there is too much disability and for other reasons. Most doctors will start their preventive treatment urging the patient to utilize various sensible behavioural changes. These include more or better sleep, cognitive behavioural therapy and dietary measures. When these fail, which is frequently the case; there is no other way of treating these patients than medication. Preventive medication has proven to be successful in the majority of the patients, but they do not always work, have to be taken once or more per day and often have many adverse effects. When preventive medication used is dosed low and increased slowly, the adverse effects can be limited. A combination of more than one drug can be used to limit the side effects and increase efficacy. At present onabotulinumtoxin A, injected once per 3 months and several antiepileptic and antidepressant medications are often used. Soon we will have CGRP antibodies, once per month or every three months, as a good way to prevent most migraine attacks. This type of medication is efficacious and the side effects are limited. Using preventive medication, the sufferers of this painful and disabling disease, affecting 12% of the adult population, can lead a normal life. In conclusion: routine and novel medication for prevention of migraine attacks are often more powerful than giving advice, talking to patients and convincing.

## **Episodic vertigo can be a manifestation of migraine, at times, unaccompanied by headache — No**

**M.J.A. Láinez**

Department of Neurology Hospital Clínico Universitario; Universidad Católica de Valencia, Spain

The association between vestibular symptoms, including dizziness and vertigo, and headache has been reported in several studies, but migraine and vertigo are among the most common health concerns in the general population. The link between migraine and vertigo was described long time ago, but the relation of causality has never been established. The diagnostic criteria for vestibular migraine is described in the International Classification of Headache Disorder (ICHD), third edition, beta version but it is included in the appendix criteria. The reason to include entities in the appendix is that there is not enough scientific evidence to include these entities in the definitive classification. It is clear that vertigo could be a manifestation of migraine, especially in patients with migraine with Braunstein aura (referred by 60% of the patient) and could also be a symptom of vestibular migraine. But there is no evidence that episodic vertigo could be a manifestation of migraine unaccompanied by headache.

## **Nutraceuticals are safe and effective as migraine treatments**

**M.J.A. Láinez**

Department of Neurology Hospital Clínico Universitario; Universidad Católica de Valencia, Spain

The use of complementary and alternative medicine has increased in patients with neurological disorders, and now appears to be in widespread use among many patients, even in tertiary headache

care. Between these alternatives, nutraceuticals are the most preferred by headache patients. Many studies with different compounds or combinations have proved efficacy and safety as preventive treatment of headaches. There are 11 studies published with feverfew; based on these studies the American Academy of Neurology concluded that feverfew is probably effective for migraine prevention with level B evidence. Riboflavin has demonstrated efficacy and tolerability for migraine prevention in adults based in case-series and several open-label studies. Magnesium has been used as an acute and preventive treatment of migraine. There are several studies of the intravenous use in acute migraine, with positive and negative results. Oral magnesium supplementation has been studied for adult and pediatric migraine prevention in several randomized clinical trials. The balance of evidence is in favor of oral magnesium for migraine prophylaxis. Coenzyme Q10 has also been used in the prophylactic treatment of migraine; after several studies published coenzyme Q10 has shown efficacy in migraine prevention. There are several studies using different combinations of these nutraceuticals with positive results. The safety and tolerability of the mentioned compounds have been excellent. In summary, nutraceuticals are safe and effective in the prophylactic treatment of migraine.

## **The criteria for the diagnosis of trigeminal neuralgia should be changed to allow a sensory loss in the trigeminal distribution — Con**

**S. Maarbjerg**

Danish Headache Center, Department of Neurology, Rigshospitalet – Glostrup, Denmark

A few studies documented sensory abnormalities in classical trigeminal neuralgia (CTN) at bedside examination. Several studies using quantitative sensory testing documented sensory abnormalities including both gain and loss of sensory function. Importantly, most clinical studies reported no sensory abnormalities at bedside examination in CTN and according to clinical experience, CTN patients rarely spontaneously report the sensory loss, and rather it is a subtle finding at careful examination. In previous editions of the International Classification of Headache Disorders (ICHD) the TN diagnostic criteria included a criterion stating that there are no sensory abnormalities in CTN. However, in the recent 3<sup>rd</sup> edition the diagnostic criteria were changed such that they no longer include a criterion on no sensory abnormalities. The diagnostic criteria are meant to be used worldwide by physicians no matter the level of experience in neurology, headache and facial pain. Deleting the criterion on no sensory abnormalities involves a risk of less experienced physicians wrongfully diagnosing CTN in a patient presenting with facial pain and sensory abnormalities. Such combination of symptoms could point to grave underlying disease other than CTN such as carotid dissection, cavernous sinus pathology or a space-occupying lesion in the cerebellopontine angle cistern. The talk will argue that by deleting the criterion on no sensory abnormalities in CTN, and thereby increasing the sensitivity of the diagnostic criteria, the trade-off in loss of specificity involves a risk of misdiagnosing other serious neurological disease presenting with facial pain and sensory abnormalities as CTN.

## **Medical cannabis is not effective in chronic headache**

**D.D. Mitsikostas**

National & Kapodistrian University of Athens, Athens, Greece

The use of cannabis for medicinal purposes is deeply rooted through history, dating back to ancient times. Currently, although clinical trials of cannabis for neuropathic pain have shown promising results, there has been little research on its use specifically for primary headache disorders, including migraine, cluster headache, and medication overuse headache. However, this evidence is primarily limited to case-based, anecdotal, or laboratory-based scientific research; no placebo-controlled clinical studies

examining the use of cannabis as mono-therapy for primary headache there are. There is some evidence highlighting the potential value of cannabis in combination therapies, as a supplement to traditional treatments, or as a secondary treatment in refractory cases, including the medication overuse headache, but again this evidence is far from any recommendation. At this time, a multicenter, double-blind, placebo-controlled study is being performed to examine the safety and efficacy of dronabinol (a synthetic cannabinoid) metered dose inhaler for the symptomatic treatment of migraine (clinicaltrials.gov, NCT Identifier: NCT00123201). The trial completed and when published, this study could give valuable insights into the efficacy and risks of cannabinoids for the acute treatment of migraine attacks. For migraine prevention, there is no similar trial. For patients suffering from refractory cluster headache who are in a desperate and vulnerable situation, illicit psychoactive substances might often be considered a last resort, but still, this indication stands far away from any scientific evidence favoring the use of cannabis in cluster headache treatment, as in any other headache subtype.

## **Nutraceuticals are safe and effective as migraine treatments**

**D.D. Mitsikostas**

National & Kapodistrian University of Athens, Athens, Greece

Nutraceuticals became sexy in medicine. Several agents including riboflavin, coenzyme Q10, magnesium, butterbur, petasites, feverfew, omega-3 polyunsaturated fatty acids, folic acid have been tested for prevention of primary headache disorders, migraine in particular. Notably, several neurological societies recommend their use in varying degrees of detail (e.g. the American Academy of Neurology and American Headache Society, the Canadian Headache Society, and the European Federation of Neurological Societies). Whether the scientific documentation is good or not remains debatable, however. None of the nutraceuticals got the A degree or class I scientific documentation resulting in the lower level recommendation, but their use is expanding dramatically in real life as long people suffering from headaches prefer them because of pharmacophobia and nocebo behaviors mainly. The lack of specific and mechanism-based drugs for the prevention of primary headaches support these fears. Because nutraceuticals do not require a prescription, many patients rely on their own judgment as to when and which one to take, often without consultation or guidance from their physician. Thus, nutraceuticals turn out to be a significant alternative choice for prevention of primary headaches and headache specialists should provide accurate and unbiased information for their potential efficacy and safety.

## **Medication overuse headache**

**A. Rapoport**

Neurology, the David Geffen School of Medicine at UCLA, USA

Dr. Lee Kudrow, a headache specialist from Los Angeles, in 1978 was the first to report on how overuse of analgesics could worsen chronic headaches such as migraine. He also demonstrated the beneficial effects of withdrawal of the offending medicine and the added benefit of an effective preventive medication (low dose amitriptyline in his study). The term “rebound headache” became popular and then changed to “medication overuse headache”. The overused medication soon included any acute care medication used too frequently, even migraine-specific triptans and ergots. It was shown that opiates and butalbital containing medications were the worst offenders and NSAIDs the least troublesome. Although NSAIDs can also cause MOH, they often work as preventives at first or at lower frequencies, without causing MOH. When Topamax (topiramate) was studied as a preventive migraine medication, a clinical trial demonstrated that it seemed to work even when the patient was not withdrawn from the overused medication. When Botox (onabotulinumtoxinA) was studied as a Chronic Migraine preventive

medication, it too was shown in a trial to work even when a patient was not withdrawn from overused medication. So, the question is, when a patient is on either topiramate or onabotulinumtoxinA as a daily preventive and is overusing an acute care medication, should they go through a detoxification or not. There is no correct answer, but many feel that it is better for the patient, and the outcome might be better if the patient is withdrawn. Often, a preventive will not even be needed.

## Pipeline in headache treatment

### A. Rapoport

Neurology, the David Geffen School of Medicine at UCLA, USA

There are several promising new and future treatments for migraine and cluster headache which will listed here. Calcitonin gene-related protein (CGRP) is a neurotransmitter found ubiquitously in the central and peripheral nervous system. Many oral small molecule CGRP receptor antagonists have shown efficacy in the acute care of migraine, without constricting blood vessels; but none have been approved for use. New types are in phase 2 and 3 trials. Monoclonal antibodies to CGRP or its receptor have completed phase 2 and 3 trials and seem to be effective in reducing headache days per month, with few significant adverse events and a dosing schedule of monthly or quarterly. Lasmiditan, in the newer class of ditans, is a serotonin<sub>1F</sub> receptor agonist which is effective like a triptan but does not constrict blood vessels. Multiple devices have been approved in the US and Europe including: a transcranial magnetic stimulator for the acute and preventive treatment of migraine; a supraorbital nerve stimulator for the acute and preventive care of migraine and a non-invasive vagal nerve stimulator for the acute care of cluster headache and soon preventive care. Not yet approved are a sphenopalatine ganglion stimulator for cluster headache acute care and prevention; caloric vestibular stimulator for prevention of migraine; occipital nerve stimulator for chronic migraine and cluster headache and a non-invasive neuromodulator placed on the arm for treating migraine. We have a lot to look forward to for treating our migraine patients who often need special techniques, alone or in combination, for significant improvement.

## Medication overuse headache (MOH) can be treated with preventive medications without detoxification — Yes

### J. Schim

The Headache Center, the Neurology Center of Southern California, USA

MOH is usually treated with detoxification from the offending agent first. There is evidence that preventive medications work regardless of detoxification. The relationship between medication overuse and headaches has been known for decades. Overuse of ergots was noted to be associated with a variety of ill effects, including increased headaches. However, not all individuals who overuse acute medications develop medication overuse headache. While there is evidence in favor of discontinuation of medication overuse to improve headache frequency, there is also evidence that instituting prevention therapy, even without educating the patient about medication overuse issues, can improve headache control. The mechanism of MOH is still unclear. Even without detoxification, headaches can improve with preventive medications alone.

## Medication overuse headache (MOH) can be treated with preventive medications without detoxification — No

**R. Shapiro**

Department of Neurological Sciences, Robert Larner College of Medicine, University of Vermont, USA

Preventive medications for medication overuse headache (MOH) are sometimes effective without withdrawal of overused acute medications. However, are such preventive medications fully effective without detoxification? Few data address this question. Topiramate appeared to be equally effective at reducing headache days (~3.5 per month), whether or not overused acute medications were present at baseline, in a European randomized controlled trial (Diener et al. 2007). However, would subjects in the MOH group have shown an even greater response to topiramate had acute medications also been withdrawn? By contrast, topiramate did not reduce the number of headache days when medication overuse was present in a US trial (Silberstein et al, 2007). Notably, MOH subjects in the US trial were more likely to be overusing analgesics or opioids, whereas subjects in the European trial more often took triptans. In subgroup analyses of phase III (PREEMPT) trial program assessing Botox for a chronic migraine, subjects showed equal reductions in headache days regardless of whether or not acute medications were overused (opioids were excluded). Again, Botox efficacy was not assessed for subjects who were overusing acute medications but then withdrew from them. In a US retrospective study of outcomes of preventive treatments for MOH (Bigal et al, 2004), all subjects were instructed to withdraw overused acute medications (45% butalbital, 30% opioids), but only those that successfully did so significantly reduced headache days. In conclusion, further studies are necessary to clarify whether optimal treatment of MOH with preventive medications also requires the withdrawal of overused acute medications.

## Episodic vertigo can be a manifestation of migraine, at times, unaccompanied by headache

**M.M. Wysocka-Bakowska**

ENEL-MED Medical Centre, Poland

Vertigo or dizziness is experienced by 51.7% of migraine patients. Patients with migrainous vertigo (MV) may experience attacks of vertigo both with and without headache, most patients show an association between vertigo and headache. Migraine and vertigo are observed in strong correlation since early childhood: Migraine equivalents in children; Benign paroxysmal vertigo; Paroxysmal vomiting. Locomotion sickness in childhood is experienced by over 60% of migraineurs. Locomotion sickness and migraine in childhood; are very common, mostly in boys, decreasing with age, as migraines decrease in frequency. With age observed transformed migraine, the occurrence of vertigo and vertebrobasilar insufficiency (VBI) seem to be related to the vascular and vestibular system. Migrainous aura and cortical spreading depression concern mostly occipital lobes of the brain. Complications of migraine, such as vascular ischemic accidents, occur more often in the posterior area of the brain: in occipital lobes, and in the brain stem. Except for migraine headache, there are other important features of the attack, such as oversensitivity to light, sounds, odors, symptoms exacerbated by sudden movements! Vestibular oversensitivity, brain hypersensitivity to stimulation and impaired habituation to stimuli, are typical of migraine and vertigo. Nausea and vomiting are typical for migraine and vestibular syndromes. The co-occurrence of those two conditions is higher than expected from the combined prevalence of both disorders in general population; vestibular symptoms associated with migraine can represent the most common cause of vertigo. Vestibular migraine (VM) was integrated as an independent entity (ICHD-3 beta, A1. 6.5). Similar descriptions of several different conditions: VM Vestibular Migraine;

MBA, migraine with brainstem aura; HM hemiplegic migraine. Migraine can often co-occur with other vestibular disorders (such as Ménière's disease) and benign paroxysmal positional vertigo (VPPB).

## **Nutraceuticals are safe and effective as migraine treatment**

**M.M. Wysocka-Bakowska**

ENEL-MED Medical Centre, Poland

The burden of migraine is well documented and shows evidence that many patients, mostly women are seriously limited by migraine. In over 38% of patients, migraine attacks are hardly controlled with abortive medications, and there is a need for prophylactic treatment. Most drugs recommended for abortive treatment of migraine attack and for prophylaxis of migraine are not perfect, have several limitations and contraindications. Patients are looking for a safer and more natural alternative treatment. There is long list and broad spectrum of nonspecific treatments of various origin, believed to be safer and more "natural" for the abortive and prophylactic treatment of migraine. The list of nutraceuticals believed to be effective is long. Several works on the effectiveness of Fever few, Riboflavine, Co Q 10, are available in literature worldwide, and many more, on each continent. We should also consider very high placebo effect in migraine patients. Nonpharmacologic treatment, acupuncture, Yoga, relaxation technics, physiotherapy, and psychotherapy may offer an important complimentary ways of migraine management. We should not neglect this options, and try to consider them, carefully discussing with each individual patients. It is especially important for high-risk patients, who cannot tolerate most medications such as triptans, betablockers or antiepileptic drugs, like valproic acid or topiramate, which are all not perfect, even if very helpful for many other migraine sufferers.

## **The criteria for the diagnosis of trigeminal neuralgia should be changed to include sensory loss in the trigeminal distribution — Pro**

**J. Zakrzewska**

Pain Management Centre, Oral Medicine, UCLH NHS Foundation Trust, UK

Trigeminal neuralgia is defined by the International Headache Association as recurrent unilateral brief electric shock like pains, abrupt in onset and termination within the distribution of the trigeminal nerve and triggered by innocuous stimuli. In the criteria for classical trigeminal neuralgia, it is stated that no clinically evident neurological deficit is found. On the other hand the International Association for the Study of Pain does state that sensory changes may be present especially to light touch. In recent cohort studies, mild clinical sensory changes have been detected in up to 70% of patients. Using qualitative sensory testing sensory changes especially to touch and temperature can be detected not just in those with MS but those with no other changes including those with or without concomitant pain. Further investigations with conventional MRI have not shown any reason for these sensory changes. However, more sophisticated imaging such as diffusion tensor imaging DTI does show structural changes which could account for these findings. In view of these findings, clinically mild sensory loss should be included in the diagnostic criteria for trigeminal neuralgia but should not be essential criteria.

# HISTORY OF NEUROLOGY IN POLAND

## To Warsaw from Lvov — Orzechowski, Frey, Rose, Choróbski

**J. Bojakowski**

Department of Neurology, Medical University of Warsaw, Poland

The lecture is devoted to those people, born in Sub-Carpathian (Lvov) region, who came to work in Department of Neurology during first years of its existence in Warsaw. The University of Warsaw has been reconstituted in 1915. Five years later Department of Neurology has been established. The circumstances of teaching neurology before and after 1920 are shortly characterized. The persons of Kazimierz Orzechowski, Łucja Frey, Maksymilian Rose and Jerzy Choróbski are recalled, to gratitude and express the admiration for Lvovians — the University of Jan Kazimierz and Jagiellonian University absolvents supported the Department of Neurology in Warsaw University.

## Professor Irena Hausmanowa-Petrusewicz and the Warsaw School of Neurology

**A. Friedman**

Neurology, Medical University of Warsaw, Poland

Professor Irena Hausmanowa-Petrusewicz headed the Department of Neurology of the Medical Academy in Warsaw for 30 years from 1958 up to 1988. During that time she promoted 63 doctoral theses and 14 habilitations. Due to her very high position in the world of neurologists, most of the promoted doctors were offered by Professor Irena Hausmanowa-Petrusewicz a possibility to go for at least one-year fellowship to best neurological centers in Europe and America. This was a reason why several of her pupils became later heads of various departments of neurology in Warsaw and also abroad. Professor Irena Hausmanowa-Petrusewicz created first in the Polish history of neurology stroke unit in the Department of Neurology and Intensive Care Neurology Unit. She formed for the first time Children Ward of Neurology. She was the one who organized first Post-stroke Rehabilitation Ward located in Konstancin near Warsaw. Due to her involvement in muscular disorders, she created Morphology of Muscles and Nerves lab. She organized first in Europe Muscular Disorders Out-patients Clinic. Definitely, Professor Irena Hausmanowa-Petrusewicz had an enormous impact on Polish neurology and merits the title of Creator of Warsaw School of Neurology.

## The scientific and clinical input of E. Flatau

**D. Koziowski**

Department of Neurology, Medical University of Warsaw, Poland

Professor Edward Flatau was born in 1968 in Płock. Graduated with honors in medical studies from the Moscow State University. His lecturers there included, among others, professors Aleksiej Kowzewnikow and Siergiej Korsakow. Then he conducted academic research in Berlin, where he deepened his knowledge of anatomy, histology and pathological anatomy of the nervous system. Despite many scientific offers (i.e. university of Buenos Aires), he returned to Warsaw. His work was in the clinical and scientific field. As the head of the Department of Neurology at the hospital on “Czyste”, he undertook a wide variety of clinical activities. He was the first organizer of the neurobiological laboratory, which

he initially founded in his own home. Later it was transformed into the Neurobiological Laboratory of the Institute of Marcei Nencki, which he directed for the rest of his life. Scientific studies resulted in many prominent publications. One of the most outstanding is: “Atlas of the human brain and fiber course” published in Berlin in 1894. The contribution to research on dystonia, which he made with Władysław Sterling, is quoted to this day and is a most important piece of study. Edward Flatau was an outstanding scientific researcher, a talented clinician, and a first-class educator. He was characterized by a rare perseverance at work, tireless energy and an exceptional ability to organize teamwork. He died in Warsaw in 1932.

## Polish neuropsychiatrists in the Russian empire

### B. Lichterman

Medical History, Russian History and Cultural Studies, The Sechenov University, Russia

After Poland was divided between Austria, Prussia and Russia in the end of 18<sup>th</sup> century many Polish physicians lived and worked in Russian Empire. For example, Jan (Ivan) Mierzejewski (1838–1908) was a professor of psychiatry and nervous diseases of Imperial Medico-surgical (later Military medical) Academy in St. Petersburg (1877–1893), chairman of St. Petersburg society of psychiatrists and First Congress of Russian psychiatrists. His illustrious pupils include Vladimir Bekhterev, Leonid Blumenau and Alexander Shcherbak (1863–1934). The latter was elected to the chair of nervous and mental diseases at Warsaw University. In 1911 he moved to Sebastopol and founded Romanovsky (later the IM Sechenov) Institute for Physical Therapy. My grandfather Boleslav Likhterman (1902–1967) was one of his pupils. My grandfather’s uncle Dr. Maurycy (Moriz) Urstein (1872–1940) from Warsaw authored more than 100 publications on psychiatry and neurology. He was a pupil of Emil Kraepelin in Germany. In the Russian-Japanese war in 1904–1905, he was a military doctor in Russian Army. In WW1 he was a director of Russian Red Cross hospital and studied mental disorders after brain injuries. Neurology of brain and spinal cord injuries was also a subject of interest of professor Władysław (Vladimir) Dzierżyński (1881–1942) who studied and worked in Russia until his emigration to Poland in 1922. He authored a first Polish textbook on neurology. To conclude, physicians of Polish origin made significant contributions to Russian and international neurology and psychiatry.

## The Circles of Edward Flatau (1868–1932)

### A. Ohry

Rehabilitation Medicine, Sackler Faculty of Medicine, Tel Aviv University, Israel

[Organized with the assistance of Prof. Piotr Jacek Flatau (1953–) Polish-American physicist] When we tried to organize the “Flatau circles”, we found that the connections of the founding father of modern Polish neurology, Edward Flatau (1869–1932), were spread over (at least) three countries: 13 neurologists on the “German list”, 6 on the “Russian list”, and 21 on the “Polish list”. We are not sure that this is the whole list. Flatau was also influential in establishing Polish medical periodicals “Neurologia Polska” and “Warszawskie Czasopismo Lekarskie”. I will focus my introduction on two of Flatau’s pupils: Teofil Simchowicz (1879–1957) and Jakub Mackiewicz (1887–1966).

## The long shadow of the Spanish flu

**L. Spinney**

Writer and journalist, Paris, France

The Spanish flu (1918–1920) infected one in three people on earth and killed between 50 and 100 million of them. For its sheer scale and the virulence of the viral strain that caused it, the disaster was anomalous in the annals of flu pandemics. I will present theories that address why it was in a league of its own and look at how this exceptionally dangerous pathogen affected every part of the human constitution, including the central nervous system. Neurological and psychiatric effects were evident while the pandemic raged, and in the months, years and possibly even decades that followed. Because the virus also affected fetuses in the womb, it left an indelible mark on a generation that has only recently passed away. For these reasons, I will argue, the Spanish flu cast a very long shadow over humanity.

# MULTIPLE SCLEROSIS

## The only certain measure of the effectiveness of multiple sclerosis therapy is serum neurofilament level — Con

**G. Arrambide**

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Increased neurofilament light (NfL) levels reflect the degree of axonal damage occurring in the central nervous system (CNS), leading to their consideration as potential biomarkers for multiple sclerosis (MS), especially to evaluate treatment response. To date, most studies assessing the value of NfL levels were carried out using cerebrospinal fluid (CSF) samples, but lumbar puncture is a relatively invasive procedure that is performed mostly for diagnostic purposes and not for follow-up. Therefore, more recent studies have focused on the reliability of measuring NfL levels in serum. Different assays have been tested, and the most sensitive appears to be a single-molecule array (Simoa) assay. However, serum NfL levels cannot be currently considered the only certain measure of treatment efficacy for the following reasons: there is a need for technical standardization to allow a direct comparability between centres, studies, and possibly even different platforms, given the high cost of the Simoa technique renders it inaccessible to most institutions. Furthermore, in the daily clinical practice, a biomarker that can be classified as positive or negative is probably more useful and easy to interpret. Therefore, cut-off values should be established in healthy controls, should probably be stratified by age, and should be determined for the different treatments currently available for MS. Finally, the study population is small in most studies, so there is still a need for larger, longitudinal studies with a longer follow-up and availability of other clinical and radiological markers of treatment response, which itself may vary depending on the disease phenotype.

## No evidence that cognitive dysfunction is improved by disease-modifying drugs in multiple sclerosis

**J. Cerqueira**

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2CA — Clinical Academic Centre Braga, Portugal  
Neurology, Hospital de Braga, Portugal

Cognitive dysfunction is very common in Multiple sclerosis (MS) patients. Not only do many early MS patients, and even persons with the radiologically isolated syndrome, display cognitive impairments, but also individual cognitive performance often deteriorates during the course of the disease. Cognitive difficulties are a key determinant of employment and autonomy, independently of motor deficits. Therefore, it is important to identify strategies to improve such difficulties. DMDs are effective at controlling relapses and most are also able, to some extent, to prevent disability progression, probably including cognitive dysfunction. Given the high prevalence of already installed cognitive dysfunction, it is also important to understand their impact on existing cognitive difficulties. A careful review of the available evidence in the literature reveals two main conclusions. Almost all DMDs have some sort of evidence suggesting a positive impact on cognitive dysfunction with relatively short-term use. However, most studies are poorly designed and do not seem robust enough for firm conclusions to be drawn. Moreover, the comparison between studies is complicated by the use, in each study, of a different set of cognitive tests. In conclusion, we will show that, notwithstanding novel data in the future, there is, at the present, no strong evidence to support an effect of DMDs in improving cognitive function.

## **Are there diagnostic markers which can reliably differentiate MS from isolated CNS SLE? — Con**

**J. Chapman**

Neurology, Sheba Medical Center, Israel  
Neurology and Neurosurgery, Sackler Faculty of Medicine, Tel Aviv University, Israel

Multiple sclerosis (MS) and systemic lupus erythematosus (SLE) are syndromes. Lupus has laboratory markers but no diagnostic neurological manifestations since there are 19 clinical syndromes associated with it. Multiple sclerosis is a mainly clinical syndrome with no diagnostic blood markers. The clinical criteria for MS of transient deficits are quite common in neuro-SLE, some cases due to vascular incidents and some inflammatory (cerebritis). MRI criteria for MS include the localization of lesions, their shape and conformation, and signal on specific sequences. Unfortunately, none of these are highly specific for MS and can be seen in strokes due to vasculitis. The diagnostic blood markers of SLE are commonly found in patients with MS. The CSF markers of MS, the oligoclonal bands, and intrathecal IgG synthesis are commonly found in SLE. Furthermore, even in patients with classical MS we sometimes find significant autoimmune systemic disease, including SLE and APS. Therapy for MS and SLE overlap to a significant extent including anti-CD20 medications. Better understanding and definition of the pathogenic mechanisms underlying these 2 syndromes will probably define specific diseases which will serve as the basis for diagnosis and treatment.

## **Is the central vein sign really helpful in differentiating MS from other white matter disease? — No**

**C. Constantinescu**

Neurology, University of Nottingham, UK

Ultra-high field MRI, available in a restricted number of centers almost exclusively for research purposes, led to the recognition of the central vein sign (CVS) as a marker for the MS white matter lesions. Some criteria have been proposed for MS, e.g.  $\geq$  lesions with CVS or  $\geq$  40–50% of the lesions having CVS. Efforts are made to detect the CVS at 3T MRI. The reason the CVS is not (yet) helpful: Additional corroborating information (evoked potentials, CSF, clinical features) is more helpful. Currently, CVS is consistently detected at ultra-high field MRI only and is restricted to research. The number of results even from 7+T MRI studies is too small. The CVS is not helpful when the number of lesions is limited. The central vein sign has limited value for the more relevant differential diagnosis situations, where a distinction between MS and other conditions is essential e.g. ADEM, sarcoidosis etc. Some conditions, e.g. neuro-Behçet may have lesions centered around a vein. CVS may be helpful diagnostically in microangiopathy in persons of a certain age with cardiovascular risk factors. Knowing the co-morbidity, clinical features adds information to the white matter changes. Inflammatory and microangiopathic lesions often coexist, and diagnosis needs time and remains clinical. A few illustrative cases will be discussed.

## Should we consider immune reconstitution for patients with more active MS? — No

C. Constantinescu

Neurology, University of Nottingham, UK

In this debate, I will briefly discuss the word “consider” and the notion of (more) active MS before focusing more on the immune reconstitution (IR), defined as re-building of the immune system after a global depletion. Depletion of specific cell populations e.g. B cells, will not be addressed in detail. IR is what happens to the immune system when recovering from global depletion. Contemporary MS treatments relevant in this context are alemtuzumab, cladribine, and haematopoietic stem cell transplantation (HSCT). IR mechanisms are diverse and vary between treatments. Reconstitution after HSCT occurs by increased thymic output and naïve lymphocytes, while homeostatic proliferation with increased effector memory cells and a relatively reduced thymic output characterizes reconstitution after alemtuzumab. This explains the high frequency of secondary autoimmunity after alemtuzumab. IR has both positive and negative consequences. The latter include the risk of infections and secondary autoimmunity. Despite great hopes HSCT offers, there is no class I evidence for its efficacy and it is currently not recommended outside of properly designed trials in specialized centres. Cladribine, a “pulsed” IR offers promise but the mechanisms of IR and safety are not fully known. IR may be dangerous in MS even without systemic immune suppression. Severe inflammatory rebound after stopping natalizumab or fingolimod can trigger IR inflammatory syndrome (IRIS). Indiscriminate offering of drastic immunosuppression followed by IR to any patient with more active disease should be avoided.

## Progressive multiple sclerosis patients have a higher burden of autonomic dysfunction compared to relapsing remitting phenotype

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<sup>2</sup>School of Medicine, University of Zagreb, Croatia

**Objective:** To determine differences in autonomic dysfunction in patients with relapsing remitting multiple sclerosis (RRMS) and progressive MS (PMS).

**Material and methods:** Valsalva maneuver, deep breathing test, and tilt-up test were performed in 40 patients with RRMS (pwRRMS) and 30 patients with PMS (pwPMS), and results were expressed in the form of a Composite autonomic scoring scale (CASS). Additionally, heart rate variability (HRV) analysis was performed on the whole sample.

**Results:** pwPMS had significantly higher adrenergic, cardiovagal, sudomotor indices and total CASS compared to pwRRMS ( $p = 0.029$ ,  $p = 0.018$ ,  $p = 0.001$ , and  $p = 0.001$ , respectively). Disease duration positively correlated with adrenergic, cardiovagal, sudomotor indices and total CASS ( $r_s = 0.294$ ,  $p = 0.02$ ;  $r_s = 0.275$ ,  $p = 0.027$ ;  $r_s = 0.409$ ,  $p = 0.001$  and  $r_s = 0.472$ ,  $p = 0.001$ , respectively), and Expanded Disability Status Scale (EDSS) positively correlated with cardiovagal and sudomotor indices and total CASS ( $r_s = 0.264$ ,  $p = 0.033$ ;  $r_s = 0.411$ ,  $p = 0.001$  and  $r_s = 0.402$ ,  $p = 0.001$ , respectively) in all the patients. Compared to pwRRMS, pwPMS had significantly lower SDNN, low frequency (LF), and high frequency (HF) during both supine and tilt-up phase (all  $p$ -values 0.006). There were no significant differences in LF/HF when supine, but pwPMS had significantly lower LF/HF ( $3.18 \pm 2.63$  vs.  $5.65 \pm 4.71$ ,  $p = 0.008$ ) and higher HF expressed in normalized units (HFnu) ( $34.37 \pm 20.39$  vs.  $23.41 \pm 15.76$ ,  $p = 0.021$ ) during tilt-up.

**Conclusions:** pwPMS have a higher burden of autonomic dysfunction. Differences in the pattern of autonomic dysfunction have been found, with the greatest discrepancy in parasympathetic and sudomotor function. Autonomic dysfunction in pwMS is in correlation with disease duration and EDSS.

## Should treatment be stopped in patients who had apparently inactive diseases for 5 years?

**A. Czaplinski**

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Effective DMTs are essential to guarantee the highest possible well-being to people with MS. For the same reason, there are circumstances in which ongoing DMT should or must be stopped to avoid that risk or costs overcome the benefits. There is a wide agreement that DMTs must be stopped in case of a serious adverse event potentially related to the drug, in patients becoming pregnant, and in subjects who are not adherent to treatment. In addition, some data and our practical experience may support the highly controversial concept of treatment cessation in patients with so-called “benign RRMS” seen in 5–10% of MS patients. Given the fact, that the label “benign multiple sclerosis” is often temporary as apparently benign disease often becomes disabling there is no general recommendation for stopping treatment. However, an individualized approach to the use of DMTs in MS patients with apparently inactive diseases should always be taken into consideration. On the other hand, growing evidence supports the notion that there may be a time in the disease course of some individuals with the initially relapsing disease when treatment with current DMTs can safely be stopped. MS patients who gradually accumulate irreversible disability without experiencing relapses and MRI inflammatory activity — i.e., have transitioned to the SP phase of the disease — most likely do not benefit significantly from any of currently available DMT, which should be therefore discontinued in this group of subjects. In those patients, priority should be given to symptomatic treatment, physical therapy, and management of disability.

## Is bone marrow transplantation the ultimate treatment in aggressive disease? — Yes

**M. Freedman**

Medicine, University of Ottawa and the Ottawa Hospital Research Institute, Canada

Aggressive MS usually means continued, damaging disease that will cause severe and irreversible disability. The 2 most outstanding features of aggressive disease are the amount of damaging inflammation and the rapidity with which it occurs. All current therapies can be effective for many non-progressive forms of MS, but none have been able to completely stop all ongoing inflammation. Patients with the aggressive disease will often have tried and failed at least one of these therapies. With time being of essence, a full ablation of the immune system will remove the damaging autoimmune cells along with the rest of the immune system, thereby fully stopping the immune attack of the CNS. A new immune system derived from autologous stem cells is fully immunocompetent yet is immune tolerant of the CNS. The timing is key — interceding early enough before cumulative damage leads to unrelenting progression. Treatment-related morbidity and mortality is now well below 1%.

## Is the central vein sign really helpful in differentiating MS from other white matter disease? — Host

**M. Freedman**

Medicine, University of Ottawa and the Ottawa Hospital Research Institute, Canada

MS cannot be diagnosed in the absence of clinical signs and symptoms of a typical demyelinating syndrome. However, there are many scenarios where signs and symptoms of disease are atypical and there is need of reliable ancillary tests to help secure an accurate diagnosis. The white matter appearance of MS lesions is not specific to MS and such changes can occur with numerous other entities, which can often lead to misdiagnosis. The pathology of an MS lesion is the hallmark perivenous inflammation. MRI is now sensitive enough to pick up the appearance of a vessel in the midst of a white matter lesion, especially using new MRI techniques such as SWI. How specific is the appearance of a “central vein” for a white matter lesion due to MS? Can it really lead to less misdiagnosis? How often do MS lesions lack the central vein sign? If sensitivity and specificity are really high, then why is it now not part of every standard MRI regimen for diagnosing MS?

## Magnetization transfer ratio, fractional anisotropy, parallel and perpendicular diffusivity to evaluate multiple sclerosis plaques

**E. Gonzalez-Toledo<sup>1</sup>, A. Thompson<sup>2</sup>, R. Williams<sup>3</sup>, H. Sun<sup>1</sup>**

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**Introduction:** Multiple sclerosis (MS) is a degenerative, immune-mediated disease of the central nervous system with demyelination and progressive atrophy. Magnetic resonance is the imaging modality of choice for diagnosis. Magnetization transfer is a sequence that can evaluate the lipoprotein content in the plaques. Diffusion tensor imaging is based on the measurements of water molecules following the white matter fibers. Fractional anisotropy measures nerve fiber integrity. Parallel diffusivity measures the axonal damage and perpendicular diffusivity, demyelination.

**Material and methods:** We examined 12 patients, 4 men and 8 women, mean age of 39 yo (SD = 5) with a 1.5 T magnet. We measured magnetization transfer (MTR), fractional anisotropy (FA), parallel (PAD) and perpendicular diffusivity (PED) in 27 plaques and the adjacent normal tissue as control. We compared the relationship of values of MTR, FA, parallel, and perpendicular diffusivity using Spearman Correlation and we calculated the p-value to differentiate normal tissue from MS lesions.

**Results:** Comparison between normal tissue and MS plaques showed significant correlation for p.

**Conclusion:** Perpendicular diffusivity is related to myelin sheath and was the measurement that better correlated with magnetization transfer ratio. There was no correlation with fractional anisotropy and moderate correlation with parallel diffusivity. For these reasons measurement of perpendicular diffusivity can give an accurate picture of myelination. A and perpendicular diffusivity have a great probability to differentiate normal brain from lesions in multiple sclerosis ( $p = 0.1$ )

## Cognitive dysfunction is improved by MS specific disease modifying drugs (DMD) — Pro

A. Kalinowska

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Cognitive impairment, although once underestimated, is now considered one of the key symptoms of multiple sclerosis (MS). It can occur as early as at the time of clinically isolated syndrome (CIS) (Amato et al. 2008). Disease-modifying drugs (DMDs) used for MS, especially when applied early in MS course, are likely to prevent and/or slow down disease progression. Therefore, we may expect that they will stabilize or even improve cognitive function, as well. Apart from the above-mentioned conclusion, the beneficial effect of DMDs on cognition in MS has been shown in several controlled studies. For instance, significant improvement in neuropsychological outcomes was shown for interferon beta-1B (Pliskin et al. 1996, Kappos et al. 2009), interferon beta-1A (Fischer et al. 2000), and stabilization occurred with glatiramer acetate (Schwid et al. 2007) and natalizumab (Weinstock-Guttman et al. 2012). Also, there is a number of uncontrolled trials supporting such notion. The challenge with assessing DMDs impact on cognition is that pivotal clinical trials did not use cognitive functions as primary endpoints, and were sometimes assessed only in subgroups of patients. Despite several methodological shortcomings, the evidence suggests that DMDs may have beneficial effects on cognitive functions. However, this could be secondary to effects on clinical parameters (i.e. relapses) (Patti 2012). Most likely, combining DMD with cognitive rehabilitation could provide even better response.

## MS is primarily an inflammatory disease with secondary neurodegeneration — Con

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Multiple sclerosis is a heterogeneous demyelinating disease of the central nervous system (CNS), with inflammatory and neurodegenerative components, typically causing relapses and remissions of diverse neurological symptoms, followed by accumulation of disability in patients. The exact pathomechanism of MS is not known. The predominant hypothesis assumes that the disease is primarily driven by myelin-autoreactive T cells, which are abnormally activated by environmental factors in immunologically susceptible subjects. It was supported by animal models, which have obvious limitations in the human translation of data. However, the primarily inflammatory hypothesis has several flaws. Firstly, while all currently approved MS therapies are directed at the inflammatory component, none of them are definitive cures and the response to therapy is variable across the patient population. Also, if one assumes that axonal degeneration is a result of multifocal inflammatory response, then in primary progressive MS, where brain lesions are typically scarce, it is not plausible. This suggests that there is another pathomechanism leading to disease progression, which may be either primary neurodegeneration, or failure of neuroregeneration strategies. The main evidence for the primary role of degeneration in MS was provided by a neuropathological study by Barnett and Prineas (Annals of Neurology 2004). They showed that in newly forming symptomatic lesions there is extensive oligodendrocyte apoptosis with activation of microglia, but few or no lymphocytic infiltrates or myelin phagocytes. Oligodendrocyte degeneration could lead to the liberation of autoantigens, resulting in a secondary immunological reaction, whose severity and course are dependent on the individual immunological profile of the patient.

## Are MS therapies safe and effective in the elderly?

**J. Kruja**

Neurology, Faculty of Medicine, University of Medicine, Albania  
Neurology, UHC Mother Teresa, Albania

Multiple sclerosis (MS) is a chronic and disabling autoimmune disease with significant neurodegenerative and inflammatory components. The onset of the disease happens mainly between 20 and 40 years. It was accepted that the natural history data of persons with MS reveal survival approximately 38 years after diagnosis. The use of disease-modifying therapies (DMTs) influenced the longevity too, and approximately 90% of people with onset of MS in their 20s may live into their 70s (according to Hurwitz, 2011). On the other hand older patients present with increased medical complexity and decreased health-related quality of life (HRQOL) requiring a comprehensive and multidisciplinary approach and making the treatment choice more difficult. The main question in this condition is if we may continue to use the MS therapies in the elderly patients avoiding the side effects and the influence on other age-related diseases and one the other hand preserving their effectivity? Shall we continue for the lifetime the DMTs ore have we to interrupt the medications, if yes, when it is the better time and/or criteria to do it?

## The only certain measure of the effectiveness of multiple sclerosis therapy is serum neurofilament level: host

**J. Kuhle**

Department of Neurology, University Hospital Basel, Switzerland

Neurofilaments are highly specific neuronal proteins. They have come closest to clinical application by their higher concentrations repeatedly demonstrated in cerebrospinal fluid (CSF) in all stages of MS, during relapses, their responsiveness to disease-modifying treatments in relapsing and progressive MS and their associations with measures of inflammatory and degenerative MRI outcomes. Digital single-molecule array (Simoa) technology improves the accuracy of bioassays in the quantification of neurofilament light chain (NfL) in serum and plasma. NfL marks a common final path of neuroaxonal injury independently of specific causal pathways. CSF and blood levels of NfL are highly correlated across various diseases including MS, suggesting that blood measurements likely are useful in assessing response to treatment and predicting future disease activity. Other biomarkers have not been studied to similar extent. Such measures, especially in blood, need further validation to enter the trial arena or clinical practice.

## Monoclonal antibodies to CGRP will not become first-line treatment for the prevention of migraine

**C. Lampl**

Headache Medical Center, Ordensklinikum Linz, Barmherzige Schwestern

Migraine is a very disabling disorder with severe impact on patients' lives and substantial costs to society in terms of healthcare costs and lost productivity. Prevention is a key component of migraine therapy. Numerous preventive options exist, however not been adequately applied to patient's need. In the 2015 Global Burden of Disease Study, migraine was the seventh leading cause of disability globally and the leading neurological cause of disability, accounting for over half of the years lost to disability from all neurological disorders. These may indicate that there is a need for improved preven-

tive treatments for migraine. Monoclonal antibodies against CGRP or its receptor are new promising therapies. They have a long half-life that makes them suitable for therapies requiring chronic activity such as migraine prevention and allows for less frequent dosing, e.g., once or twice monthly. Four monoclonal antibodies are currently in development for migraine prevention: three against CGRP itself: galcanezumab (LY2951742), eptinezumab (ALD403), and fremanezumab (TEV-48215) and one against the CGRP receptor erenumab (AMG-334). Initial safety and tolerability data from phase II trials appear excellent for the anti-CGRP monoclonal antibodies. However, there are some unknown facts to be discussed: Their long-term safety is entirely unknown at this time. The full range of CGRP's physiologic functions is complex. CGRP is a potent vasodilator, and thus, a theoretical risk exists that CGRP blockade could hinder vasodilation in physiologically appropriate situations such as cardiac or cerebrovascular ischemia. Additionally, since antibodies have a relatively long half-life, any untoward effects could not be quickly reversed. CGRP receptors are found outside of the nervous and vascular systems, including in the adrenal glands, kidneys, pancreas, and bone. The effect of chronic CGRP antagonism on other organs is unknown. Their site of action in migraine prevention is unclear. The cost of treatment, once the monoclonal antibodies become commercially available, will certainly be high. In a healthcare system of limited resources, this cost will need to be balanced with the magnitude of benefit. An important group of patients, those that failed more than two preventive categories, was largely excluded from the trials, and thus, it is unknown what benefit this population would derive.

## **Episodic vertigo can be a manifestation of migraine, at times, unaccompanied by headache**

**C. Lampl**

Headache Medical Center, Ordensklinikum Linz, Barmherzige Schwestern

The manifestations of migraine-associated vertigo are quite varied and may include episodic true vertigo, positional vertigo, constant imbalance, movement-associated disequilibrium. Symptoms can occur before the onset of headache, during a headache, or, as is most common, during a headache-free interval. Consequently, many patients who experience migraines have vertigo or dizziness as the main symptom rather than headache. Although the definition of migraine-related vertigo and the continuum of the symptom complex remains poorly defined, the relationship is clearly more than a chance association. The clinical presentation of vestibular symptoms that often correlate with migraine includes — but is not limited to — dizziness, motion intolerance with respect to head, eyes, and/or body, spontaneous vertigo attacks (often accompanied by nausea and vomiting); diminished eye focus with photosensitivity; sound sensitivity and tinnitus; balance loss and ataxia, cervicgia (neck pain) with associated muscle spasms in the upper cervical spine musculature. While migraine is often associated with benign recurrent vertigo of adults or paroxysmal vertigo of childhood, some migraine patients also present with true benign paroxysmal positional vertigo (BPPV) even after the migraine headache event has ceased. This is thought to be caused by a combination of vascular events along with an alteration of neural activity associated with the migraine event. Verapamil and amitriptyline are particularly useful because of their anticholinergic properties may help control vertigo independently of whether they are useful for migraine.

## **The only certain measure of the effectiveness of multiple sclerosis therapy is serum neurofilament level: host**

**D. Leppert**

Novartis Pharma AG  
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Neuroaxonal damage is a hallmark of multiple sclerosis (MS) leading to brain atrophy, translating into progressive disability. Magnetic resonance imaging (MRI) is the current standard to quantitate brain atrophy but is retrospective by nature. There is a need for a real-time, easy to perform and less costly biomarkers to monitor disease course and drug response, both in clinical trials and in routine clinical practice. Neurofilament light chain (NfL) is a structural protein specific to neurons. Earlier studies were done in cerebrospinal fluid (CSF) and demonstrated that NfL levels are increased in MS and several neurological conditions that affect neuronal integrity. The recent advancement of assay sensitivity has now allowed measurement of NfL in serum and plasma to a degree that physiological levels in healthy subjects can be quantified, and a linear correlation between levels in serum and CSF has been demonstrated. In MS, a number of studies have shown that elevated NfL correlates with relapse activity and long-term disability worsening. Moreover, NfL has been established as drug response marker. However, these results are derived from cross-sectional comparison between patient cohorts in clinical trials, and longitudinal evaluation in retrospective studies. The question is now whether (a) normative databases can be established, (b) the pharmacokinetics in CSF and blood can be elucidated and (c) cut-off values can be established as a premise for the use of NfL for evaluation of disease activity and therapeutic decision making in individual patients.

## **In patients with clinical evidence of MS-like disease and a confirmatory MRI, CSF examination can be avoided in most cases**

**R.A. Linker**

Department of Neurology, University Hospital Erlangen

In the recent years, cerebrospinal fluid (CSF) examination for diagnostic work-up of relapsing-remitting multiple sclerosis (RRMS) was only needed for delimitation of differential diagnoses. The 2010 McDonald criteria for the diagnosis of RRMS were only based on clinical evidence and magnetic resonance imaging (MRI) data. In the 2010 McDonald revision, the presence of oligoclonal bands (OCB) in the CSF was only part of the criteria for primary progressive MS. Yet, recent data suggest that incorrect interpretation of non-specific white matter abnormalities is the most common reason for misdiagnosing RRMS. Thus, basing the diagnosis of MS solely on non-specific MRI lesions needs utmost caution. According to the recently published 2017 McDonald criteria, CSF examination may again help to establish the diagnosis of RRMS. In the setting of a first clinical demyelinating event and evidence for dissemination in space on MRI, the presence of OCB in the CSF may serve to prove the dissemination in time thus allowing for an earlier and at the same time still accurate diagnosis of RRMS. In the present discussion forum, we will tackle the question in which settings CSF analyses will allow for a faster diagnosis of RRMS. We will discuss which patients should definitely undergo CSF examination and whether the absence of OCB in the CSF excludes the diagnosis of MS. Finally, we will address whether it is sufficient to only examine OCB in the CSF work-up or if further, more sophisticated CSF parameters are also of interest.

## **In patients with clinical evidence of MS-like disease and confirmatory MRI, CSF examination can be avoided in most cases**

**J. Losy**

Department of Clinical Neuroimmunology, Poznan University of Medical Sciences, Poland

Diagnosis of MS is based on careful clinical evaluation and MRI examination of the brain and spinal cord. An important role in final diagnosis and in differential diagnosis of MS plays the examination of cerebrospinal fluid. One of the most important results we look for examining CSF is the presence or absence of oligoclonal bands. Their presence in the CSF and not in serum reflects intrathecal immunoglobulin synthesis in the CNS. Oligoclonal bands are present in about 90% of patients with MS, but they are not specific for MS and may be also present in other neurological diseases. About 5–10% of patients with MS never show these CSF abnormalities. Therefore CSF analysis itself cannot confirm or rule out a diagnosis of MS and must be part of the total examination. According to the current 2017 revisions of the McDonald criteria of MS, CSF examination is recommended when clinical and MRI evidence is insufficient to support a diagnosis of MS, when there is a presentation other than a typical clinically isolated syndrome, when clinical, imaging and other laboratory features are atypical of MS and in population in which MS is less common (e.g. children, older individuals) Can this examination be avoided in certain cases? According to 2017 criteria, CSF examination is not mandatory in unequivocal demonstration of DIS and DIT based on clinical and MRI data in absence of atypical clinical or imaging features or in patients with a typical clinically isolated syndrome supported by characteristic MRI findings.

## **Second-line therapies should be first-line in patients with aggressive disease**

**J. Losy**

Department of Clinical Neuroimmunology, Chair of Neurology, Poznan University of Medical Sciences, Poland

Disease modifying therapies approved for relapsing multiple sclerosis, which interfere with a variety of immunological mechanisms, reduce relapse rate, accumulation of disability and MRI activity. Most patients start with first-line therapy including interferon beta, glatiramer acetate, dimethyl fumarate or teriflunomide. In the case of treatment failure and breakthrough disease activity, second-line therapy with more powerful drugs such as natalizumab, fingolimod or alemtuzumab are recommended. These drugs can also be chosen for highly active forms of the disease based on careful risk-benefit stratification. In subgroup analysis in patients with highly active MS, natalizumab reduced annualized relapse rate by 81% (AFFIRM Study) and 76% (SENTINEL Study), as well as reduced the risk of disability progression sustained for 24 weeks by 64% (AFFIRM Study) and 58% (SENTINEL Study). In another study in 70 patients with highly active RRMS (at least 2 relapses and progression of disability of at least 1 point during the year before treatment, sustained for at least 6 months). After two years of natalizumab treatment 48% patients were free from disease activity. Post-hoc subgroup analysis of FREEDOMS study demonstrated that 0.5 mg fingolimod in rapidly evolving severe RRMS patients (at least 2 relapses in the year before baseline and at least 1 Gd+ lesion at baseline) reduced ARR by 67% versus placebo over 24 months (54% in the overall study population). Alemtuzumab is also highly effective medication and can be a good choice for therapy in aggressive MS.

## Should we consider immune reconstitution for patients with more active MS?

**J. Losy**

Department of Clinical Neuroimmunology, Chair of Neurology, Poznan University of Medical Sciences, Poland

Currently we face two main approaches in MS therapy. One approach is chronic/maintenance therapy that is given continuously and adjusted to the progress and activity of the disease. Another approach and concept is immune reconstitution therapy (selective or non-selective) inducing immune reset with the potential for drug-free remission. In this approach such drugs like cladribine, alemtuzumab or ocrelizumab may be examples. Cladribine, purine nucleoside analogue, selectively depletes lymphocyte population. The results have shown that cladribine reduces relapse rate, progression of the disease and MRI activity. When administered in short pulsed course, delivered in two cycles. That generates long-lasting lymphopenia and maintained drug-free remission for additional years. The effects are greatest in patients with highly active disease, Cladribine is recommended by EMA in patients with highly active disease in whom the clinical benefits are bigger than risks of long-term lowering in lymphocyte numbers. Treatment with alemtuzumab, anti CD52 monoclonal antibody (two cycles of i.v. administrations), produces also lymphopenia immune reset and results in disease remission, which can extend beyond period of active treatment. Alemtuzumab is used as a second-line treatment and recommended as well in highly active, aggressive forms of MS. The anti CD-20 antibody, ocrelizumab, given every 24 weeks, produces selective depletion of a segment of B cell lineage and is effective in RRMS and beneficial in PP MS. HSCT (haematopoietic stem cell transplantation) shows that antigen receptor repertoire can be altered and is used in aggressive MS.

## Is the switch from ethical to generic drugs safe and justified? No!

**R. Milo**

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Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel

As intellectual property protections are beginning to expire, cheaper generics for small molecule drugs (e.g. fingolimod), biosimilars for interferon-beta (IFN- $\beta$ ) and follow-on glatiramoids for the non-biologic complex drug (NBCD) glatiramer acetate (GA) are entering the vibrant market of MS therapies. In contrast to generics for small molecule drugs where only pharmaceutical equivalence and bioequivalence are required for demonstrating therapeutic equivalence, the greater complexity of biologics and the possibility of structural modifications and differences in bioavailability and immunogenicity introduced by manufacturing differences make their comparability to their innovator products more difficult, and may result in unpredictable differences in efficacy or safety. These complexities and the lack of appropriate regulation in some parts of the world may explain why several IFN- $\beta$  biosimilars failed to show therapeutic or biological equivalence to their innovator products. Therefore, additional preclinical testing and properly conducted clinical trials are needed and strict regulation is essential. The NBCD GA is a heterogeneous mixture of potentially millions of distinct, synthetic polypeptides, which presents even greater degree of complexity as no two glatiramoid mixtures prepared by different manufacturers can be shown to be “identical”. The innovative GA (Copaxone®) and several glatiramoids show some similarities using conventional methods, but also substantial differences in their physico-chemical properties, immunogenicity, gene expression, impact on biological pathways, safety profiles and most importantly — clinical efficacy. These differences should preclude their use as “generics” for GA, and call for more stringent regulations and carefully designed, comparative clinical trials to ensure the efficacy and safety of follow-on glatiramoids.

## Progressive forms of MS respond to agents used for relapsing forms of the disease. Yes!

**R. Milo**

Neurology, Barzilai Medical Center, Israel  
Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel

Several disease-modifying therapies (DMTs) used for the treatment of relapsing forms of MS (RMS) have shown some efficacy in progressive forms of the disease: Selective B-cell depletion using ocrelizumab consistently improved clinical and radiological measures of disease progression in primary-progressive (PP) MS patients, while rituximab was effective in a subgroup of younger PPMS patients with inflammatory lesions. Recently, the selective sphingosine-1-phosphate (S1P) modulator siponimod demonstrated positive effect on clinical and MRI measures in patients with secondary-progressive (SP) MS, suggesting beneficial effect of S1P receptor modulators in both RMS and SPMS. Treatment with several other MS drugs did not meet primary endpoints in clinical trials in PPMS or SPMS, however, beneficial effect was demonstrated in sub-groups of younger patients or those with more inflammatory disease characteristics, or on some other clinical and MRI endpoints. Inflammation and neurodegeneration co-exist in all stages and all forms of MS as part of a continuum, making the differences in these pathological traits more quantitative than qualitative. There is also evidence that inflammation drives neurodegeneration in MS, and that inflammation tends to be more sequestered and trapped within the central nervous system in the progressive forms of the disease. Thus, drugs used to treat RMS which target mainly inflammatory pathways may have an impact on inflammation and subsequent neurodegeneration in progressive MS, especially if they cross the blood-brain barrier. Moreover, most MS drugs have some effect on mechanisms involved in neurodegeneration, and may contribute to reduced brain damage and neuroprotection in progressive MS.

## Hydrodynamic hypothesis as an attempt to explain the Uhthoff's phenomenon mechanism

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The worsening of visual symptoms caused by heat and physical exertion in Multiple Sclerosis (MS) has been described in 1890 by Uhthoff and named by him in 1961. This condition was to become known as Uhthoff's phenomenon (Up) and was later found to be caused by a rise in body temperature. Over 80% of MS patients develop a panoply of neurological signs during hyperthermia, 60% of which are "new" to that patient. There are few theoretical explanations of pathomechanism of this phenomenon which is still controversial, i.e. decreasing of conduction in demyelinated optical nerve, effects of serum calcium, blockade of ion channels, circulatory changes, heat shock proteins, hyperpolarization reduced by blocking electroneutral Na<sup>+</sup> movement; and unidentified humoral substances. We would like to present our own original hydrodynamic hypothesis which is based on Bernoulli's rule (1738) and the phenomenon of pressures equalization in the eyeball (intraocular and choroid blood pressure) in patients with arterial hypotension (Lauber 1936, Reese and McGavic 1942). This symptom could be intensified in MS patients in increased body temperature due to physiological blood circulation decentralization, or in bleeding (for example menstruation); hypovolemia with decreased blood viscosity and density in reduced haematocrit. It creates a relative ocular hypertension with the intensified press on fundus with intraocular vessels, optic disc, and retinal nerve fibers. This causes secondary intracranial pressure increase, due to Bernoulli's phenomenon related to the circulation of fluids between brain and eyeball, where obstructed intraocular flow determines an obstacle to a normal circulation in this hydraulic "cerebrophthalmic loop".

## Cognitive dysfunction is improved by disease modifying drugs

**F. Paul**

Clinical Neuroimmunology, Charité Universitätsmedizin Berlin; NeuroCure Clinical Research Center, Germany

Cognitive dysfunction is a highly frequent symptom in people with multiple sclerosis (MS), prevalence rates of up to 70% are reported. Cognitive dysfunction may occur at disease onset but tends to increase in frequency as the disease advances. As current disease-modifying drugs (DMD) were aimed at reducing relapse rates and eventually disability progression when investigated in clinical trials, evidence that these medications may beneficially influence cognitive function or may prevent cognitive decline over the course of the disease is meagre. Insights into effects of DMD on cognitive function mainly stem from open-label studies or *post hoc* analyses of exploratory endpoints in pivotal trials. This session will touch upon the controversial debate as to whether cognitive function can be influenced by DMDs and whether cognitive deterioration should trigger switch or escalation of immunotherapy.

## In patients with clinical evidence of MS-like disease activity and a confirmatory MRI CSF examination can be avoided in most cases — Con

**U. Rot**

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CSF examination in suspected MS has an added value to the clinical and paraclinical evidence of dissemination in time and space because it reveals inflammatory nature of the disease. This is especially important in patients with early MS who often have cellular CSF and in patients with atypical clinical presentation. The novel, 2017 criteria for MS allow the diagnosis in patients with a first symptom (clinically isolated syndrome, CIS), positive CSF oligoclonal bands (OB) and MRI evidence of dissemination in space without evidence of dissemination in time. Enhancing lesions are seen in approximately 50% of patients with CIS. On the other hand evidence of dissemination in space is present in more than 70% and positive OB in 85% of CIS patient's therefore early diagnosis of MS can now be made in a substantial proportion of CIS patients with the help of CSF. CSF findings also have prognostic information. For example, it was shown that OB-positive status predicted worse disability in patients with MS. Neurofilament light chain (Nfl) protein is integral part of axonal structure and is released in the CSF with axonal damage. Correspondingly increased levels of Nfl predicted relapses, disability progression, development of gadolinium-enhancing lesions and recovery after attack. In addition, markers of microglial activation (YKL-40) were also found to be associated with relapses and disability progression in patients with MS.

## Are MS therapies safe and effective in the elderly?

**O. Stuve**

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A first-time diagnosis of MS is relatively uncommon during childhood and after age 50. Consequently, MS is widely considered a disease of young adults, and the diagnosis is most commonly established during the second or third decade of life between the age of 18 and 45. In this regard, MS is very simi-

lar to other autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome. The mechanisms that confer relative disease resistance during childhood, early adolescence, and senescence are unknown. Clinically and pathologically, early inflammatory MS appears to be different from degenerative MS. In new, active lesions there is evidence of macrophage and lymphocyte infiltration, as well as endothelial activation. In contrast, old chronic-inactive plaques are often glial scars with decreased numbers of axons. Often, very few inflammatory cells can be detected. A recent histopathological study in elderly patients (median 76 years) with longstanding disease (median 372 months) found that inflammatory infiltrates declined to levels similar to those found in age-matched controls and the extent of axonal injury, too, was comparable with that in age-matched controls. Given that CNS inflammation and adaptive immune responses are diminished in elderly MS patients, it is not surprising that the efficacy of immunomodulatory or immunosuppressive agents can typically only be demonstrated in young or middle-aged recipients. In addition, due to the fact that adaptive immune responses in the elderly are altered and diminished, these agents may put elderly MS patients at greater risk for infectious and neoplastic complications.

## **Is the switch from ethical to generic drugs safe and justified? — Pro**

**O. Stuve**

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Numerous disease-modifying therapies (DMT) are currently approved for the treatment of relapsing-remitting multiple sclerosis (RRMS), and recently the first agent was approved for patients with primary-progressive MS (PPMS). Many of the recently approved molecules are the result of rationale drug design: They have a known molecular or cellular target, and their biological effects can be measured. Thus, generic versions of these agents can be tested for efficacy, safety, and other pharmacological properties. Another question is whether the benefits of individual DMTs justify their enormous cost, or whether less expensive alternatives should be thought. The United States (US) Census Bureau reported that US inflation-adjusted median household income was \$51,939 in 2013. The number of medically-related personal bankruptcies in the US is well above 50% of all filings. Families with health insurance reported average out-of-pocket medical expenses of \$17,749, while uninsured individuals averaged \$26,971. Patients with MS have the highest personal costs for medications of any chronic disorder assessed in a study funded by the Robert Wood Johnson Foundation: An average of \$34,167 per annum in 2009 when the price of DMTs was between \$22,272 and \$33,804. Prices have doubled or even tripled for some agents since 2009. With the increase in the number of treatments, the economics of competition that we were taught in economics 101 certainly does not hold true. We are currently unable to evaluate the merits of a less expensive approved DMT for less severe disease, as nearly all agents are priced similarly.

## **Is bone marrow transplantation the ultimate treatment in aggressive disease? — Con**

**B. Weinschenker**

Department of Neurology, Mayo Clinic, USA

Bone marrow transplantation is undoubtedly an effective and potent treatment that can be considered in patients with aggressive inflammatory forms of MS. However, the following are now indisputable: (1) It is not effective for progressive MS without ongoing inflammation; (2) It is not a cure, and reacti-

vation of MS disease activity may occur in a sizeable proportion of patients who are followed 5 years following transplantation; (3) Some, albeit a low proportion of patients die of complications of this treatment; (4) Other non-transplantation-based pharmacotherapies are now available for MS that are likely safer, easier to administer, and approach the effectiveness of transplantation. While some may argue that more aggressive approaches to immunoablation might lead to even greater efficacy than current regimens, the trend in some institutions has been toward lesser toxicity with less aggressive treatment. Confident complete elimination of clones of autoreactive T-cells, especially in certain hard to eradicate locations in the nervous system, is not feasible with current methodology. Treatment may improve, but a new strategy that “guarantees” a high long-term remission rate is what is required before bone marrow transplantation may be considered the standard “the ultimate treatment” for any patients with MS, aggressive or otherwise.

## Are MS therapies safe and effective in elderly? — Yes

**B. Weinstock-Guttman, K. Kavak, C. Vaughn**

UB Neurology, Jacobs School of Medicine and Biomedical Sciences, Jacobs MS Center for Treatment and Research, USA

The average age of persons with multiple sclerosis (PwMS) is increasing worldwide. Improvements in treating the vascular comorbidities associated with aging as well as new available MS disease-modifying therapies (DMTs) contribute to more stable disease and to longevity. Recent estimates suggest that as much as 10–15% of PwMS are 65 years old. Aging PwMS are rarely included in clinical trials for DMTs. Approximately 30% of PwMS 65 years or older still have relapsing-remitting disease that is highly amenable to treatment. Furthermore, approximately 8% of PwMS present with very late-onset multiple sclerosis (VLOMS) acute onset after age 60 requiring treatment with DMTs. Older PwMS have a higher tolerance for DMT-related risks. To evaluate the effects of DMT discontinuation in aging PwMS, we extracted 135 participants from the New York State Multiple Sclerosis Consortium with stable disease who were at least 50 years of age and  $\geq 15$  years' disease duration. Of these 35.6% worsened in EDSS after discontinuation (34.1% in patients 55 years and 37.7% in patients 55 years or older). Patients  $\geq 50$  who continued treatment with interferon beta or glatiramer acetate were no more likely to experience EDSS or Timed 25-Foot Walk (T25FW) worsening over time than patients 50 years on same medications. Conclusion: Aging PwMS represent a challenge to the MS community. A stable disease course does not protect against disability progression after treatment discontinuation. Additional studies are needed to assess benefit and safety on use of DMTs in aging PwMS.

## Progressive forms of MS respond to agents used for relapsing forms of the disease — Con

**R. Zivadinov**

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Center for Biomedical Imaging at Clinical Translational Science Institute, University at Buffalo, State University of New York, USA

Multiple sclerosis (MS) is a chronic inflammatory demyelinating autoimmune disease of the central nervous system. The pathogenesis of MS includes inflammatory and neurodegenerative disease processes that affect both white and gray matter. These pathogenic mechanisms underlie the relapsing and progressive course of MS. The majority of MS patients are diagnosed with relapsing MS that experience acute relapses with neuropathologic evidence of focal inflammatory demyelinating lesions within the brain and spinal cord, which are usually followed by remissions along with residual and escalating disability. A subset of patients (10–15%) is diagnosed as primary-progressive MS (PPMS) and manifest gradual disability and occasional plateaus, and are considered as a distinct subgroup. The prediction of long-term individual prognosis and conversion to progressive phase is not yet possible.

Because revised MS diagnostic criteria allow early diagnosis, most patients are starting disease-modifying therapy (DMT) in an early phase of the disease. Currently, there are 16 approved MS DMTs, but their long-term benefits to conversion into progressive MS course remains unclear. At this time, it is also currently unknown whether progressive forms of MS respond to agents used for relapsing forms of the disease. Apart from the current insight in terms of peripheral T-cell activation and T-cell driven CNS auto-immunity, other additional immune cells may have bigger role in the disease initiation and propagation. Future studies should show whether, expanding our research observations towards more encompassing approach of the innate immune system, interplay between B- and T-cells may unravel new novel and potent DMTs for treating progressive MS.

## **Is the central vein syndrome really helpful in differentiating MS from other white-matter disease? — Pro**

**R. Zivadinov**

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While the magnetic resonance imaging (MRI) has played a crucial role for diagnosing and monitoring of patients with multiple sclerosis (MS), the current MRI criteria for MS diagnosis still have imperfect sensitivity and specificity, and erroneously diagnosed cases are commonly encountered. Therefore, more accurate and pathologically specific MRI criteria are still needed to exclude other disorders that can mimic MS. Recently, the North American Imaging in Multiple Sclerosis (NAIMS) Cooperative proposed the “central vein sign” (CVS) as a novel MRI biomarker to improve the accuracy and speed of MS diagnosis. The evidence supports that the presence of the CVS in individual lesions can accurately differentiate MS from other diseases that mimic MS. The NAIMS consensus statement aims to provide recommendations for the definition, standardization, and evaluation of the CVS for the diagnosis of MS. However, many questions remain currently unanswered. The CVS predictive value for the development of clinical MS in patients with suspected demyelinating disease is still unknown. The lack of standardization for the definition and imaging of CVS currently limits its clinical implementation and validation. Large, prospective, multi-center trials including patients at first presentation of neurological signs are currently needed to evaluate the clinical value of the CVS for MS diagnosis. Until its diagnostic value has been formally established, care should be taken when using the CVS in routine clinical practice.

# NEUROIMMUNOLOGY

## Can multiple sclerosis be reliably differentiated from isolated CNS lupus? — Pro

**A. Kalinowska**

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Differentiation of systemic lupus erythematosus (SLE) from multiple sclerosis (MS) may pose a clinical challenge, especially when neuropsychiatric symptoms are accompanied by white matter lesions within the central nervous system (CNS). The clinical tools lack discriminative power. In MS the currently applied McDonald criteria are designed to confirm the diagnosis in subjects with high likelihood of MS and a typical clinical picture but are not designed as a differentiation tool. Anti-dsDNA antibodies, which are a hallmark of SLE, could be absent in neuro-lupus. In SLE nervous system is involved in up to 75% of patients. In 30–40% of neuropsychiatric SLE, neurological symptoms occur around the time of lupus diagnosis, so they can manifest as clinically isolated neurological syndrome (CIS) before other systemic manifestations occur. If CNS pathology in lupus is associated with anti-phospholipid (aPL) syndrome, then the diagnosis will be confirmed by aPL antibodies measurement. When they are absent, neuroradiological measures could aid in the reliable distinction between the two disorders. Firstly, lesion load is typically higher in MS, especially with longer disease duration, but this will be less helpful at disease onset. In this case, differentiation could be made based on MRI volumetric measurements. Brain volumetry shows different patterns of atrophy in MS, where it is present early (including CIS), and in SLE, where it should not appear until late stages of the disease. Once normative MRI data are established, we are likely to have a reliable tool in distinguishing SLE from MS, even early in the disease course.

## MS and isolated CNS SLE

**I. Kurkowska-Jastrzebska**

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An extremely important diagnostic problem for a neurologist is to distinguish multiple sclerosis from other demyelinating diseases. There are some biomarkers which may help us to differentiate between MS and other diseases, no one of them is, however, enough reliable to be a sufficient criterion of recognition or exclusion. Systemic lupus erythematosus (SLE) restricted to the CNS, presenting as a demyelinating syndrome and myelopathy are one of the examples that sometimes cause diagnostic problems and can be easily misdiagnosed with MS. The symptoms indicating possible SLE pathology in a patient with the first clinical demyelinating syndrome are known as “red flags”. Renal involvement, livedo reticularis, rash, arthritis, arthralgia, myalgia, headache, meningismus, seizures accompanying symptoms of demyelization should be considered as possible SLE. The various antibodies and proteins, and magnetic resonance imaging help also in proper diagnosis, however, some patients still need observation to make a final diagnosis. Here, we tried to answer a questions if we can properly differentiate isolated CNS-SLE from MS, if there is a necessity for considering SLE always when diagnose MS since SLE with CNS involvement is rare, what biomarkers we may rely on the most and if any older/novel biomarkers give hope for better understanding pathology and distinguishing of these two diseases.

## Neuroinflammation and neurodegeneration

**J. Leszek**

Department of Psychiatry, Wrocław Medical University, Poland

Neuroinflammatory response is primarily a protective mechanism in the brain. However, excessive and chronic inflammatory responses can lead to deleterious effects involving immune cells, brain cells and signaling molecules. Neuroinflammation induces and accelerates pathogenesis of neurodegeneration disorders like Alzheimer's disease (AD), Parkinson disease (PD) or Multiple sclerosis (MS). The sustained release of inflammatory mediators works to perpetuate the inflammatory cycle, activating additional microglia, promoting their proliferation, and resulting in further release of inflammatory factors. Interactions between activated glia and neurons around ABeta plaques maintain a chronic, self-sustaining inflammatory state in affected brain. Receptors of innate immunity participate in triggering and driving inflammatory reactions. For example, Toll-like receptors (TLRs) and receptor for advanced glycation end product (RAGE), major receptors of innate immunity, play a central role in perpetuation of inflammation. Proinflammatory molecules, which are elevated in neurodegenerative diseases, can increase the expression of TLRs in CNS cells. RAGE activation should be perceived as a primary mechanism which determines self-perpetuated chronic inflammation, and RAGE cooperation with TLRs amplifies inflammatory signaling. In this presentation, I highlight and discuss that RAGE-TLR crosstalk emerges as an important driving force of chronic inflammation in neurodegeneration disorders like AD. It is important to emphasize that RAGE-TLR crosstalk may be considered as a potential target for the future treatments in neuroinflammatory diseases.

## NMO immunosuppression should be withheld in pregnant patients

**F. Paul**

NeuroCure Clinical Research Center, Charité Universitätsmedizin Berlin, Germany

Neuromyelitis optica spectrum disorders (NMOSD) are severe autoimmune conditions of the CNS with the predominant affection of the optic nerve, spinal cord, and brain stem. In up to 80% of patients, serum antibodies to the astrocyte water channel aquaporin-4 are detected that are associated with an increased risk of recurrent disease following the first attack. Thus, immediate initiation of immunosuppressive treatment following the first attack is warranted in seropositive patients. As NMOSD also affect women in fertile age, the question how an NMOSD diagnosis impacts the course of a pregnancy and vice versa is raised by many female patients, including the critical issue as to whether immunosuppression should be stopped before or during pregnancy in light of the potential risks. This presentation will summarize current knowledge on course and complications of pregnancy in patients with NMOSD and provide arguments in favor of withholding immunosuppression in pregnant women.

## All pathology in NMO is AQP4-IgG and complement dependent

**F. Paul**

NeuroCure Clinical Research Center, Charité Universitätsmedizin, Berlin, Germany

Attacks in NMO are believed to result from binding of AQP4 to its target antigen, the astrocyte water channel AQP4, with subsequent complement activation and other mechanisms leading to tissue damage and macroscopically visible NMO lesions. Drugs targeting complement activity have shown to significantly reduce relapse activity in NMO, further underscoring the role of complement in disease

pathogenesis and lesion formation. However, recently other players of the immune system such as neutrophils or T cells have been identified as contributing to lesion evolution, and not all lesions seem to be characterized by complement activation and tissue necrosis. This presentation will provide arguments against a standalone role of complement and will shed light on additional disease mechanisms we are now beginning to understand.

## **All pathology in NMO is AQP4-IGG and complement dependent — Pro**

**B. Weinschenker**

Department of Neurology, Mayo Clinic, USA

The pathology of lesions in neuromyelitis optica spectrum disorders (NMOSD) with aquaporin-4 IgG has been shown to be necrotic with prominent antibody and complement activation, evidenced by C9neo antigen detection indicating terminal complement activation. While other pathologies are now reported in NMOSD, including diffuse non-lesional astrocyte hypertrophy, and non-lytic lesions without demyelination despite the loss of immunoreactive aquaporin-4 and inflammation, the significance of these pathologies remains unclear; they are not clearly associated with the cardinal manifestations of NMOSD, namely optic neuritis and myelitis. Whether or not there are cognitive, emotional or other behavioral phenomena in patients with NMOSD as a result of these pathologies is uncertain and the subject of ongoing study. Experimental models of passively induced NMO by transfer of pathogenic immunoglobulin into rodents clearly establish that in the absence of any one of AQP4 expression (AQP4 knockout mice), AQP4-IgG (use of control IgG) and complement (failure to administer concomitant human complement), pathological changes cannot be produced. Selective complement depletion is highly effective in the prevention of NMOSD attacks. It would be more accurate to argue that “all acute attacks of optic neuritis and myelitis in NMOSD are likely AQP4-IgG and complement dependent”, but if these manifestations could be controlled by effective treatment, most patients and physicians would be pleased with the results and would consider that at least 90% of NMOSD has been vanquished.

## **NMO immunosuppression should be withheld in pregnant patients — Con**

**B. Weinschenker**

Neurology, Mayo Clinic, USA

Traditionally, immunosuppressive medication has been withheld in patients with MS and many other autoimmune diseases because of potential teratogenic risks to the fetus and possibly because of additional risks to the mother who is already in a somewhat immunosuppressed state because of pregnancy. However, neuromyelitis optica spectrum disorders (NMOSD) are an exception, although not the only exception, to this general rule about the use of immunosuppressants during pregnancy. The principal target antigen of NMOSD, aquaporin-4, is expressed in placenta, especially in early pregnancy. A number of pregnancy-related complications occur at significantly increased frequency in patients with NMOSD, such as spontaneous abortion and preeclampsia. While the risk of a relapse during pregnancy is reduced in MS, it does not seem to be the case in NMOSD, and, as is the case for MS, the risk of relapse is greatly increased postpartum. Unlike MS where relapses tend to be mild and generally self-limited or easily treated with a brief course of corticosteroids, NMOSD attacks are often severe, leave permanent sequelae and may require complex treatments such as plasma exchange. Use of certain effective immunosuppressants such as azathioprine and rituximab that are widely used to prevent attacks of NMOSD appears to be relatively safe and well tolerated to mother and infant when administered either immediately before conception or continued throughout pregnancy. For these reasons, in patients with recently active NMOSD, immunosuppression should be administered with either azathioprine or rituximab throughout pregnancy.

# OTHER

## Welcome remarks

**U. Fiszler**

Department of Neurology and Epileptology, Centre of Medical Postgraduate Education, Poland  
Committee of Neurological Sciences, Polish Academy of Sciences, Poland

The 12<sup>th</sup> World Congress on Controversies in Neurology offers a unique opportunity to welcome distinguished and well-known experts from all over the world, who kindly agreed to share their experience during this important meeting. We have noticed an unprecedented technological progress in diagnostics and therapy of numerous neurological diseases. Nevertheless, there is still a wide disparity between what patients expect and what practicing neurologists consider as being adequate and available to provide in terms of services. In the future, the escalation in human lifespan will depend on healthier lifestyles and the availability of improved biomedical advances and biotechnologies. Here comes a valid question: would it correspond with the decrease of neurological cases in this population? At the same time, one of the present major public health issues becomes obesity, which causes dyslipidemia, metabolic dysfunction, and inflammation. These changes could lead to neural death. Therefore, one should ask whether the dietary intervention in combination with physical exercise may be considered an effective therapy against neurological disorders? Another attention-drawing phenomenon concerns the bi-directional gut-brain-microbiota axis, which, if subjected to pathological changes, may increase the risk of other neurodegenerative diseases. The topics discussed during the Congress will focus on a number of contemporary controversial and unresolved issues in neurology. The fact that the 12<sup>th</sup> World Congress on Controversies in Neurology takes place in Warsaw, a city with a great history and remarkable tradition, but also tragic past — a city which is booming again — makes us here very pleased and proud.

## Challenges for neurology in the informatics era

**R. Frackowiak**

Blue Brain Project, EPFL, Switzerland

The human brain is massively redundant in its organization. When brain systems are damaged, or when reinforced by learning mechanisms, they reorganize by strengthening synaptic connections, or by engaging new pathways or constituent brain regions. Can the mechanisms underpinning reorganization be enhanced or modulated? What is the implication for slowly progressive neurological disorders? Clinical scientists have deployed non-invasive functional imaging to examine such reorganization and better methods of detecting pre-clinical neuronal loss have been found recently. This work has paralleled methodological advances in MR imaging that reflect physical features of the brain quantitatively. These techniques have been complemented by novel analysis methods that allow complex image classification and hence more sensitive and precise diagnoses. The eventual clinical ambition of the Human Brain Project is to link genetic and proteomic levels of brain organization with rules that govern the cellular segregation of protein expression. From protein expression rules that determine cellular morphology should predict connectivity and so on until a constructive process of predictive simulation discovers the mechanisms of emergent properties. In this way, we hope to define brain systems as interacting brain regions organized as behavior-specific modules. This framework provides a new approach to understanding mechanisms of compensation for neurodegeneration and the basis of functional plasticity at the mesoscopic level. I will describe these ideas with reference to pre-clinical states in conditions such as Alzheimer's disease. Frackowiak RSJ, Markram H. (2015) the future of human cerebral cartography: a novel approach. *Phil Trans R Soc; B* 370: 20–32.

## **With the use of atypical neuroleptics, tardive syndromes have practically disappeared**

**P.J. Garcia Ruiz**

Department of Neurology Fundacion Jimenez Diaz. Madrid. Spain, Garcia Ruiz Pedro J, Spain

Tardive syndrome including tardive dyskinesia (TD) is one of the most frequent side effects of neuroleptics. Over the last three decades, a number of so-called atypical neuroleptics have entered the clinical practice. These new atypical neuroleptics are characterized by predominant action upon serotonin rather than dopamine and theoretically they exert much less tardive syndromes compared with the classic neuroleptics. However and although the new antipsychotics are associated with less sedation and weight gain, they still are associated with tardive syndrome including the much feared tardive dystonia and the still frequent TD. In fact, recent epidemiological studies put into questions the apparent reduction in neuroleptics-related tardive syndrome. This controversy will review recent epidemiological and neuropharmacological data on the subject.

# PARKINSON'S DISEASES AND OTHER MOVEMENT DISORDERS

## Neuroimaging diagnostic workup in parkinsonian syndromes: always DAT SPET first: a joint debate with European Association of Nuclear Medicine (EANM)

**J. Arbizu**

Nuclear Medicine, University of Navarra Clinic, Spain

In recent years different neuroimaging biomarkers have been included in the clinical diagnostic criteria of neurodegenerative diseases. One of the possible explanations could be related to the remarkable progress and advances undergone by imaging techniques in the last decade. Specifically, nuclear medicine molecular imaging, such as positron emission tomography (PET) or single photon emission computed tomography (SPECT). However, these techniques have largely contributed to our knowledge regarding the physiopathology of different neurodegenerative diseases, but also to diagnosis in the early phases of the disease, when structural changes are not yet evident. The diagnosis of neurodegenerative diseases presenting as a parkinsonian syndrome may be complex in the early phases due to the initial overlapping of symptoms between different diseases. Diagnostic accuracy improves with disease progression, when some atypical signs, incompatible with the diagnosis of idiopathic Parkinson's disease (PD), become evident. In this scenario, the possibility of *in vivo* noninvasive imaging of the integrity of the dopaminergic nigrostriatal pathway, neuronal activity of the basal ganglia and cortex, as well as myocardial sympathetic innervation may be useful to complement the clinical diagnosis, thereby improving the specificity and facilitating decision making. This variety of molecular neuroimaging techniques with common objectives has resulted in some degree of controversy regarding the role of each technique. Consequently, it is necessary to define their use in the clinical diagnosis of patients with parkinsonian syndromes of uncertain origin.

## Real-time MR-guided gene therapy for Parkinson's disease and AADC deficiency in children

**K. Bankiewicz**

Neurosurgery and Neurology, University of California San Francisco, USA

Gene transfer technology can correct genetic mutations in the brain. Neuro gene delivery via direct intraparenchymal injections of adeno-associated viral (AAV) vectors is a locally administered treatment that requires accurate delivery to maximize safety/efficacy. Gene therapy using adeno-associated virus (AAV2) carrying the amino acid decarboxylase (AADC) gene has the potential to improve the clinical response to levodopa when infused into the putamen of Parkinson's patients (PD) or to generate dopamine production in children with AADC gene mutation after administration to substantia nigra and ventral tegmental area. Neurotrophic factors hold great promise in the treatment of PD. Prior clinical trials have shown possible benefit but may have been limited by inadequate anatomical vector delivery or off-target vector distribution. Using intraoperative MRI and co-infusing the vector with gadoteridol allows real-time visualization of infusions. The infusion strategy evolved during the trial to maximize anatomical coverage. Analysis of bilateral MR-guided putaminal infusions of over 30 PD patients and 3 children with AADC deficiency in ongoing Phase Ib/2 clinical trials were performed. In both PD and AADC, deficient children AADC gene transfer significantly increased clinical outcome as manifested by 4 hrs. increases in ON time in PD patients at 12 months and increase of motor performance and

reduction or elimination of oculomotor crises in AADC-deficient children. PET with (18F)DOPA detected expression (AADC trials) and effects of gene therapy (GDNF). These results show that advances in surgical techniques have markedly improved vector delivery and that AAV2-AADC has strong therapeutic potential in both indications presented here.

## Is PD a prion disease? — Yes

**E. Bezard**

Institute of Neurodegenerative Diseases, University of Bordeaux, France

Parkinson's disease is characterized by the presence of Lewy Bodies that are intraneuronal proteinaceous cytoplasmic inclusions and by severe neuronal losses in several brain regions associated with deposits of aggregated proteins. Synuclein has been identified as a major protein component of Lewy Bodies and heavily implicated in the pathogenesis of Parkinson's disease. In the past few years, evidence has emerged to explain how this aggregate-prone protein can undergo spontaneous self-aggregation, propagate from cell to cell, and mediate neurotoxicity. Current research now indicates that oligomeric forms are probably the toxic species. Such peculiar behaviour of misfolded oligomeric Synuclein has led to the proposal that it might actually behave as a prion. The speaker will review some of the data in favour of such hypothesis without neglecting alternate explanations.

## The etiology of sporadic Parkinson's disease

**A. Friedman**

Department of Neurology, Medical University of Warsaw, Poland

The role of genetics in familial Parkinsonism is well known. There is no question that the known and also unknown mutations cause the symptoms in the affected individuals. The situation in sporadic Parkinsonism is much less clear. Some studies suggest that the main role in etiology play environmental factors, either through nose or gut. On the other hand, it is known that patients with the sporadic disease more often than the control subjects have in their families other subjects with the symptoms of Parkinson's disease. Does it mean that the sporadic cases are also genetic? Is this related only to a kind of susceptibility that is genetic dependent? Or maybe the genetics has no role whatsoever in sporadic Parkinson's disease? The answers to these questions are the base of our debate.

## Parkinson Disease (PD) with lysosome dysfunction and PD associated with mitochondrial dysfunction are different diseases

**N. Galvez-Jimenez**

Neurology, Cleveland Clinic Lerner College of Medicine and the Wertheim College of Medicine, USA

There is evidence for neuronal cell organelle failure, as causing PD. This is not new, however, as early work on the understanding of this complex disorder was that of dopamine-producing nigral cell dysfunction. Since its original description, evidence has accrued supporting mitochondria and/or lysosomes as contributors for apoptosis. There is evidence linking PD as a consequence of autophagy-lysosomes pathways (ALP) and ubiquitin-proteasome system (UPS) failure. Alpha-synuclein is widely distributed in brain tissue and the accumulation and clumping of such protein has been found widely distributed in PD, Lewy body disease, Alzheimer's disease and others. Hence, ALP failure results in

accumulation of unwanted toxic-synuclein containing proteins, furthering inhibition of ALP function by binding tightly to the receptor on the lysosomal membrane, enhancing neuronal cell degradation. This complex and toxic intra-neuronal cell environment affects mitochondrial function with activation of the instrumental mitochondrial-dependent apoptosis. Current evidence suggests many different morphological types of cell death co-existing in the PD brain, some induced by mitochondria programmed dependent cell death and other independent processes resulting in necrosis. Linking the consequences of these two organelle failure is of utmost importance for furthering the understanding of neuro-degeneration via mitochondrial oxidative stress, accumulation of oxidized dopamine species, reduced glucocerebrosidase enzymatic activity, lysosomal dysfunction and alpha-synuclein accumulation. It has been suggested dopamine abnormal oxidation links mitochondrial and lysosomal dysfunction in PD. Today we will ask ourselves if there is a unifying theory or if PD differs when due to lysosomal dysfunction versus mitochondrial dysfunction.

## Parkinson's disease is not genetic (in most cases)

**D. Goldstein**

Clinical Neurocardiology Section, National Institute of Neurological Disorders and Stroke, NIH, USA

In 1997 A53T mutation of the gene encoding alpha-synuclein was found to cause PD in a rare kindred with autosomal dominantly transmitted PD. In the same year, Lewy bodies, a pathologic hallmark of PD, were reported to contain abundant alpha-synuclein. Since then several genome-wide association studies have confirmed an association of alpha-synuclein genetic variants with PD, and about 20 rare genetic forms of PD have been described. Most PD patients, however, have no family history of PD, and in those with a family history, there is no identified genetic abnormality. Post-encephalitic PD was common in people who contracted von Economo's encephalitis in the early 20<sup>th</sup> century, and Japanese encephalitis, the leading cause of viral encephalitis currently in Southeast Asia, is also associated with later development of parkinsonism. 1-Methyl-4-phenyl-1, 2,3,6-tetrahydropyridine evokes immediate, permanent parkinsonism, and environmental exposures to pesticides and heavy metals increase PD risk. The concept has emerged recently of PD resulting from autotoxic effects of products of oxidation of dopamine such as 3,4-dihydroxyphenylacetaldehyde (DOPAL). No genetic animal model reproduces the drastic putamen dopamine depletion that characterizes PD. Moreover, it is now known that PD entails marked myocardial norepinephrine deficiency, and whether genetic animal models have this abnormality has not been explored. At this point, it seems most likely that PD is rarely genetic. Instead, relatively common genetic changes may bias toward the development of PD, but for the disease to be expressed may require interactions of genetics with aging, environmental exposures, and auto toxicity.

## The heart of Lewy body diseases is the heart

**D. Goldstein**

Clinical Neurocardiology Section, National Institute of Neurological Disorders and Stroke, NIH, USA

Lewy body diseases such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB) feature depletion of the catecholamine, dopamine, in the nigrostriatal system — especially in the putamen. Many in vivo neuroimaging and several indirect post-mortem immunohistological studies have indicated that Lewy body diseases also entail severe loss of cardiac sympathetic noradrenergic nerves. Here we tested directly whether Lewy body diseases are associated with myocardial norepinephrine deficiency. We simultaneously assayed apical myocardial concentrations of norepinephrine, dopamine (from which norepinephrine is synthesized in storage vesicles in sympathetic nerves), and 3,4-dihydroxyphenylglycol (DHPG, the main neuronal metabolite of norepinephrine) in patients with autopsy-proven Lewy body diseases (PD, DLB, or pure autonomic failure) and in control subjects. Compared to controls, Lewy body

disease patients had a 96% mean decrease in tissue norepinephrine content ( $p = 0.0001$ ), accompanied by a 90% mean decrease in dopamine ( $p = 0.0001$ ) and an 89% decrease in DHPG ( $p = 0.0001$ ). The results demonstrate drastic cardiac norepinephrine deficiency in Lewy body diseases, establishing these conditions as neurocardiologic disorders.

## **REM sleep behavior disorder should be considered as a precursor and marker of synucleinopathies and promote therapeutic intervention**

**T. Gurevich**

Movement Disorders Unit, Neurological Institute, Tel Aviv Medical Center, Sackler School of Medicine, Sagol School of Neuroscience, Tel Aviv University, Israel

Initially, REM sleep behavior disorder (RBD) was felt to be an idiopathic clinical entity. Revolutionary observation of Schenck et al in 1996 that individuals initially diagnosed with RBD eventually developed Parkinson's disease (PD) paved the way to the long line of research that demonstrated that idiopathic RBD represents the premotor stage of PD and other alpha-synucleinopathies, which is going along with the Braak's theory of rostral propagation of neurodegeneration beginning in the brainstem. Synucleinopathy was found to be the underlying pathology on the autopsy of 94% of RBD patients in the largest pathological study. Longitudinal cohort studies have shown that up to 90% of patients with RBD are eventually diagnosed with PD, dementia with Lewy bodies, or multiple system atrophy. The majority of idiopathic RBD patients meet the criteria for prodromal PD and possess additional biomarkers of synucleinopathy. In view of the fact that RBD is the earliest known symptom of neurodegeneration and carries a pronounced risk of full-blown clinical syndrome of synucleinopathy development, along with the evidence that disease-modifying interventions may be more successful if applied at the earliest stage of disease, therapeutic interventions must be implemented during the stage of idiopathic RBD (prodromal alpha-synucleinopathy), before irreversible damage appears. As Dr. James Parkinson noted, "It is obvious, that the chance of obtaining relief will depend in a great measure on the period at which the means are employed. As in every other disease, so here, the earlier the remedies are resorted to, the greater will be the probability of success".

## **Parkinson's disease associated with lysosome dysfunction is a different disease from that associated with mitophagy dysfunction**

**J. Hardy**

Department of Molecular Neuroscience, UCL Institute of Neurology, UK

In this debate, I will argue that typical Parkinson's disease is generally associated with problems with lysosomal function. This disease is associated with Lewy bodies. In contrast, much early-onset disease, which has a more restricted clinical picture, largely occurs without Lewy Bodies, is associated with deficits in mitophagy. This disease used to be called Autosomal Recessive Juvenile Parkinsonism. I will suggest that, as the original nomenclature suggests, these are generally different disease. However, I will acknowledge that it is not possible to cleanly separate either the etiologies or pathologies of these diseases and will discuss what the purpose of naming diseases is.

## Is Braak staging true for all Parkinson disease?

**K. Jellinger**

Institute of Clinical Neurobiology, Institute of Clinical Neurobiology, Vienna, Austria, Austria

Braak et al. [1] proposed that cases with Lewy pathology (LP) in peripheral nervous system, spinal cord, and brain stem should be considered as prodromal Parkinson disease (PD), suggesting a hypothesized progression of PD pathology. While most studies assessing typical PD cases show that the vast majority (80–100%) fit the Braak staging scheme, a number of pathological studies argue against it. People with incidental Lewy body disease and PD can show LP in SN or other brain areas without the involvement of the DMV [2]. The Braak staging is mainly valid for PD patients with young onset, long duration and predominant motor symptoms, but not for others, e.g., late onset and rapid course PD [3]. 10–15% of PD cases that are associated with genetic mutations show a pattern of LP that is quite distinct from that of idiopathic PD, fitting the Braak staging scheme [4]. The hypothesized cell-to-cell transmission [5] for PD has produced a paradigm shift in research into the propagation of the majority of late-life neurodegenerative conditions. In view of the currently discussed “prion-like” spreading of pathologic  $\alpha$ -synuclein, the validity of Braak staging of LP and its relationship to neurodegeneration in various subtypes of PD warrants further study.

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## Is PD a prion disease? — Con

**A. Korczyn**

Tel-Aviv University Medical School, Israel

The idea that neurodegenerative diseases are actually prion disorders has been spread uncritically. The main support for this theory comes from laboratory experiments which are prone to artifacts. The clinical evidence is meager and not convincing.

As far as PD is concerned, it is unclear which alpha-synuclein species is the presumed villain, is involved only in cell-to-cell transmission or is the same species also neurotoxic, and why it has cell specificity.

In any case, there is a critical difference between transmissible and transmitted.

## Is PD more common in patients with ET? — Con

**D. Kozirowski**

Department of Neurology, Medical University of Warsaw, Poland

Essential tremor (ET) is one of the most common diseases in the world. Parkinson's disease (PD) is the second most common neurodegenerative disease in the world. The prevalence of both diseases increases with age. There are no case-control studies, to my knowledge, that demonstrated the higher occurrence of PD in patients with ET. Neuropathologically, both diseases are completely different. PD is a typical neurodegenerative disorder with well-known pathology with synuclein inclusions. The neuropathology of ET is not strictly neurodegenerative and affects a different brain area (cerebellum)

and has a different pathology (torpedo incisions). Most PD cases are sporadic. The genetic basis of PD occurs in about 10% of patients. We have many genes, mutations that are responsible for the monogenic forms of PD. In many cases of ET family history is common, but there are no certain genes that would be associated with typical mendelian forms of the disease. Clinical manifestation includes completely different symptoms. Parkinson's disease is a complex syndrome and in some cases, tremor does not occur at all. On the other hand, position and kinetic tremor are axial symptoms of ET. The coexistence of both diseases is high due to their prevalence. However, there is not enough epidemiological evidence to determine whether a prior diagnosis of PD was more prevalent in the ET cases. Neuropathology, genetics, and symptomatology do not show the relationship between these disorders.

## With the use of atypical neuroleptics, tardive syndromes have practically disappeared

**J. Kulisevsky**

Movement Disorders Unit, Neurology Department, Sant Pau Hospital, Autonomous University of Barcelona, Universitat Oberta de Catalonia, Spain

Tardive syndromes (TS) remain a prevalent and potentially irreversible motor complication of chronic dopamine-receptor blocking agents (DR-BA). It occurs most commonly associated with antipsychotics but can present with other DR-BA used as antiemetics or prokinetics. The most common TS is "tardive dyskinesia" (TD). Diagnosis of TS is clinical and is typically made in people who have taken DR-BA for at least three months and have characteristic abnormal purposeless, rapid, repetitive, stereotypic, involuntary movements affecting the tongue, lips, face, trunk, and extremities. TD occurs in > 20% of people who use first generation antipsychotics (FGA) continually for > 3 months, and every year about 5% of those who continually use these drugs begin to show signs of TD. After the introduction of clozapine and a number of other second generation antipsychotics (SGA) (like olanzapine, quetiapine, risperidone, ziprasidone), evidence suggests that patients treated with these drugs have less risk for developing TS than those treated with FGA like haloperidol. Available evidence indicates that the use of SGA reduces the cumulative risk for TD by one-third or that SGA has a decreased annual liability of TD (1% vs 5% for FGA). A recent Meta-Analysis (Carbon 2017) disclosed a global mean TD prevalence of 25.3% across 41 selected studies with significantly lower rates with SGA (20%) vs FGA treatment (30%). A particular low TD prevalence (7.2%) was found in the treatment arms with FGA-naive subjects, relative to SGA-treated cohorts with likely prior FGA exposure ( $p < 0.001$ ).

## Vagotomy: a clue to the pathogenesis of PD?

**M. Lew, A. Jocsón**

Department of Neurology, Division of Movement Disorders, Keck/University of Southern California (USC) School of Medicine, USA

Gastrointestinal dysfunction is a common prodromal non-motor symptom of Parkinson's disease. Studies reveal pathologic aggregates of GI tract  $\alpha$ -synuclein may exist many years prior to clinically evident PD. The Braack hypothesis entails that  $\alpha$ -synuclein pathology arises in the enteric nervous system and progresses retrograde to the CNS.  $\alpha$ -synuclein fibrils have the capacity for antero- and retrograde transport along the vagus nerve and aggregates have been detected in the dorsal motor nucleus of the vagus (DMV) in rats injected in the duodenum with  $\alpha$ -synuclein. Mice models with gastric exposure to rotenone showed  $\alpha$ -synuclein aggregation with secondary spread to the CNS. Hemivagotomy not only prevented abnormal protein accumulation in the DMV of these animals but also prevented neuronal death in the ipsilateral SNpc. These models suggest that vagotomy may diminish a pathway of introduction for peripheral  $\alpha$ -synuclein transport and modify the risk/pathogenesis of PD. In Danish and Swedish cohorts, PD risk in truncal vagotomy patients versus the general population was lower compared to matched controls. Neither study, however, met statistical significance. The Swedish study reported lost decrease

in risk 20 years from vagotomy. The PD index rate for truncal vagotomy patients was statistically significantly lower after 20 years in the Danish study. Interestingly, for both studies, there was a higher risk for PD in selective vagotomy patients. Conflicting data clearly exist. This will fuel a lively debate regarding whether vagotomy modifies the pathogenesis and subsequent risk of developing PD.

## Is Braak staging true for all Parkinson's diseases?

**A. Ludolph**

Neurology, University of Ulm, Germany

Parkinson's disease was defined clinically by James Parkinson in 1817. One hundred years later, Lewy described the morphological hallmark of Parkinson's disease, the Lewy body. During the recent 20 years, attempts are being made to (re)classify Parkinson's disease by genetic means. This controversy is concerned with the definition of Parkinson's disease; is it defined clinically, is it defined neuroanatomically/neuropathologically or is its definition genetic? It is still accepted since Charcot that a neurological disease is defined by the famous clinical neuroanatomical relation. Therefore the gold standard remains that a clinical disease is mirrored by its neuropathology and neuroanatomy. Therefore, the question whether Braak staging is true for all Parkinson's disease must be answered by Charcot's and Lewy's definition — with a clear-cut yes. However, the question remains, whether all genetic forms which are associated with a Parkinsonian syndrome do reflect Parkinson's disease as defined by James Parkinson and Lewy. I will make the argument, that this is not the case in a number of mutations. It is clear, that some autopsies from patients with specific genetic mutations and associated with clinical PD or Parkinsonism do not show the typical features of Braak staging. However, in my view, this means that these mutations are not associated with Parkinson's disease and Lewy's concept and therefore they are associated with a Parkinsonian syndrome and consequently do not reflect the entity PD, but rather a similar, but unrelated entity.

## Neuroimaging diagnostic workup in Parkinsonian syndromes: always DAT SPECT first — Con

**S. Morbelli**

Nuclear Medicine, San Martino University Hospital, University of Genoa, Italy

Dopamine Transporter (DAT) SPECT with [<sup>123</sup>I]FP-CIT is by far the most widely used radiotracer to image nigrostriatal pathway in Europe. The assessment of the integrity of the nigrostriatal dopaminergic pathway with DAT SPECT has been approved by the FDA and the EMA both for the differential diagnosis between parkinsonian syndromes (PK) on one side and essential tremor or non-neurodegenerative PK on the other side as well as between DLB and AD. However the in the era of diagnosis in preclinical stages and with the increasing attention devoted to atypical parkinsonism, new individualized flowcharts need to be implemented for the use of molecular imaging in PK in specific settings. In this framework two tracers able to explore other (extra-dopaminergic) pathways might be used, even before DAT SPECT, to support the clinical diagnosis in patients with PK. In recent years it was demonstrated that the diagnostic accuracy of <sup>18</sup>F-FDG-PET for discriminating PD/DLB from atypical PK is considerably higher with respect to <sup>123</sup>I-IBZM-SPECT, a post-synaptic D2-receptor imaging modality, previously proposed in this setting (notably each PK shows a peculiar pattern of hypometabolism). Several new perspectives have also been provided on the use of cardiac <sup>123</sup>I-MIBG imaging in the evaluation of prodromal DLB and premotor PD. Finally, a recent prospective longitudinal study compared the diagnostic accuracy of DAT SPECT and MIBG scintigraphy, concluding that MIBG method appears to be reliable and accurate for excluding non DLB dementias, avoiding over-diagnosis, especially when parkinsonism is the only core feature exhibited by the patient.

## Is PD more common in patients with essential tremor?

**R. Pahwa**

Neurology, University of Kansas Medical Center, USA

Parkinson's disease (PD) is a neurodegenerative disorder whose prevalence increases with aging. Essential tremor (ET) is the most common movement disorder and its prevalence is greater than five times of PD. Although ET can start at any age, it often begins more disabling with advancing age. Elderly patients often develop mild parkinsonian features secondary to aging or they may also develop other parkinsonian disorders like PD. The gold standard for diagnosis these conditions continue to be clinical criteria. Although these are two exclusive movement disorders, due to overlapping features between the two conditions there is continuing controversy if ET is a risk factor for the development of PD. Since ET is considered a genetic disorder, ET patients and their family are concerned about the risks of developing PD in the future. In this session, the speakers will debate this controversial topic.

## Animal models are useful in understanding PD pathogenesis — Pro

**B.O. Popescu**

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Laboratory of Molecular Biology, "Victor Babes" National Institute of Pathology, Romania  
Department of Neurology, Colentina Clinical Hospital, Romania

Parkinson's disease (PD) is the second most frequent neurodegenerative disease, characterized by the slow spread of alpha-synuclein pathology over decades and a multitude of motor and non-motor clinical signs. As in other neurodegenerative disorders, data from experimental studies in classical animal models for PD did not translate into similar results in PD patients. One of the main limitations of the PD models is targeting solely dopaminergic neurons, therefore not being able to reproduce the complex pathological aspects of PD, including non-motor degeneration. However, from each such model, valid pieces of information can be integrated in our understanding of PD pathogenesis. Moreover, the current development of new animal models, such as alpha-synuclein expressing models, seems to be much closer to PD pathological scenario as compared to classical lesion-based models, and will probably add more valuable information in future.

## Is vagotomy protective against PD?

**I. Rektorova**

Movement Disorders Centre, First Department of Neurology, Faculty of Medicine and St. Anne's University Hospital, Brno, Czech Republic,  
Central European Institute of Technology, CEITEC MU, Masaryk University, Brno, Czech Republic

The a-syn has the propensity for spontaneous misfolding and displays prion-like properties in vitro, including cell-to-cell propagation. Animal studies showed both retro- and anterograde axonal transport of a-syn fibrils in the vagal nerve. However, so far we lack formal evidence that similar prion-like spreading occurs in human PD patients.

If the vagal nerve constitutes a major highway for centripetal spreading of a-syn pathology, it follows that vagotomy could be protective against PD. Three principal types of vagotomy have been employed: full truncal vagotomy; selective vagotomy where only vagal branches to the stomach are cut, and the most refined superselective vagotomy, where only the corpus and fundus is denervated. When the stomach of mice was exposed to the neurotoxin rotenone, a-syn aggregation and subsequent spreading to the brain stem via the vagus has been demonstrated. Both partial sympathectomy and hemivagotomy

significantly delayed the development of motor symptoms in the animals. Moreover, hemivagotomy prevented accumulation of  $\alpha$ -syn in the ipsilateral dorsal motor nucleus of vagus (DMV) and prevented cell death in the ipsilateral substantia nigra pars compacta (SNc). Nowadays, data from two recent epidemiological studies suggest and provide some preliminary evidence that the truncal vagotomy might decrease the risk of PD after > 5 years of follow-up when compared with the background population, and also when compared with the selective/super-selective vagotomy group.

## **REM sleep behavior disorder (RBD) should be considered as a precursor and marker for alpha-synucleinopathies and promote therapeutic intervention**

**I. Rektorova**

Movement Disorders Centre, First Department of Neurology, Faculty of Medicine and St. Anne's University Hospital, Brno, Czech Republic,  
Central European Institutes of Technology, CEITEC MU, Masaryk University, Brno, Czech Republic

Rapid eye movement sleep behaviour disorder (RBD) is characterized by dream enactment and complex motor behaviours during rapid eye movement (REM) sleep and loss of normal REM sleep muscle atonia during polysomnography. The prevalence of idiopathic RBD (iRBD) was previously estimated to be between 0.38% and 0.5% within the general population; probable RBD (without polysomnographic confirmation) is likely even more frequent, affecting 5–6.8% of the older general population after age 60–70 years. Postmortem evidence shows that some RBD patients have degeneration within the areas that control REM sleep and have Lewy bodies and neurites in these areas (synucleinopathy was the underlying pathology in 94% of autopsied patients in the largest multicenter autopsy series of RBD). Therefore, it seems most likely that RBD is caused by synucleinopathic degeneration. Consistent with early neurodegeneration, patients with RBD demonstrate subtle motor, cognitive, and autonomic impairments. Approximately 50% of patients with spontaneous RBD will convert to a parkinsonian disorder within a decade. Ultimately, nearly all (81–90%) patients with RBD develop a neurodegenerative disorder. Among patients with Parkinson's disease, RBD predicts a non-tremor-predominant subtype, gait freezing, and an aggressive clinical course. RBD arises from degeneration of the circuits that control healthy REM sleep and the more classic motor and cognitive symptoms associated with synucleinopathies develop as degeneration spreads rostrally into the brain structures that control these behaviors. Although this idea remains speculative, it nonetheless fits well with Braak's classic staging model of Parkinson's disease pathogenesis, which proposes that neurodegeneration starts in the brain stem before ascending rostrally. Neuro-protective strategies for targeting  $\alpha$ -synuclein in RBD could be beneficial in slowing or even halting the progression of synucleinopathies.

## **Is PD more common in patients with ET? — Pro**

**J. Slawek**

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Department of Neurology, St. Adalbert Hospital, Copernicus, Poland

Both Essential tremor (ET) and Parkinson's Disease (PD) are common, especially in the elderly and may be misdiagnosed. Several epidemiological studies suggest that ET is linked to PD, increasing its lifelong risk 4–5-fold (LaRoia& Louis 2011). ET is no longer considered a benign disorder (many patients present parkinsonian, cognitive symptoms, cerebellar pathology), with increased risk for PD and Alzheimer's Disease. Comparing the risk of atypical parkinsonism and PD in prior ET patients — it was more prevalent in PD (7.1 vs 2.4%) (Louis&Frucht 2007), confirmed by others (Tan et al. 2008), with 3 years follow-up (Benito-Leon et al., 2009). There are several clinical overlapping features suggesting a common pathophysiology. Both may present action and rest tremor, the latter observed in 30% of ET

patients. Developing PD the rest tremor starts on dominating side of ET (Thenganatt&Jankovic 2016). The substantial number of patients may present both ET-PD phenotype with bradykinesia, olfactory deficits and mild dopaminergic deficit on DAT imaging. Benign tremulous parkinsonism may represent this overlap. Incidental Lewy bodies were observed in locus ceruleus in 24.2% of ET brains (Louis et al., 2007). The most recent publication showed Lewy bodies in 25% of ET cases, which was higher than in controls (Choe et al., 2016). Genetic studies demonstrated links between ET and PD (LINGO1 and its paralog LINGO2) (Vilarino-Guell et al., 2010), and also the association between a known PD risk variant, LRRK2 R1628P, with ET. Subjects carrying the R1628P variant had twice the risk of developing ET (Chao et al., 2015).

## Measuring self-conscious emotions (self-disgust, shame and guilt) in patients with Parkinson's disease (PD)

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In considering PD patients' emotion recognition and expression deficits in basic emotions, little is known about their self-conscious emotions like self-disgust, shame and guilt. In the current study, the goal was to measure whether the two groups (PD patients and controls) differ in the aforementioned emotions. Forty-five (45) PD patients and 45 matched Healthy Controls (HC) were recruited. Specifically, participants completed the Self-Disgust Scale (Overton et al. 2008) and TOSCA (Test of Self-Conscious Affect, which measures shame and guilt) scales. A  $2 \times 3$  MANOVA was conducted to test whether self-conscious emotions differed between the two groups as measured by scales administered. Results showed that self-disgust, as well as shame levels, were increased in PD patients as compared to the control group ( $p = 0.002$ ). Levels of guilt were also higher in PD patients; however, this increase was not significant. Additionally, a  $2 \times 3$  MANCOVA, with the HADS depressive scores as a covariate variable, was also conducted to identify whether the main effect of group was still significant after controlling for depression scores. After controlling for depression, PD and HC differed significantly only on self-disgust levels ( $p = 0.027$ ). Overall, according to the findings of the current study, PD patients seem to have higher levels of trait self-conscious emotions when compared to HC and this result seems to be more robust for self-disgust. Further analysis will shed light on the other factors affecting the relationship between PD and self-conscious emotions.

## Neuroimaging diagnostic workup in Parkinsonian syndromes: always DAT SPECT first? — Pro

E. Van de Giessen

Neuroimaging Committee, European Association of Nuclear Medicine, Netherlands  
Radiology and Nuclear Medicine, Academic Medical Center, Netherlands

Imaging of dopamine transporters (DAT) in the striatum in the brain using single photon emission tomography (SPECT) is a well-established method to distinguish neurodegenerative from non-neurodegenerative parkinsonism's. In neurodegenerative parkinsonism's the dopaminergic cells with projections to the striatum degenerate, resulting in a decline of dopamine transporters and loss of signal on the SPECT scan. It is a useful clinical tool that can detect neurodegeneration early in the disease process. Therewith it is often a good first step to help the clinician in the diagnostic process, e.g. to answer the question whether a patient has essential tremor or suffers from neurodegenerative Parkinsonism. During this session, the advantages and limitations of DAT SPECT will be discussed, including scan

technique, analysis method, correlation with clinical measures, and suitability for particular clinical questions, costs, and possibility to use the method for follow-up.

## **Animal models are useful in understanding PD pathogenesis**

**L. Vecsei**

Department of Neurology, Faculty of Medicine, Albert-Szent-Györgyi Clinical Center, University of Szeged and MTA-SZTE Neuroscience Research Group, Hungary

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. Nigrostriatal dopaminergic neurodegeneration is shared with other parkinsonian disorders: including some genetic forms of Parkinsonism, but many of these disorders do not have Lewy bodies. An ideal animal model of PD should exhibit age-dependent and progressive dopaminergic neurodegeneration, motor dysfunction, and abnormal alpha-synuclein pathology. Mitochondrial oxidative phosphorylation, autophagy-lysosomal metabolism, ubiquitin-proteasome protein degradation, and endoplasmic reticulum stress/unfolded protein response are impaired cellular functions in PD (Jiang and Dickson 2018). Many rodent models have been developed to investigate PD using genetic or toxin-based strategies, but all have significant limitations. On the other hand, there are several promising therapeutic agents for the treatment of PD. Therefore we need much better models of the disease (Majláth et al. 2016, Török et al. 2016, Chen et al. 2017, Tronci and Francado 2018, Francado 2018).

## **REM sleep behavior disorder (RBD) should be considered as a precursor and marker for alpha-synucleinopathies and promote therapeutic intervention — Con**

**L. Vecsei**

Department of Neurology, Faculty of Medicine, Albert-Szent-Györgyi Clinical Center, University of Szeged and MTA-SZTE Neuroscience Research Group, Hungary

Much interest has arisen around the association between RBD and a group of neurodegenerative diseases involving abnormal aggregation of the protein alpha-synuclein, comprising Parkinson's disease (PD), multiple system atrophy (MSA), dementia with Lewy bodies (DLB), and pure autonomic failure (PAF) collectively termed „the synucleinopathies”. Recently, it was published that excessive daytime sleepiness predicts neurodegeneration in idiopathic RBD. The Movement Disorder Society (MDS) has proposed a set of the research criteria for prodromal PD, which specified RBD as the most predictive prodromal marker with the highest likelihood ratio. Thus, there is increasing attention on searching the biomarkers that might predict the progression of RBD toward PD, such as olfactory loss, color vision deficit, depression and mild cognitive impairment. Clinical data suggest that isolated RBD in middle-aged and older adults could herald future synuclein-related neurodegeneration, dignifying it as an early marker of later degeneration. However, in some other studies, the presence of autonomic dysfunction does not seem to either predict or be associated with further neurodegeneration. RBD should be considered part of a broader spectrum of neurodegeneration, in line with the proposed Braak's staging model of synucleinopathies, in which central and peripheral autonomic degeneration is predicted to occur at the earliest stages. Recent findings focus on alpha-synuclein aggregation inhibitors and their therapeutic role, with special attention to heat shock proteins, immunotherapy (active and passive), the potential of targeting the Ser129 phosphorylation site, and the antibiotic possibilities. Some controversies of RBD in clinical practice will be discussed.

## Clinical genetics of tauopathies

**Z. Wszolek**

Neurology, Mayo Clinic Florida, USA

A discovery of *MAPT* gene mutations in 1998 opened the road to understanding of pathophysiological implications of tauopathies. The list of tauopathies is growing and includes progressive supranuclear palsy, corticobasal degeneration, Pick disease, chronic traumatic encephalopathy, globular glial tauopathy, argyrophilic grain disease, primary age-related tauopathies, and frontotemporal dementia with Parkinsonism linked to chromosome 17. Alzheimer disease, the most common neurodegenerative disorder is considered to be both amyloidopathy and tauopathy. Many of the newer tauopathies can be diagnosed only on pathological grounds. Some of them are clearly the genetic disorders usually transmitted in autosomal dominant fashion. As a matter of fact the younger the symptomatic disease onset is, the higher the chance that this tauopathy is of inherited form. Interestingly in about a half of autopsied *LRRK2* gene mutation carriers, the tau pathology is present. The *LRRK2* Parkinson disease (PD) is the most common form of genetic PD described so far. The carriers of *LRRK2* mutations usually clinically present with classic PD phenotype, and their illness is usually well responsive to medical and surgical therapies utilized in PD. During my lecture, I will discuss the clinical presentations of common tauopathies and their genetic forms.

## The etiology of Parkinson disease is predominantly genetic — Pro

**Z. Wszolek**

Neurology, Mayo Clinic Florida, USA

I would argue that in almost all cases of Parkinson disease (PD), there is a genetic background. In some cases, the genetic factors are very strong and lead to the development of the first symptoms very early in life. The earlier symptomatic disease onset of PD, the more likely it is that the pathogenic variant will be found in genes already known to be associated with PD. In such cases, the targeted clinical genetic testing could be very rewarding. If there is also a positive family history of PD in other family members, and if they are willing to provide the blood or saliva specimens, the exome sequencing might be successfully utilized and even more cost-effective than targeted clinical genetic testing. Eventually, whole genome sequencing will be the method of choice to establish the precise genetic causation of PD for the cases with positive family history or with early symptomatic disease onset. But even for sporadic cases such genetic testing might be very much considered for possible participation in clinical trials. Such clinical trials might be specifically devised to recruit the research subjects with known genetic mutation status. The PD genome-wide association studies albeit not so helpful for the immediate translational utility also demonstrated the presence of multiple genetic risk factors contributing to the etiology of PD. We are only at the beginning of our understanding of the genetic nature of PD. In near future, a novel genes associated with PD undoubtedly will be identified.

# REHABILITATION

## Is vagotomy protective against PD? — No

**A. Benazzouz**

Institut des Maladies Neurodégénératives, Univ. de Bordeaux, France

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer disease. It is characterized by the manifestation of motor symptoms, attributed to the degeneration of dopamine neurons in the pars compacta of substantia nigra and fibers in the striatum. The majority of drug treatments of Parkinson's disease focus on replacing and mimicking the effects of dopamine to improve symptoms. However, they cannot delay or stop the disease progression. Several experimental studies focused on the use of strategies to prevent or block the degeneration of dopamine neurons; however, even if they worked in animal models, they have aborted in Parkinsonian patients. One of the hypotheses for the etiology of Parkinson's disease is that a neurotropic pathogen enters the brain by a nasal and/or gastric route by axonal transport through the vagal nerve. From experimental animal models, it has been shown that alpha-synuclein forms can be transmitted to the brain from the gut and that vagotomy, which is a surgical procedure in which the vagus nerve is resected, can eliminate transport of pathological proteins from the gut to the central nervous system. Hence, Vagotomy can be a very interesting approach to prevent cell death and the development of Parkinson's disease. This hypothesis is supported by some epidemiologic studies showing that truncal vagotomy conferred a protective effect on subsequent Parkinson's disease risk, whereas super selective vagotomy was associated with a minor or no protective effect. However, the number of studies is limited and no causal effect has been demonstrated until now.

## Treatment of a rare fatal disease with common symptoms: Tafamidis for TTR-FAP

**A. Dori**

Neurology Department, Sheba Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Transthyretin (TTR) amyloidosis (ATTR) is a devastating hereditary disease which affects multiple organs including the peripheral nerves, gastrointestinal tract, and heart, and is fatal within approximately 10 years. Mutations in the TTR protein destabilize its tetrameric structure, leading to its dissociation into monomers that misfolded and aggregate into toxic amyloid deposits in tissues. TTR is the major carrier of thyroxine in rodents' blood, but in humans, the thyroxine binding sites are virtually unoccupied. In vitro studies revealed that thyroxine binding to TTR resulted in its stabilization. This launched the search for a nontoxic compound, which could bind the TTR-thyroxine-binding site, and development of Tafamidis. This new medicine selectively binds and stabilizes wild-type and mutant TTR and halts the amyloidogenic cascade initiated by tetramer dissociation. However, early treatment is crucial for effective prevention of disease progression. TTR familial amyloid polyneuropathy (FAP) is a rare disorder, which presents with common peripheral and autonomic neuropathy and non-disease specific symptoms. Therefore, in the absence of ATTR family history, correct diagnosis is often delayed, limiting effective treatment. "Red-flag" symptom clusters were therefore highlighted to identify these patients. TTR-FAP should be suspected if a progressive peripheral sensory or sensory-motor neuropathy is observed in combination with one or more of the following: family history of ATTR, autonomic dysfunction, cardiac hypertrophy, gastrointestinal disturbances, unexplained weight loss, carpal tunnel syndrome, renal impairment, or ocular involvement. In suspected cases, confirmation by transthyretin genotyping and identification of amyloid in tissue biopsy direct early initiation of pharmacologic treatment.

## Clinical phenomenology of TTR Neuropathy

**J. Finsteter**

Kar Messeri-Institute, Austria

Transthyretin-related (TTR) familial amyloid polyneuropathy (FAP), also known as hereditary amyloid TTR-FAP (ATTR-FAP), is an autosomal-dominant, adult-onset, rare; either isolated hereditary neuropathy or associated with multisystem involvement. TTR-FAP is characterized by irreversible, progressive, and persistent peripheral nerve damage. TTR-FAP is due to mutations in the TTR gene, of which the most frequent is p. Val30Met. Mutations in the TTR gene lead to destabilization and dissociation of TTR tetramers into variant TTR monomers, resulting in the formation of amyloid fibrils, which are consecutively deposited in various tissues including the peripheral nerves. Deposition of amyloid in the peripheral nerves leads to sensory-motor and autonomic neuropathy and several non-neuropathy specific abnormalities. Types of TTR variants, age at onset, penetrance, and clinical presentation attributable to a specific mutation may vary between countries. Phenotypic and genetic variability and non-disease-specific symptoms often delay diagnosis and lead to misdiagnosis. Suggestive of a TTR-FAP are the polyneuropathy, the positive family history, and autonomic dysfunction with gastrointestinal disturbances, cardiac involvement, carpal tunnel syndrome, unexplained weight loss, and resistance to immunotherapy. If only sensory A-delta or C-fibers are affected, small fiber neuropathy ensues and may represent a diagnostic challenge. Diagnostic tests for small fiber neuropathy include determination of epidermal nerve fiber density, laser-evoked potentials, heat- and cold-detection thresholds, and measurement of the electrochemical skin conductance. Pharmacotherapy with tafamidis, a TTR-stabilizing agent, can be highly effective if started early in the disease course. Another therapeutic option, particularly in countries where tafamidis is not yet approved is liver transplantation.

## Is physiotherapy helpful in functional motor disorders?

**N. Galvez-Jimenez**

Department of Neurology, Cleveland Clinic Lerner College of Medicine, USA

Traditionally speaking, disorders of motor control have as predominant underlying pathophysiology alterations of the basal ganglia function, connectivity, genetics and/or failure of the normal pallidal frequency-firing pattern among others. However, functional motor disorders also known as psychogenic movement disorders have a yet unknown underlying unifying pathophysiology in the context of patients having a variety of psychiatric and other co-morbid conditions. The traditional view is that of a person suffering from psychogenic movement disorders is that who has anxiety, depression, bipolar conditions, fibromyalgia, history of sexual abuse, prior traumatic events including local injury among many other causes singly and/or in various combinations. The findings on examination are those of distractibility, entrainability, give-away or false weakness, induction of movement by non-physiologic interventions, variable and inconsistent findings out of proportion on the neurological examination. The lack of unifying pathophysiology and/or psychological theory coupled with the complexity of the milieu/context in which these disorders occur results in treatments which are extremely challenging for some and best fraught with frustrating/poor outcomes and shortcomings for others. Physiotherapy has been used by many during the rehabilitation planning with special attention in retraining and focusing in basal ganglia and cognitive functions, control attention, focusing on function rather than impaired movement and in some cases coupled with supportive psychological therapy, casting of limbs and pharmacotherapy including the use of botulinum toxin therapy. We will be discussing opposing points of view on this complex condition in search for proper therapy. Therefore asked today: Is physiotherapy helpful in functional motor disorders?

## **Is Tai Chi effective in the management of Parkinson's disease?**

**A. Milert**

Department of Physiotherapy, University of Physical Education in Krakow, Poland

Complex movement disorders of patients with Parkinson's disease (PD) require comprehensive and multi-directional health enhancement procedures. Besides current methods of physiotherapy adapted to the stages of PD, the forms of exercises until recently considered unconventional are gradually included. Among others, these include Tai Chi derived from Traditional Chinese Medicine (TCM). Tai Chi is based on natural, smooth, harmonious movements of the trunk and limbs combined with physical and mental relaxation. This form of exercise has been practiced for many centuries among the elderly in China — for preventive and therapeutic purposes. Clinical studies conducted so far confirm the beneficial effects of Tai Chi on improving balance, coordination, muscle strength, gait and reducing the risk of falls of the elderly. The presentation will include the main assumptions of Tai Chi practice and conclusions from the review of the current scientific literature regarding the effectiveness of Tai Chi of patients with PD. The results of the research on the impact of Tai Chi on muscle strength, body posture, spatio-temporal gait parameters, balance, and coordination will be discussed. Methodological guidelines for individual and group Tai Chi exercises of PD patients will also be presented, depending on the stage of the disease. Due to the growing popularity of this form of movement among the elderly as well as the lack of reports of adverse impact on the practitioners, it is worth encouraging the inclusion of Tai Chi as an attractive, complementary form of therapy for traditional methods of physiotherapy.

## **The importance of rehabilitation therapy for clients with paralysis due to the conversion reaction**

**A. Ohry**

Rehabilitation Medicine, Reuth Medical Center, Tel Aviv, and Sackler Faculty of Medicine, Israel

For the rehabilitation medicine community, comprehensive therapy approach towards clients with paralysis due to somatoform disorder is the logical and self-evident fact. Medicine and psychiatry could not find a definite cure for these syndromes. The model that we had developed, was reported in the literature and is significantly beneficial for at least 50% in our clinical experience. It is mandatory to include in our team approach, members who belong to the behavioral and mental professions.

## **Is physiotherapy helpful in functional motor disorders?**

**T. Simuni**

Neurology, Northwestern University, USA

Functional motor disorders (FMD) refer to weakness or movement disorders that are genuine but do not relate to an underlying neurological disease. FMDs are responsible for up to 16% of referrals to neurology outpatient clinics and are among the top five reasons for referrals. Despite high prevalence, the etiology and pathogenesis of FMDs remain obscure. FMD treatment is challenging and overall prognosis has been poor. However, over the last couple years, there has been progress in standardization of treatment approaches. Psychotherapy including cognitive behavioral therapy has been used though there are limited published data. Comprehensive rehabilitation strategies including physical, occupational therapies in conjunction with the motor retraining have been increasingly utilized. Consensus recommendations for physical therapy of FMDs have been published in 2014. Despite that progress,

a small number of intense physiotherapy trials demonstrated beneficial outcome compared to standard of care. Long-term data on maintenance of effect are still missing. Future treatment approaches for FMD will be based on better understanding of the pathophysiology of the condition. In this debate format presentation, the speakers will present the current data, pros, cons and knowledge gaps on the role of rehabilitation approaches for management of FMDs.

# STROKE

## The role of phagocytes in brain repair after cerebrovascular crisis

**J. Aronowski**

Roy M. and Phyllis Gough Huffington Chair in Neurology, University of Texas Health Science Center, McGovern Medical School, Department of Neurology, Houston, Texas, USA

Shortly after the onset of intracerebral hemorrhage (ICH), brain tissue macrophages (microglia) are activated and assume their healing or damaging phenotype depending on the environmental cues. This early event is followed by infiltration of masses of polymorphonuclear neutrophils (PMNs) followed by monocytes/macrophages, a process that can often last for days or weeks. PMNs and macrophages, similar to microglia can be modified by various signaling events to assume either injurious or beneficial (anti-inflammatory, phagocytic, anti-oxidative and trophic) phenotype, a process that could be instrumental in establishing the efficacy of repair of ICH-affected brain. Over the years, we have learned that the healing (assisting in repair) phenotype of these phagocytic cells can be achieved by targeting specific cellular processes regulation function of these cells. We showed that some of these approaches demonstrate robust efficacy in animals' models of ICH and some of them are currently evaluated in clinical trials in patients with ICH.

## The role of the brain microcirculation in acute stroke

**O. Bajenaru**

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

The clinical consequences of an ischemic stroke are determined by the localization and extent of the loss of brain tissue. The ischemic loss of the brain tissue is a direct consequence of the impossibility of normal metabolic changes, in particular, oxygen and glucose supply from the vessels to the brain, at the level of the blood-brain barrier, which normal integrity and functionality are mainly dependent to the integrity of the brain microcirculation. The disruption of the microvascular compartment during and after an acute ischemic event is not the same in all patients with a similar occlusion of a cerebral artery, in terms of caliber and location; the differences are determined by many other factors, among endothelial dysfunction, the presence of previous vascular risk factors, the development of collateral circulation, the time duration since the initial occlusion of the artery are most important. These events at the level of the microcirculation are the key-elements which allow or not the reperfusion of the brain tissue in the ischemic area, even if the therapeutic interventions are performed in therapeutic window. Understanding the role of the brain microcirculation during the acute ischemic stroke is essential to understand the no-reflow phenomenon, the risk of hemorrhagic transformation and other clinical relevant problems related to the failure of the most performant actual acute reperfusion therapies.

## Should we perform left atrial appendage closure in all patients with high risk of stroke and atrial fibrillation who can not take oral anticoagulants? — No

**D. Bereczki**

Department of Neurology, Semmelweis University, Hungary

About 15–20% of all strokes can be attributed to cardioembolism due to atrial fibrillation (AF). In the majority of such cases, the left atrial appendage (LAA) is the source of the embolus. Oral anticoagulation is recommended by current guidelines to decrease stroke risk in those with AF. Oral anticoagulation, however, is contraindicated in some patients, mainly in those with high risk of bleeding. Difficulties in adjusting treatment and low compliance may also affect the benefit of oral anticoagulation. Surgical excision of the LAA is an option to decrease stroke risk, but thoracotomy and the intervention itself have their certain risks and complications. Implantation of an LAA occluder device via the femoral vein and transeptal passage is a new method of LAA exclusion from the circulation. Anatomical variation of the LAA and strict methodological requirements during implantation of the LAA closure device are certainly challenges for the interventionalist. Serious complications were reported in 2–9% in the periprocedural period, some of them like cardiac perforation and tamponade, thromboembolism, or air embolism, can be life threatening. Those who have a thrombus present in the LAA or those with enlarged LAA ostium are not appropriate for LAA device closure. Patients older than 75 have higher periprocedural bleeding risk. LAA device closure is certainly a significant development for stroke prevention, especially in those AF patients who cannot take oral anticoagulation. This technique, however, has certain restrictions, therefore, cannot be applied in all patients who have contraindications against oral anticoagulants.

## The diabetic brain and stroke

**M. Chopp**

Department of Neurology, Henry Ford Health System, USA

Diabetes, particularly in the elderly contributes to cognitive and learning deficits. In addition, diabetes is a major risk factor for stroke, and approximately one-third of all stroke patients are diabetic. Here, I will describe our work on the neurovascular dysfunction in the diabetic brain, first without stroke and then after stroke. Type 2 diabetes (T2DM) in the older rat will be shown to induce neurovascular dysfunction and significant cognitive loss compared with the non-diabetic aged-matched brain. The diabetic brain exhibits increased the loss of axons and oligodendrocytes, reduced myelination and reduced spine density, as well as substantial fibrin deposition compared with non-diabetic aged-matched brains. In addition, the T2DM aging brain exhibits an impaired glymphatic system, which is highly correlated with cognitive loss. Stroke in the T2DM brain greatly exacerbates neurovascular dysfunction and neurological sequelae in the diabetic brain. The diabetic brain post-stroke exhibits increased inflammation and axonal damage. In addition, stroke in the diabetic animal induces significant cardiac dysfunction which drives post-stroke cognitive dysfunction. Molecular mechanisms underlying the exacerbation of neurological outcome and neurovascular function after stroke in the T2DM animal will be described, including the roles of substantially reduced microRNA-126, an important non-coding RNA which plays a vital role in orchestrating neurovascular and cardiovascular health. Novel restorative therapies using exosomes, nano-sized bilipid layer particles containing noncoding RNAs and proteins which promote neurovascular remodeling and enhance both neurological and cardiovascular recovery in the T2DM animal with and without stroke will be described.

## Should we perform left atrial appendage closure in patients with high risk of stroke and atrial fibrillation who cannot take oral anticoagulants?

**G. Chrysant**

Cardiology, INTEGRIS Heart Hospital, USA

Patients with nonvalvular atrial fibrillation are at increased risk of thromboembolic events like stroke and require systemic anticoagulation. For patients with a high risk of bleeding or who have experienced clinically significant bleeding, left atrial appendage closure (LAAC) affords a roughly 90% reduction in stroke risk. The left atrial appendage can be ligated surgically, percutaneously, or can have the appendage filled with a nitinol-based self-expanding device. The most notable and studied is the Watchman device. The PROTECT-AF study, PREVAIL study and the ASAP study show noninferiority to warfarin and a good safety and efficacy profile. The ASAP trial demonstrated the safety and efficacy of LAA closure with aspirin and Plavix without a warfarin transition. The patient population averaged a CHADS-VASc score of 2–3 and the vast majority (in some cases 90%) of patients had experienced clinically important bleeding. There is 5-year follow-up data further demonstrating safety and efficacy. Commercially, LAAC has been promoted as an alternative to warfarin therapy. Since the pivotal trials mentioned above, many patients with atrial fibrillation have been placed on novel oral anticoagulants that have been proven to be a safer alternative to warfarin as it pertains to bleeding events. There are no direct comparison trials between LAAC and novel oral anticoagulants; therefore, some important questions remain regarding who and how many patients should receive LAAC.

## Should secondary stroke prevention include NOACs in addition to antithrombotics?

**L. Csiba**

Neurology, Debrecen University, Hungary

Recently, the efficacy of rivaroxaban plus aspirin combination was investigated for secondary vascular prevention (1). More than 27 000 patients with stable atherosclerotic vascular disease were randomized for rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), or lonely rivaroxaban (5 mg twice daily), or lonely aspirin (100 mg once daily). The composite of cardiovascular death, stroke, or myocardial infarction were the primary outcome. The study was stopped for the superiority of the rivaroxaban-plus-aspirin group. The rivaroxaban-plus-aspirin group had only 4.1% primary outcome event while the lonely aspirin group experienced 5.4% ( $p < 0.001$ ). The major bleeding events occurred in more patients in the rivaroxaban-plus-aspirin group (3.1%) vs. 1.9% in the aspirin group ( $p < 0.001$ ). There were fewer deaths (3.4%) in the rivaroxaban-plus-aspirin group as compared with 4.1% in the aspirin-alone group. The lonely rivaroxaban therapy resulted in more major bleeding events without significant decrease of a composite of cardiovascular death, stroke, or myocardial infarction. The benefit was consistent in the post-stroke subgroup (more than 1000 patients). The benefit was also present in patients with baseline blood pressure below or above the mean and in patients with baseline cholesterol levels below or above the median, confirming the conclusion that the benefits of combination therapy are additive to standard secondary preventive interventions. On contrary, the lonely rivaroxaban (5 mg twice daily) alone did not result in better outcome but more major bleeding events. Should secondary stroke prevention include NOACs in addition to aspirin? My answer: yes.

Eikelboom JW, et al. *N Engl J Med.* 2017; 377(14): 1319–1330.

## Small asymptomatic intracranial aneurysm — to intervene or not?

**V. Demarin**

Neurology, International Institute for Brain Health, Croatia

Unruptured intracranial aneurysms (UIA) are relatively common finding, occurring in approximately 2–3% of the population. Most of these lesions are incidentally found, asymptomatic and typically carry a benign course. In making the treatment decision, understanding the natural history of an aneurysm is imperative and the size, location, shape of an aneurysm, age and existing risk factors should be evaluated. A number of studies were investigating the risk of rupture and growth of asymptomatic aneurysms in order to establish the best therapeutic approach. In the International Study of Unruptured Intracranial Aneurysms (ISUIA), a large-scale prospective epidemiologic cohort study, 5-year cumulative rupture rate for patients without a history of SAH with aneurysms located in ICA, ACoA, ACA, and MCA was 0% for smaller aneurysms of less than 7 mm. For the same size of an aneurysm located in PCA and PCoA, it was 2.5%. These rates are often equalled or exceeded by the risks associated with surgical or endovascular repair. In many other studies, size was also found as being predictive for aneurysm growth and eventual rupture, while in others hypertension, young age and posterior circulation were found to be significant risk factors for rupture. PHASES score was introduced to contribute to predicting the risk of growth and rupture. Careful examination of each patient in electing therapeutic approach is mandatory. In the majority of patients with small UIAs intervention is not an option.

## What should be the optimal imaging to select patients for thrombectomy beyond 3 hours: Is CTA enough or should CTP be added?

**R. Eichel**

Shaare Zedek Medical Center, Jerusalem, Israel

Until recently patients with Acute Ischemic Stroke (AIS) and Large Vessel Occlusion (LVO) in the anterior circulation were eligible for Endovascular Treatment (EVT) up to 6 hours from symptom onset (as defined last seen normal) of their stroke. The Current Trials DAWN and DEFUSE 3 lead to new guidelines and extend our ability to treat AIS patients with LVO up to 24 hours but with additional need to evaluate the infarct core by the use of CT Perfusion (CTP) or MRI Diffusion (MR-D). With these new guidelines, CTP or MRI-D becomes a “Must” in assessing AIS patients to be eligible for EVT after 6 hours of stroke onset. CTP and MRI-D are in need of some basic cooperation of patients during performing the imaging and standardized analysis of CTP is not readily available in all comprehensive stroke centers. So some believe that the current approach of AIS patients with up to 6 hours symptom onset, with using CT head without contrast (using ASPECT to grade ischemic tissue) and CTA, is also enough to evaluate penumbra size and guide us in our decisions for patients over 6 hours. Besides of missing high-quality data to prove such a new rudimentary approach of selecting patients, the use of CTP and MR-D has additional value in guiding us in our treatment decisions. CTP and MR-D are known to increase the sensitivity of identifying patients with AIS, especially when trying to diagnose patients with uncommon symptoms or distal occlusions, that are sometimes missed when evaluating them CTA alone. This presentation intends to show the superiority of adding CTP or MR-D to a standard AIS neuroimage evaluation.

## Should we perform left atrial appendage closure in patients with high risk of stroke and atrial fibrillation who can not take oral anticoagulants — Pro

**M. Grygier**

Chair and 1<sup>st</sup> Department of Cardiology, Poznan University of Medical Sciences, Poland

According to current European Society of Cardiology (ESC) Guidelines, patients with atrial fibrillation (AF) are at risk of stroke and should be treated with antithrombotic therapy based on the risk factors for stroke and bleeding as evaluated by the CHA<sub>2</sub>DS<sub>2</sub>-Vasc and HAS-BLED scores, respectively. Warfarin and new oral anticoagulants (OAC) reduce significantly the thrombo-embolic risk associated with AF. However, some patients even at high thrombo-embolic risk cannot be treated with oral anticoagulants due to major contraindications or intolerance of these drugs. Moreover, platelet inhibition, as it was shown in few studies, is ineffective in stroke prevention. Ninety percent of thrombi leading to stroke in patients with non-valvular AF is formed in the left atrial appendage (LAA). In order to reduce the risk for stroke in these patients, percutaneous LAA occlusion has been developed. Randomized trials (PROTECT AF, PREVAIL) have shown that closure of LAA with Watchman device (Boston Scientific, USA) is non-inferior to warfarin in stroke prevention in warfarin eligible patients. Efficacy regarding stroke prevention in OAC ineligible patients has also been shown in few recently published registries. Current ESC Guidelines state that endovascular LAA occlusion may be considered in patients with a high risk of stroke and contraindications for long-term anticoagulation (Class IIb recommendation). One year data from EVOLUTION registry confirms safety and efficacy of such treatment strategy which should be used more widely.

## Should closure of PFO be the standard of care in patients with ESUS?

**W.D. Heiss**

Neurology, Max Planck Institute for Metabolism Research, Germany

Stroke is among the leading causes of mortality and serious long-term disability. Around one-third of the patients hospitalized with stroke are under the age of 65 years. Around 25% of all strokes are cryptogenic, and this reaches approximately 50% in the younger age group. Epidemiologic data reveal significant association between patent foramen ovale (PFO) and cryptogenic stroke both in the younger and older patient populations. Despite medical therapy, the rate of stroke recurrence in patients with PFO is estimated to be 25% within a 4-year period. Observational data and meta-analyses of observational studies suggest that percutaneous transcatheter closure of PFO is safe and has a low recurrence rate of stroke as compared to medical therapy. However, several randomized controlled studies published up to 2013 have not shown the superiority of PFO closure over medical therapy. An exploratory analysis of long-term data from 1 trial found a significantly reduced stroke risk with closure. Recently published trials also reported positive results. Pooled analyses of these additional data will almost certainly find a statistically significant benefit of closure. As pointed out in the recent Viewpoint by Kamel (2017) the studies on which the meta-analysis was based have some methodological shortcomings and therefore decisions to close or not to close a PFO must still be based on the individual data in a single patient. Nonetheless, the combined clinical, epidemiological, and trial evidence indicate that PFO can cause ischemic stroke and that closure can reduce the risk of recurrence.

## Small asymptomatic intracranial aneurysm — to intervene or not? — Pro

**A. Kobayashi**

Department of Neuroradiology, Department of Cerebrovascular Interventions, Institute of Psychiatry and Neurology, Poland

Unruptured intracranial aneurysms are present in up to 10% of the general population. The risk of rupture is low and the occurrence is 2–20 per 100,000 populations per year. The treatment of patients with an aneurysm-related subarachnoid haemorrhage (SAH) is indisputable, but the treatment of asymptomatic aneurysms is still a matter of debate. Intracranial aneurysms apart from causing SAH can also cause several other neurological symptoms resulting from mass effect and also sentinel headaches. These can also be debilitating or increasing the risk of a SAH. The ISUIA trial showed that small unruptured aneurysms have a lower risk of bleeding and those located in the anterior circulation and less than 7 mm are associated with a higher risk of intervention than rupture. Nevertheless, the ISUIA trial was biased by the fact that it was a non-randomized, observational study where surgical or conservative management was left to the physician's discretion. The trial showed that all posterior circulation aneurysms and those found in patients with a previous SAH from another aneurysm should be considered for treatment regardless of size. More recent studies show that not only size is associated with rupture risk and subsequently with the indication for surgical treatment. These factors include location (anterior and posterior communicating arteries), female gender, daughter sac and irregular morphology, aneurysm growth, increasing time from the first diagnosis, Finnish or Japanese origin, hypertension, smoking, elderly age, earlier SAH from another aneurysm. All of the above together with family history of SAH should be considered before the decision for intervention.

## Small unruptured intracranial aneurysms — to intervene or not?

**H. Mattle**

Neurology, University of Bern, Switzerland

Saccular unruptured intracranial aneurysms (UIAs) are increasingly detected as an incidental finding because of today's frequent use of cranial imaging. They have a prevalence of 3% in the adult population. When they are large the risk of rupture is substantial and calls for treatment. However, small UIAs (5 mm) have a low risk of rupture. Nevertheless, some UIAs do rupture and cause subarachnoid hemorrhage. This indicates that rupture risk cannot be determined solely by their size or location. In addition to size and site of the aneurysm, additional factors such as aneurysm growth, advanced patient age ( $\geq 70$  years), smoking, hypertension, previous SAH from another aneurysm, and the patient's ethnic origin may increase the risk of rupture. Scores like PHASES and UIATS help to predict aneurysm rupture risk, but surgery or endovascular preventive treatment carries a risk as well. Therefore, what strategy to choose, to treat or wait and see, and what strategy will save more quality-adjusted life years for a given patient is often difficult to decide. Furthermore, anxiety caused by the awareness of having an aneurysm can make the decision for the best management of an individual patient even more complicated. In such a situation treatment approaches are debatable and often controversial. The speakers of this debate will address their points of view whether to treat an UIA or whether to wait with treatment and monitor the patient.

## Should closure of PFO be recommended treatment and standard of care in patients with ESUS?

**H. Mattle**

Neurology, University Hospital of Bern, Switzerland

Thrombi that dislodge from the venous system are caught in the pulmonary vasculature. In the presence of right-to-left shunts, however, thrombi can cross paradoxically to the arterial circulation and cause ischemic stroke or infarcts in other organs. This is the case in patients with a patent foramen ovale (PFO) that represents the most common cause of a right-to-left shunt. In stroke patients with PFO and no identifiable source of thromboembolism, the risk of recurrent stroke is as low as 1.2% per year. Randomized controlled trials (RCTs) have shown that percutaneous closure of the PFO in cryptogenic stroke can reduce the recurrence risk to 0.5% per year and thus provide a substantial benefit in the future. However, the RCTs have included only patients from 16 to 60 years of age. Therefore, many questions of management of patients with PFO remain unresolved to date. Should PFOs in patients older than 60 years or younger than 16 years be closed after cryptogenic stroke? Should PFOs in patients with cryptogenic stroke and many vascular risk factors be closed, or how to manage PFOs in patients with concurrent stroke etiology? Which PFO is pathogenic and which PFO is only an innocent bystander? Should PFOs that are identified incidentally in healthy persons be closed? These are some of the many questions that cannot be answered with the current evidence on PFO closure. The speakers of this debate will address many of those questions and hopefully shed some light on the controversy on PFO closure.

## From neurobiology to evidence-based medicine concepts in neurorehabilitation

**D.F. Muresanu**

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

Nowadays, it is still difficult to find the correct therapeutic approach for brain protection and recovery in stroke, especially because we do not fully understand all of the endogenous neurobiological processes, the complete nature of the pathophysiological mechanisms and the links between these two categories. Endogenous neurobiological processes, such as neurotrophicity, neuroprotection, neuroplasticity, and neurogenesis, are central to protection and recovery and represent the background of endogenous defense activity (EDA). Stroke pathological cascades contain a limited number of pathophysiological processes. It is characterized mainly by excitotoxicity, oxidative stress, inflammation, apoptotic-like processes and important metabolic disturbances. Pathophysiological processes share some common mechanisms with EDA (e.g. excitotoxicity and neurotrophicity together with neuroplasticity have, as a common important driver, the NMDAR activity; inflammation has an important contribution for neuroregeneration, stimulating neuroplasticity, via trophic factors). Postlesional brain regulation is currently better understood. Every lesion in the nervous system triggers in the first minute an endogenous neuroprotective reaction. An endogenous repair process, combining neuroplasticity and neurogenesis follow this as a second answer. All these processes are initiated and regulated by endogenous biological molecules. The biological reality of the nervous system is far more complex. In fact, there is an endogenous holistic process of neuroprotection and neurorecovery that should be approached therapeutically in an integrated way. The current tendency to exclusively frame drug activity in terms of single mechanisms and single focus effect might distract from other paradigms with greater explanatory power and hinder the development of more effective treatment strategies. A change of concept is required in pharmacological brain protection and recovery in stroke therapy. This presentation briefly reviews the current and future considerations in this therapeutic strategy,

including an integrated pharmacological approach, focusing on drugs with multimodal activity rather than single mechanism drugs, which usually are chemical drugs. In line with this strategy, the current presentation will also highlight the result of CARS Trial, one of the latest double-blind placebo randomized controlled trial in the field.

## Can diet prevent stroke? — No

**M. Niewada**

Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Poland

Diet is not a single dietary pattern, so it is difficult to establish what really works for stroke prevention — is it specific component or total food/caloric intake. Certainly, excess salt intake increases hypertension risk and consequently stroke risk, but so far many specific diet components were inconsistently reported in clinical studies on stroke risk. Relevant clinical data interpretation is challenging as it is not feasible to control for many cofounders, which can affect stroke outcomes much more than just diet. Consequently related epidemiological paradoxes were reported, i.e. obesity paradox which refers to the more favorable prognosis for obese stroke survivors. INTERSTROKE study showed the relation between diet and stroke risk but it was susceptible to biases and not causal, making the population attributable risk estimates uninterpretable. Moreover, diet was the only one risk factor reported conflicting impact on stroke risk for different regions. Randomized data on diet benefits are still limited. The largest PREDIMED trial is neither a pure test of a Mediterranean-style diet nor a pure test of extra-virgin olive oil and nuts and shares with Lyon Diet Heart Study the interpretation challenges. Generalizability of PREDIMED findings is limited as all the study participants lived in a Mediterranean country and were at high cardiovascular risk. Association between diet and stroke risk was substantially smaller in prospective PREDIMED study compared to INTERSTROKE. Individual impact of diet on stroke risk is therefore highly uncertain.

## What should be the optimal imaging to select patients for thrombectomy beyond 3 hours, is CTA enough or should CTP be added

**D. Ryglewicz**

1<sup>st</sup> Neurological Department, Institute of Psychiatry and Neurology, Poland

Recanalization of main stem cerebral arteries may lead to a good clinical outcome, but also may increase the risk of clinical deterioration. The time between stroke onset and artery reopening has been shown to be the most important determinant of hemorrhagic transformation. In the US according to the AHA and ASO recommendation therapeutic window for intravenous thrombolysis in severe stroke is 3 hours and in mild stroke 4.5 hours, in Europe (ESO recommendation) 4.5 hours. These recommendations were created on the basis of experimental studies and available statistical data of patients with good clinical outcome treated in the different time of stroke onset. These are statistical data, but in the real life, each patient is different. Size of ischemic brain tissue which may be salvage with reperfusion depends not only on stroke onset time. The efficiency of collateral circulation has a significant impact on the volume of infarct area. The DAMN study has shown that on the basis of neuroimaging examination we may prolong the time up to 24 hours. The mismatch between the severity of clinical deficit and the infarct volume seems to be a good indicator for thrombectomy above statistical 6 hours. Is CTA sufficient to evaluate the effects of cerebral circulation or should we additionally perform CTP according to DAMN study?

## What should be the optimal imaging to select patients for thrombectomy beyond 3 hours: Is CTA enough or should CTP be added?

**A. Shuaib**

Department of Medicine, Stroke Program, University of Alberta, Canada

Acute stroke care has improved significantly during the last decade. Advances in brain imaging allow for better patient selection for thrombolysis and thrombectomy and increasing number of patients are being successfully treated. In addition, imaging is helpful in detection of abnormalities that may increase the risk of complications, especially intracranial hemorrhage (ICH). Imaging is also very helpful in allowing for patient selection beyond the traditional 4.5 hours' time-window, especially where thrombectomy is being considered. Whereas there are several modalities of imaging available in the acute stroke settings, CT and CTA are sufficient for proper patient selection in decision making for thrombectomy. A plain scan with an ASPECTS score of 6 and good collaterals on CTA are allowed to proceed to thrombectomy in patients with MCA or T-occlusions. Most recent trials (with the exception of DAWN) where thrombectomy was compared to the standard of care (in treatment time windows of up to 12 hours) utilized CT and CTA as sufficient. My presentation will argue that CT and CTA are sufficient to make decisions regarding patient selection for thrombectomy beyond 3 hours from time of onset.

## Can diet prevent stroke?

**H. Sienkiewicz-Jarosz**

1<sup>st</sup> Department of Neurology, Institute of Psychiatry and Neurology, Poland

**Objectives:** The purpose of this presentation is to discuss the role of diet, especially Mediterranean diet and DASH (Dietary Approaches to Stop Hypertension) in primary and secondary stroke prevention.

**Material and methods:** The INTERSTROKE study showed, that diet may be one of ten most important modifiable risk factors for stroke, although there were some regional differences in the direction of the effect (South Asia vs all other regions) as well as in the effect size (younger vs. older stroke patients). Recent data has brought some evidence that Mediterranean diet may protect against cardiovascular disease and specifically stroke, decreasing 5-year stroke risk by approximately 30%. Similarly, DASH diet, which differs from the Mediterranean diet with the contribution of fat, low-fat dairy products, sweets, sugar-containing beverages and alcohol has been shown to be inversely correlated with ischemic stroke risk. There is insufficient evidence from RCTs for any effect of whole grain diets, low glycaemic index diets or high polyphenols intake on cardiovascular outcomes. The research on the dietary pattern after stroke on secondary stroke risk is limited.

**Conclusion:** There is still some controversy regarding the role of specific diets in secondary stroke prevention, stronger evidence exists for the role of diet in the primary prevention of cerebrovascular diseases. However, apart from pharmacological therapy, healthy diet, regular physical activity, and weight loss in overweight or obese patients may represent an interesting approach to stroke prevention with low risks and high potential benefits from a public health perspective.

## Is the identification of rare/short atrial fibrillation episodes sufficient to prescribe anticoagulants?

**A. Slowik**

Neurology, Jagiellonian University, Poland

Current treatment guidelines offer oral anticoagulant (OAC) to patients with atrial fibrillation (AF) taking into account risk of thromboembolic event (CHA<sub>2</sub>DS<sub>2</sub>-VASc) and risk of bleeding. These guidelines do not account for AF burden (pattern, frequency, duration), and do not indicate, if atrial high rate episodes (AHREs) (no symptomatic, 190 beats/minute, detected with long-term continuous monitoring by cardiac implantable electronic devices, CIEDs) including subclinical atrial fibrillation episodes (SCAF) warrant life-long OAC treatment. Increasing number of studies using CIEDs bring new data on AHRE natural history and the risk of thrombo-embolic events. The incidence of AHRE in patients without the history of AF is high (approximately 25% after 1 year and 35% after two years of follow-up). Interestingly, patients with short AHREs may develop longer AHREs or new clinical AF. AHREs also increase the annualized risk of stroke and thromboembolic events or silent ischemic brain lesions, however, lower, as compared to patients with clinical AF. Growing number of evidence indicate the correlation between AHRE duration and stroke risk. Interestingly, it is thought that AHRE may be a biomarker of embolic risk since there is lacking evidence of a temporal relationship between AHRE and stroke. All these data indicate that at least some of AHRE victims may benefit from OAC treatment taking into account stroke risk and AHRE burden; recent EHRA Consensus indicates OAC for patients with the threshold of 5.5 hours/day of SCAF burden and at least two CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factors. However, clinical trials addressing this question are ongoing (ARTESiA, NCT01938248; NOAH-AFNET6, NCT02618577).

## Should closure of PFO be recommended treatment and standard of care in patients with ESUS?

**J.D. Spence**

Stroke Prevention & Atherosclerosis Research Centre, Robarts Research Institute, Western University, Canada

Patent foramen ovale (PFO) is very common (~25% of the population), so among patients with stroke who have a PFO, ~80% of PFOs are incidental. Even among patients with cryptogenic stroke and a PFO, only ~half are causally related. This created a major problem for the clinical trials of PFO closure: if most patients with stroke and PFO have an incidental PFO, it is very difficult to show the benefit of closure. A paradoxical embolus is by definition a pulmonary embolus. This is why the studies have shown a greater benefit of PFO closure vs. antiplatelet agents, than vs. therapies that included anticoagulation. Clinical clues to paradoxical embolism include dyspnea or a Valsalva maneuver at the onset of stroke, waking up with stroke, a previous history of deep vein thrombosis, varicose veins, prolonged sitting (such as a long airplane ride), migraine, and sleep apnea. Among patients with paradoxical embolism, Transcranial Doppler (TCD) saline studies are more sensitive and predictive than trans-esophageal echocardiography. TEE missed 15% of right-left shunts seen on TCD, and of these 47% were large shunts. Patients with a larger right-left shunt on TCD were more likely to have recurrent TIA/stroke. Before embarking on PFO closure it is crucial to evaluate whether the PFO is incidental, or probably causal. A careful history and a TCD saline study will refine the decision for PFO closure. Patients with paradoxical embolism should probably be anticoagulated so closure (which requires antiplatelet agents) may increase the risk of pulmonary embolism.

## Can diet prevent stroke?

**J.D. Spence**

Stroke Prevention and Atherosclerosis Research Centre, Robarts Research Institute, Western University, Canada

There can be no doubt that the Cretan Mediterranean diet can prevent stroke. In the Seven Countries Study, it was discovered that the coronary risk in Crete was only one fifteenth what it was in Finland. In the Israeli diet study, the Mediterranean diet was better for diabetes and insulin resistance than a low-fat diet or a low-carbohydrate diet. In the Lyon Diet Heart Study, in secondary prevention, among patients with a prior coronary event, the Mediterranean diet reduced stroke by more than 60% in four years, compared to a “prudent Western diet” that approximated the low-fat diet then recommended. This was twice the effect of simvastatin in the contemporaneous 4S trial. In primary prevention, the Mediterranean diet was equally impressive. In the Spanish PREDIMED trial, in high-risk primary prevention, there was a significant reduction of cardiovascular events in both Mediterranean arms of the study (Mediterranean diet supplemented by mixed nuts, and Mediterranean diet supplemented by olive oil), compared with a low-fat diet. With the Mediterranean diet supplemented by nuts, there was a 47% reduction of stroke in five years. Besides cholesterol, red meat contains carnitine and egg yolk contains phosphatidylcholine, which result in formation of toxic trimethylamine n-oxide (TMAO). TMAO levels in the top quartile increased risk 2.5-fold in three years in patients referred for coronary angiography. Patients at risk of stroke should consume a Cretan Mediterranean diet, avoiding egg yolk and red meat. This dietary pattern definitely reduces the risk of stroke.

## Should secondary stroke prevention of vascular diseases include NOAC's in addition to aspirin? — No

**J. Streifler**

Former Head, Neurology Unit and stroke program, Rabin Medical Center, Petach Tikva, Israel  
Senior Lecturer, Sackler School of Medicine, Tel Aviv University, Israel

Antithrombotics (AT), in particular antiplatelet (AP) agents, are first line treatment in secondary stroke prevention. AP includes ASA, clopidogrel and dipyridamole (which can augment ASA effect with sustained release dipyridamole [Aggrenox]). The anticoagulant (AC) group includes warfarin and NOAC's. AP treatment prescribes first for more than 75% of patients, as it blocks the coagulation cascade initiated by endothelial injury in brain arteries affected by atherosclerosis processes. In cardio-embolic, venous thrombosis and coagulation abnormalities, AC's are more effective — therefore used as first line. Arterial disease warfarin was inferior to ASA, with more bleedings, not recommended as an alternative. The NOAC group has lower bleeding rates. The addition of low dose Rivaroxaban (5 mg/day) to 100 mg ASA in patients with stable (atherosclerotic) cardiovascular disease (CVD) was more effective in the composite outcome than ASA alone, associated with higher bleeding rates. Rivaroxaban alone was not superior to ASA alone and with similar higher bleeding risk. Triple AT combination in AF patients, who need coronary artery stent insertion is a matter of debate; attempts to reduce a duration or to convert to dual therapy are ongoing, in part successful. Thus, even with NOAC's bleeding rates raise concern and its addition to AP remains problematic. Adopting this strategy for stroke patients may be hazardous at present. Another approach was to compare NOAC to ASA for patients with cryptogenic strokes, yet only for those with the embolic type. These strokes are called “embolic stroke of unknown source” (ESUS). However, one of the 2 studies, still recruiting, was prematurely stopped for futility.

## Does carotid stenosis cause cognitive decline — No

**J. Streifler**

Former Head, Neurology Unit and stroke program, Rabin Medical Center, Petach Tikva, Israel  
Senior Lecturer, Sackler School of Medicine, Tel Aviv University, Israel

Asymptomatic significant ( $\geq 50\%$ ) carotid stenosis (ASCS) is frequently found in elderly, mainly in patients with several vascular risk factors. Its most feared complication is stroke. The same risk factors are associated with the increased risk for cognitive decline (CD). Associated brain imaging pathology manifestations are “small vessel type”, including leucoaraiosis, microbleeds, and lacunar infarctions (often “silent”). Overt strokes are also important contributors to CD. Thus, is there an association between ASCS and CD? Yes! The natural history of ASCS is, however, quite benign. Studies, done with “best medical treatment” (BMT, including statins), show an annual stroke risk of  $< 1\%$ . This is why carotid endarterectomy (CEA), done for stroke risk reduction in ASCS patients, is still under investigation. Studies done before current BMT was introduced show only modest benefit ( $\sim 1\%$  annual risk reduction). Advocating surgery for such patients would mean screening for ASCS (and operating all appropriate candidates). The US task force, however, is advising against such screening. The association between ASCS and CD, its significance and possible treatment approaches, is supposedly more complicated.

## Development of preclinical diagnostics of neurodegenerative diseases — illusions or reality?

**M. Ugrumov**

Lab of Neural and Neuroendocrine Regulations, Institute of Developmental Biology RAS, Russia

Numerous attempts to develop a preclinical diagnosis of neurodegenerative diseases (NDD) — Parkinson’s and Alzheimer’s disease, by searching peripheral biomarkers as changes in biological fluids and non-motor functions were not successful. A drawback of this methodology is the search for markers in patients at clinical stage without guarantees that they are characteristic for preclinical stage. Indeed, all markers detected so far are nonspecific. We propose to upgrade this methodology, using only markers found both in patients and animals at modeling clinical and preclinical stages of NDD. Detection of the same marker in patients and symptomatic animals is believed to indicate adequate reproduction of pathogenesis along this metabolic pathway, and detection of this marker in presymptomatic animals proves its specificity for preclinical stage. We showed that 50% and 20% of the markers found in blood of patients were characteristic of MPTP-treated symptomatic and presymptomatic mice, respectively. Besides, we propose a different approach to early diagnosis of NDD — a provocative test that has long been successfully used in internal medicine. We showed that the systemic administration of  $\alpha$ -methyl-p-tyrosine, a reversible inhibitor of dopamine synthesis (provocative agent), to MPTP-treated mice at presymptomatic stage results in a reversible decrease in dopamine level in the striatum up to the threshold (30%) and short-term motor disorders. In controls, although the dopamine level decreases under  $\alpha$ -methyl-p-tyrosine administration, it does not reach the threshold level and is not accompanied by motor disorders. Thus, we proposed a new complex methodology for the development of preclinical diagnosis of NDD.

# Wilson's disease

## Wilson's disease epidemiology

**O. Bandmann**

Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, UK

There is ongoing uncertainty about the incidence and prevalence of Wilson's disease (WD). Scheinberg and Sternlieb first estimated the prevalence of five WD to be five per million. Subsequently, a prevalence figure of 30 per million with a heterozygote carrier frequency of one in 90 was frequently quoted. However, considerably higher incidence and prevalence figures have been reported for population isolates, the highest being 885 per million, from within the mountainous region of Rucar in Romania. Different strategies including both biochemical and genetic screening have been used to establish the frequency of WD in the general population. A large number of different ATP7B mutations can cause WD, but studies can be further confounded by the uncertain relevance of some sequence variants with unproven pathogenicity. We undertook the largest genetic prevalence study on WD in the UK. The entire ATP7B coding region was sequenced in 1000 control samples from a perinatal blood spot screen. In addition, three mutation hot spots (exon 8, 14 and 18) were sequenced in 5000 controls. Using very strict criteria to assess the pathogenicity of the detected sequence variants, we calculated a revised figure of 0.040 or 1:25 of heterozygote mutation carriers in the UK. The resulting predicted frequency of individuals carrying two pathogenic ATP7B mutations was 142 per million, more than four times the often quoted prevalence figure of 30 per million. Future studies need to determine whether this apparent high genetic prevalence can be validated in other cohorts.

## Kinnier Wilson and Wilson's disease

**E. Broussolle**

Department of Neurology C, Université de Lyon and Institut des Sciences Cognitives Marc Jeannerod UMR 5229 and Hôpital Neurologique Pierre Wertheimer, France

British physician, Samuel Alexander Kinnier Wilson (1878–1937) was one of the world's greatest neurologists of the first half of the 20<sup>th</sup> century. Early in his career, Wilson spent one year in Paris in 1903 where he learned from Pierre-Marie. He subsequently retained uninterrupted links with French neurology. He also visited in Leipzig German anatomist, Paul Flechsig. In 1904, Wilson returned to London, where he worked for the rest of his life at the National Hospital for the Paralysed and Epileptic (today the National Hospital for Neurology and Neurosurgery) in Queen Square, and also at Kings' College Hospital. He wrote on "the old motor system and the new", on disorders of motility and muscle tone, on the epilepsies, on aphasia, apraxia, tics, and pathologic laughing and crying. Wilson's most important contribution was his publication in 1912 in *Brain* of a newly recognised illness he called "Progressive lenticular degeneration, a familial nervous disease associated with liver cirrhosis", which was later named hepatolenticular degeneration or Wilson's disease. Wilson analysed 12 clinical cases, four of whom he followed himself, but also four cases previously published by others and a further two that he considered in retrospect had the same disease as he was describing. The pathological profile combined necrotic damage in the lenticular nuclei of the brain and hepatic cirrhosis. When describing these patients, Wilson introduced for the first time the terms extrapyramidal syndrome and extrapyramidal system, stressing the role of the basal ganglia in motility.

## Introduction — the importance of proper management of Wilson's disease

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Wilson's disease (WD) is an exceptionally rare genetic disorder. Patients with WD, when treated properly, have a similar life expectancy as healthy people. However, when no treatment is given, the disease progresses and can lead to death in several years, usually due to liver failure or neurological impairment causing immobility and then medical complications. Although diagnostic methods are now widely available, it usually takes several years since the onset of symptoms to diagnose WD. Because the symptoms of WD are diverse, the diagnosis must be supported by laboratory studies, such as copper metabolism (ceruloplasmin, urinary copper excretion) and genetic analysis. Moreover, liver biopsy, imaging of the liver and brain, and incorporation of radioactive copper are helpful. A complete workup for WD should be offered to all siblings of patients with WD, including those without symptoms, and to other family members, regardless of their age, who have hepatic, neurologic, or psychiatric symptoms. In WD, prognosis depends largely on the patient's clinical state at diagnosis and on the patient's compliance. Although current pharmacological treatments for WD are lifelong, up to a half of patients stop taking medications, reduce their doses, or take medications irregularly. Diagnosis of WD is difficult, and patients treated for WD need a lifelong follow-up and require multidisciplinary care (hepatologist, neurologist, and psychiatrist). Thus, each country should have a WD centre with physicians experienced in WD care. Patient support groups are also important in the management of WD.

## Wilson's disease — neurological presentation

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Neurological presentation of Wilson's disease (WD) is common, and it affects approximately 50% of patients. Neurological symptoms occur later compared to hepatic manifestations, typically in the 3<sup>rd</sup> or 4<sup>th</sup> decade. Most common symptoms include various combinations of movement disorders, namely tremor, dystonia, Parkinsonism, and chorea associated with dysarthria, dysphagia, and drooling. Damage to the central nervous system in WD is caused by the toxic effect of accumulated copper. It can be visualised as atrophy and increased signal of affected regions on T2 weighted magnetic resonance images. T2 hyperintensities may reflect tissue oedema, demyelination, gliosis and rarefaction, whereby the latter 2 abnormalities are irreversible. The best treatment for neurologic symptoms is prevention; they do not occur when adequate lifelong anti-copper treatment is initiated in the asymptomatic or hepatic stage of the disease. Currently, there is no consensus about the optimal treatment of the neurologic manifestation and different WD centers favour Zinc, chelating agent, or combination of both. Neurological deterioration, sometimes irreversible, that is observed after the initiation of the treatment in 20–50% patients remains the most arduous problem in the WD treatment.

## Clinical manifestations of Wilson's disease — other organs

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Wilson's disease (WD) presents mainly with hepatic and neuropsychiatric features. However, copper accumulates not only in the liver and brain, but also in other organs. The clinical manifestation of WD involves ophthalmological, renal, cardiac, skin, osteoarticular, or endocrinological disturbances. The

most typical ophthalmological sign is Kayser-Fleischer ring as a result of copper accumulation in the cornea. Sunflower cataract is rare, but also characteristic sign. Degeneration of the retina observed in WD patients as a marker of neurodegeneration correlates with the degree of impairment of the nervous system. Cardiac injury may include arrhythmia, cardiomyopathy, and autonomic dysfunction. Electrographic abnormalities detected in WD patients include left ventricular atrophy, biventricular hypertrophy and early depolarisation. In most patients cardiac disturbances are mild. Renal abnormalities include tubular dysfunction and nephrolithiasis. Bone demineralisation is a common manifestation in patients with WD. Endocrine system manifestations, such as infertility or repeated miscarriages, growth and puberty disturbances, hypothyroidism, and hypoparathyroidism, are also observed. Although the increased risk of spontaneous abortion in well treated WD patients, it is possible to become pregnant. Other clinical aspects of WD include pancreas involvement, immunological disturbances, presence of lipomas, and skin changes. Awareness of other possible WD manifestations is important in the differential diagnosis of WD.

## **New Wilson's like disease: a treatable metabolic manganese disorder causing Parkinsonism and dystonia**

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A new metabolic genetic condition related to manganese accumulation into the brain and particularly into basal ganglia has been described some years ago and was characterised mainly in early infantile and child age by dystonia and in adult by dystonia parkinsonian syndromes. This condition was due to genetic mutation in a manganese transport protein able to transfer manganese from tissue outside the cells and eliminates through urines. Metal accumulation is evident by MRI showing metal deposits mainly in basal ganglia. We described our experience on this syndrome, describing the clinical phenotype in childhood and adulthood, the MRI abnormalities and the effect of chelating treatment by EDTA on manganese level and on the clinical symptoms. Some experimental data will be also reported investigating the *in vitro* apoptotic process in cultured fibroblast, showing that this process is abnormally regulated in the patients samples if related to normal subjects.

## **Wilson's disease: current anti-copper therapy is sufficient**

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Wilson's disease (WD) is one of the few genetic, neurodegenerative disorders which could be successfully treated with pharmacological treatment, if early diagnosed and correctly treated. Currently few groups of drugs are used in WD treatment: 1) chelators (D-penicillamine and trientine), which produce increase copper urinary excretion; and 2) zinc salts which inhibit the copper absorption from digestive tract. Both kinds of treatment lead to negative copper body balance, what stop the tissue copper pathological accumulation in the course of disease, as well as clear affected organs from copper overloading. Additionally, in case of acute liver failure or progressive liver disease without effect of pharmacological anti-copper treatment, liver transplantation is established as definitive treatment of WD. Historically, non-treated WD led definitively to death due to hepatic or neurological complications. Since the currently available WD treatment was discovered and the progress in WD diagnosis, including DNA testing and diagnosis algorithms appeared, the prognosis for WD patients remarkably improved. Actually, it seems that, beside the different expert opinion about pharmacological agents used in WD treatment, the early WD diagnosis, as well as correct and long-life treatment of WD, are the key factors of WD treatment success.

## Role of botulotoxin type a in the complex treatment of the hypokinesia in patients with Wilson's disease

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**Introduction:** Hypokinesia is common extrapyramidal sign in patients with Wilson's disease; it leads to significant disturbances of life quality and reduces independence of personal living skills.

**Aim:** To evaluate effectiveness of Botulotoxinum in complex treatment of rigidity and extrapyramidal signs in female patient with trembling and rigidity symptoms.

**Material and methods:** Female patient (onset of disease — 8 years). She was on permanent complete bed rest due to severe hypokinesia and rigidity; no voluntary movements were possible; severe joint contractures; permanent hyperkinetic disorders and severe pseudobulbar syndrome were described. The patient was on constant therapy (dopaminergic, neurotrophic, copper eliminating agents).

**Results:** Due to non-sufficient results of constant base line therapy, Botulotoxinum (Dysport<sup>®</sup>, Bofur Ipsen, 1000 U) was added. Positive result was observed starting from the 14th day. It has been resulted in the appearance of voluntary movements in upper and lower limbs, increase of movements, and decrease of hyperkinesia and pain syndrome. Evaluating of injected muscles showed significant decrease of muscle hypertonia during one month (from grade 4 to 2 Ashworth scale). After 1,5 month after the injection the patient managed to eat by herself; after three months managed to change position from bed to wheelchair without assistance.

**Conclusions:** Complex therapy of severe Wilson's disease using Botulotoxinum was recognised as effective.

## Wilson's disease: pathogenesis, genetic and epigenetic factors

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Wilson's disease is an autosomal recessive genetic disease caused by mutations affecting the *ATP7B* gene with consequent accumulation of copper in the liver and in the brain. *ATP7B* transporter is involved with both copper biliary excretion and trafficking within the hepatocytes. Missense and nonsense mutations are the most frequent and, in general, absence of *ATP7B* activity has been correlated with earlier and more severe clinical presentation. The most common mutation in patients of European descent is the missense H1069Q, possibly associated with neurological presentation according to some studies. However, studies attempting to link phenotype and genotype in Wilson's disease have not shown convincing results. This could be related to the high prevalence of compound heterozygotes, but other genes may be contributing to the pathogenesis and disease severity. Environmental and nutrition factors could affect the phenotype of Wilson's disease. In particular, animal models have shown a possible involvement of epigenetic mechanisms of gene expression regulation in the disease onset and progression. Copper accumulation is associated with inhibition of the expression and activity of the enzyme S-adenosylhomocysteine hydrolase (SAHH), which is the bi-directional enzyme responsible for the synthesis of homocysteine. When SAHH is inhibited, the resulting accumulation of its substrates, SAH, is associated with inhibition of DNA methylation reactions with consequent effects on methylation status. In conclusion, Wilson's disease is a complex disease with challenging pathogenic mechanisms that most likely involve the interaction between genetic, metabolic, and environmental factors.

## Acquired copper deficiency in ten patients with and without Wilson's disease

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**Introduction:** Acquired copper deficiency (ACD) is a rare condition, usually diagnosed from haematological changes.

**Objectives:** Characterise the diagnosis features and evolution of patients with ACD.

**Material and methods:** Clinical, biological and MRI data were analysed at diagnosis and during follow-up.

**Results:** 10 patients with ACD were studied: three with Wilson's disease (WD-CD) and seven without WD (CD). Mean time to diagnosis was twice longer in WD-CD than in CD patients. Only 1 patient with WD-CD was diagnosed on pancytopenia, all other patients had a progressive posterior cord syndrome associated with anaemia and lymphopenia. Electrodiagnostic tests diagnosed a lower limbs sensory neuropathy in six patients. Spinal cord MRI was normal in 3/7 CD patients and in all WD-CD patients. Serum copper, exchangeable copper and urinary copper excretion were low. All WD-CD patients had an iron deficiency associated. A decrease copper intake after bariatric or other digestive surgeries and a chronic use of denture adhesive paste containing zinc were the aetiologies of CD patients. All WD-CD patients were on zinc salts. CD patients received copper supplementation, while doses of zinc salts were reduced by two third or stopped in WD-CD patients. Evolution was different between the 2 groups of patients. Haematological disturbances resolved gradually in two months in CD patients, while it took 15 months in WD-CD. Neurological symptoms improved in 7/9 patients after a mean follow-up of two years.

**Conclusions:** Anaemia and lymphopenia associated or not to a posterior cord syndrome must raise the possibility of an ACD, even in WD patients.

## Is liver transplantation a reasonable alternative in neurologic Wilson's disease patients resistant to chelators? Lessons from the French experience in 18 cases

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The discovery of chelators and zinc for Wilson's disease (WD) turned a life-threatening illness into a chronic disease. Despite this substantial progress, few patients with severe neurologic presentation are from the onset resistant to classical chelation and develop severe handicap or die. Liver transplantation (LT) improves survival in case of hepatic failure, but its indication in severe neurological forms without liver failure is controversial. To evaluate the effect of LT in patients with severe neurological worsening resistant to active chelation, we studied French WD patients who underwent a LT for pure neurological indication between 1994 and 2016. Neurologic impairment with Unified WD Rating Score (UWDRS) and modified Rankin score (mRS) were assessed before LT and at the last follow-up. The primary outcomes were the survival rate and disability at last follow-up. Prognosis factors were further assessed. Eighteen patients had LT. They were highly dependent before LT (mRS 5 in 16/18 patients). Neurological symptoms were severe (mean UWDRS  $101.3 \pm 22.1$ ), with dystonia and Parkinsonism. The cumulated survival rate was respectively 88.8%, 82.5%, 72.2% at 1, 3 and 5 years. At last follow-up, 14 patients were alive. Their mean mRS and UWDRS were significantly lower ( $p = 0.0001$  and

$p = 0.0003$ ) compared to the pre-LT state. Severe sepsis ( $p = 0.011$ ) and ICU admission ( $p = 0.001$ ) in the month before LT were significantly associated with death. LT is a therapeutic option, that should be proposed in selected neurologic WD patients resistant to decoppering therapies, as it allows them to gain physical independency with a reasonable risk.

## Brain atrophy and neurological impairment in Wilson's disease

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**Objectives:** To determine whether brain volume was associated with neurological and functional impairments and with copper overload markers in patients with Wilson's disease.

**Material and methods:** In 48 treatment-naïve patients, we assessed neurological and functional impairments, with the Unified Wilson's Disease Rating Scale; measured normalised brain volumes, based on magnetic resonance images and assessed copper overload indices, i.e., the concentration of non-ceruloplasmin-bound copper and the presence of corneal copper deposits. We correlated brain volume measures with neurological and functional impairment scores and copper overload indices.

**Results:** Neurological and functional impairments correlated with all brain volume measures, including the total brain volume and the volumes of white matter and grey matter (both peripheral grey matter and deep brain nuclei). Moreover, higher non-ceruloplasmin-bound copper concentrations were associated with lower brain volumes, and patients with corneal copper deposits had significantly lower brain volumes than patients without these deposits.

**Conclusions:** Our findings provided the first *in vivo* evidence that the severity of brain atrophy is a correlate of neurological and functional impairments in patients with Wilson's disease and that brain volume could serve as a marker of copper toxicity.

## Wilson's disease — liver presentation

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There are 2 major clinical presentations of Wilson's disease — liver and neurological (rare in children). Liver symptoms may vary in severity — from asymptomatic forms, to cirrhosis and acute liver failure. There are adult guidelines and recently elaborated paediatric position paper on diagnosis and therapy of Wilson's disease. Diagnostic criteria for adult, paediatric, neurological and liver presentations are similar and use the same scoring system, which is a combination of different clinical symptoms and laboratory tests (ceruloplasmin concentration, 24-hour urinary copper excretion, copper content in the liver and molecular analysis). WD should be considered in the differential diagnosis of children already above the age of 1 year, presenting with any sign of liver disease ranging from asymptotically increased serum transaminases to cirrhosis with hepatosplenomegaly and ascites or acute liver failure. Biochemical tests may be less sensitive in very young children. Pharmacological therapy is mainly based on chelating agents, like penicillamine and trientine and zinc preparations. It was proven to be very effective, but the major problem on long term is poor compliance. Chelating agents should be preferably used in patients with signs of significant liver disease, such as cirrhosis or abnormal INR. Zinc salts could be used in pre-symptomatic children identified through family screening, or as maintenance therapy after de-coppering with chelators, as long as serum transaminase levels remain normal. Liver transplantation is indicated only in selected cases, mainly with acute liver failure and medical decision can be based on a special prognostic scoring system.

## Transcranial brain parenchyma sonography in Wilson's disease and healthy controls: quantification and correlations with clinical parameters

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Transcranial sonography (TCS) allows easy access, rapid, low-cost, and radiation free imaging of brain parenchyma. In Wilson's disease (WD), TCS has shown an even higher sensitivity than conventional MRI. We compared TCS findings in patients with predominantly neurological, treated Wilson's disease ( $n = 40 / m = 22$ ) and healthy, matched controls ( $n = 49 / m = 29$ ) and correlated TCS findings with clinical data, including: serum copper and iron parameters, Unified Wilson's Disease Rating Scale (UWDRS), Addenbrooke's Cognitive Examination-Revised, Mini Mental State Examination, and Beck Depression Inventory (BDI). Highly significant differences between patients and controls were found for the hyperechogenicity of lenticular nucleus, substantia nigra, thalamus, and midbrain tegmentum/tectum, and for the values of the midbrain axial area and of the third ventricle width. The echogenic area sizes of lenticular nucleus, substantia nigra, and caudate nucleus allowed highly accurate discrimination between patients and controls (areas under the curve 95.4%, 79.4%, and 80.5%, respectively). In WD, both dystonia and dysarthria correlated with the hyperechogenicity of lenticular nucleus, the midbrain axial area, and the third ventricle width. Parkinsonism, UWDRS total and neurological scores, and reduced cognitive performance correlated with an increased third ventricle width. Symptoms of depressed mood (BDI15) correlated with a reduced midbrain axial section area. Male sex correlated with substantia nigra echogenic area and serum ferritin levels. TCS hyperechogenicity can clearly differentiate treated WD patients with neurological manifestations from healthy subjects. Particular TCS findings correlate with various dimensions of WD symptoms. The discriminative capacity of TCS in detecting brain involvement should be further tested in early-stage WD cohorts.

## China's experience on treatments of Wilson's disease

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Wilson's disease (WD), also named hepatolenticular degeneration, is an autosomal recessive genetic disorder caused by defects of ATP7B gene. This disease occurs sporadically all over the world. It is found in individuals aged 3–80 years, but mainly in children and adolescents. Clinical presentations of WD are highly varied, mainly consisting of hepatic and neurological symptoms. Hepatic symptoms include acute and chronic liver diseases, such as fulminant hepatic failure (also named as abdominal Wilsonian disease) and liver cirrhosis. Neurological symptoms mainly include extrapyramidal symptoms and neuropsychiatric symptoms. The extrapyramidal symptoms are dystonia and tremor. Once diagnosed with WD, the patient should have a low-copper diet and receive anticopper treatment for the rest of their life. The medicines for WD patients are d-penicillamine, sodium dimercaptosuccinate, dimercaptosuccinic acid, trientine, zinc preparation, tetrathiomolybdate, etc. Traditional Chinese medicine has also shown to be associated with significant positive outcomes in the treatment of WD. WD patients treated with an anti-hepatolenticular degeneration decoction exhibited increased copper excretion. Positive treatment effects (80–90%) can greatly improve the quality of life. Unfortunately, diagnosis of this disease is usually difficult. However, thinking of it and finding it out. Over some decades, an increasing number of clinical studies have used molecular genetics techniques as the clinical diagnosis index, leading to increased accuracy in diagnosis. About 24 000 of WD in-patients in China have been studied at a few of University hospitals from Hefei to Shanghai.

## Determination of copper poisoning in Wilson's disease and other metal dysbalances using laser ablation inductively coupled plasma spectrometry (LA-ICP-MS)

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Wilson's disease (WD) is an autosomal recessive disorder occurring in about one in 30,000 people due to mutations in the Wilson's disease (*ATP7B*) gene. Affected persons build up extensive copper accumulates in the body. The main accumulation and storage sites of copper are liver and brain. We have previously introduced novel LA-ICP-MS techniques for quantitative imaging of various metals in tissue obtained from experimental WD models or clinical samples from WD patients (Boaru et al., J Cell Mol Med 2015; 19: 806–814; Weiskirchen and Uerlings, Cell Mol Med: OA 2015; 1: 3). These innovative metal imaging techniques have extended the repertoire of analytical possibilities in WD diagnosis. Here we have optimised and extended these studies and showed that the accumulation of copper in the brain of *ATP7B* null mice is majorly found in special regions, while hepatic copper is distributed uniformly within the liver. Gene therapy in *ATP7B* null mice with an AAV8 vector expressing a codon-optimised version of the *Atp7B* gene directed under control of the  $\alpha 1$  antitrypsin promoter resulted in a massive reduction of hepatic and cerebral copper as assessed by LA-ICP-MS (Moreno et al., J Hepatol, in press; Uerlings et al., submitted). These data highlight the fact that LA-ICP-MS technology is one of the most powerful and sensitive techniques allowing simultaneous imaging and quantification of various trace metals with good sensitivity in experimental WD models. The applicability of the LA-ICP-MS technology in the diagnosis of WD, other metal-associated disorders, or potential future applications in experimental research and clinical daily routine will be discussed.

## Wilson's disease treatment — we need more options

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Wilson's disease is a rare genetic disorder of impaired copper transport and excretion, caused by loss of function of the *ATP7B* copper-transporter. Wilson's disease is clinically primarily characterised by varying degrees of liver, neurological and psychiatric manifestations related to damage toxicity of excess copper causes to the liver and brain. Treatment of Wilson's disease remains largely unchanged since the introduction of chelators and zinc. With the current standard treatments, improving symptoms can take several years and patients with neurological symptoms show a poorer response to therapy than hepatic patients. Thus considerable unmet medical needs still exist, what will be discussed in the presentation. These unmet needs include more effective copper control, improving symptoms and associated disabilities, reducing the risk of neurological worsening after the treatment initiation and simplification of dosing regimen for improved compliance.

# **E-POSTER ABSTRACTS**

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# Alzheimer's disease and dementia

## Comorbidity variations of depression and dementia in the elderly

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**Material and methods:** Cornell Dementia Depression Scale (CSDD), Mini Mental State Examination (MMSE) and clock drawing test.

**Results:** 231 patients aged 70 years and older with cognitive impairment of varying degrees were examined. The results of the study revealed the presence of moderate cognitive impairment syndrome in 118 patients, unequivocally proven dementia symptoms in 113. Depressive disorders have been detected in 88 patients. Depending on the psychopathological structure of the depression syndrome, five major clinical types were identified: anxiety, hypochondria, apathy, drowsiness and psychotic depression with delirium. In analysing the possible pathogenetic mechanisms of the development of depressive disorders in Alzheimer's disease, three variants of their formation were identified: depression caused primarily by reactive and situational mechanisms (38.5%), arising spontaneously, i.e. regardless of the connection with psycho-traumatic factors (27.7%), and the intermediate between these two variants of depressive disorders (33.8%), in which, along with the reactive-situational content of emotions, there was often a pronounced affection of anxiety or anxiety, the primary sense of guilt, characteristic circadian rhythm with attenuation of depression symptoms closer to evening, ideator and motor retardation.

**Conclusions:** A clinical picture of depression in Alzheimer's disease or vascular dementia can occur with atypical manifestations, and a number of symptoms of dementia can be mistakenly classified as a manifestation of depressive disorder. In a number of cases, patients with initial manifestations of dementia can establish the psychogenic (nosogenic) nature of depression. In the vast majority of cases, the biological pathogenetic relationships of Alzheimer's disease and depression are suspected.

## Progressive non fluent aphasia: two different clinical cases

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**Introduction:** Progressive non fluent aphasia (PNFA) is a common variant of Frontotemporal Dementia (FTD). It is well known the overlap of FTD symptoms and Motor Neuron Disease (MND) or Parkinsonism. We present two clinical cases with symptoms of PNFA, with more progressive clinical deterioration, associated to MND and Parkinsonism.

**Material and methods:** Case 1: A 64-year-old male, presented with a two years history of PNFA with lately gait disturbances, difficulty in swallowing and pseudo-bulbar affect. The patient had a family history of an autosomal dominant (AD) pattern. A physical exam revealed pyramidal signs, as well as fasciculations and atrophy in limb muscles and low score MMSE and MOCA. EMG confirmed the diagnosis of MND. Brain MRI showed atrophy of bilateral frontal and temporal lobes. Diagnosis: FTD-MND. He passed away six months after. Case 2: A 61-year-old male, with 18 months history of PNFA with lately difficulty in managing the left hand and slow movements. Positive family history of AD inheritance. Bilateral rigidity and apraxia, bradykinesia, more prominent on the left arm, low score MMSE and MOCA, signs of depression. No signs of autonomic dysfunction. Normal EMG. Brain MRI revealed brain atrophy, prominently on the frontotemporal areas. Non responsive to L-Dopa. Diagnosis: FTD and Cortico Basal Degeneration.

**Conclusions:** The overlap of MND symptoms and Parkinsonism in FTD can lead to a more rapid clinical deterioration and a poor outcome, compared to other FTD variants. Genetic tests, neuroimaging and neuropathology may bring further insights in understanding these complex pathologies.

## A protein-protein interaction connecting neuroinflammation and neurodegeneration in Alzheimer's disease

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Neuroinflammation is associated with Alzheimer's disease (AD) and it is considered a secondary response to amyloid-beta ( $A\beta$ ) deposition and neuronal cell death. The neuroinflammatory response is driven by interferon-gamma ( $IFN\gamma$ )-mediated microglia activation, but how neuroinflammation and neurodegeneration are connected is unclear and is a subject of this study. We show that  $IFN\gamma$  can interact with  $A\beta$  and modulates its aggregation behaviour by using biophysical techniques. Moreover, the exposure of microglia to the formed  $IFN\gamma$ - $A\beta$  complex resulted in an enhanced pro-inflammatory response compared to the individual interaction partners. We suggest that the interaction between  $A\beta$  and  $IFN\gamma$  may explain the observed connection between neurodegeneration and neuroinflammation in AD.

## Eye gaze and aging: the role of working memory and inhibitory control

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Eye-tracking is increasingly used to study cognitive and biological markers for the early signs of neuropsychological and psychiatric disorders. However, in order to make further progress in our understanding of these early indicators, a more comprehensive understanding of the neurotypical age-related effects on eye-tracking is essential. Speculation on the cause of the observed age-related differences in the antisaccade task largely centres around 2 sources of cognitive dysfunction: inhibitory control and working memory. The inhibitory control account views cognitive slowing and task errors as a direct result of the declining of inhibitory cognitive mechanisms. An alternative theory considers that a deterioration of working memory is the cause of these age-related effects on behaviour. The current study assessed inhibitory control and working memory processes underpinning saccadic eye movements in young and older participants. This was achieved with three experimental conditions that systematically varied the extent to which working memory and inhibitory control are taxed in the antisaccade task; a memory-guided task was used to explore the effect of increasing working memory load; a Go/No-go task was used to explore the effect of increasing inhibitory load; a "standard" antisaccade task retained the standard working memory and inhibitory loads. The results revealed that neurotypical ageing is associated with changes in both inhibitory control and working memory. Increasing the inhibitory load was associated with increased reaction times in the older group, whilst the increased working memory load and the inhibitory load contributed to an increase in the anti-saccade errors.

## Is dementia a psychiatric or neurological disease? Different angles of the same illness — a psychiatrist's view

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**Introduction:** Dementias are illnesses with well-known neuropathology, but it is not only “an illness”, it is a change in one's experience of surroundings, processing of information, understanding and comprehending of feelings and emotions. Neurology and psychiatry offer different angles of understanding patients suffering from dementia.

**Material and methods:** The author, based on personal experience, discusses different angles of medical understanding of dementia and consequent differences in therapeutic approaches. In the context of the long historical relationship between neurology and psychiatry, the increased awareness of the complexity of the nervous system, the rapid emergence and advancements of neuroscience over last 2 decades, the author analyses what makes dementia a psychiatric or a neurological disorder and how both neurology and psychiatry can collaborate to improve the outcomes of treatment in major neurocognitive disturbances.

**Conclusions:** The author concludes that psychiatry offers unique opportunity to integrate patients' experiences into evidence-based physical medicine. By unique focus on human emotions and behaviour in health and disease, acknowledging the overlap between neuronal disturbances and psychological distress, psychiatry offers the enhancing of well-being and treatment beyond the use of pharmacological drugs.

## Bexarotene and astaxanthin modulate cholesterol and amyloid-beta metabolism in cerebrovascular endothelial cells

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**Introduction:** This study investigated the effects of a pharmacologic retinoid-X receptor (RXR) agonist, bexarotene, and a PPAR- $\alpha$  agonist and strong antioxidant, astaxanthin, on pathways of cellular cholesterol metabolism, APP processing, A $\beta$  production and transfer at the BBB.

**Material and methods:** Primary, porcine brain capillary endothelial cells (pBCEC) were incubated with Bex ( $\leq 100$  nM) or Asx ( $\leq 10$  nM) for 24 hours. *ApoA-I*, *ABCA1*, *LRP1*, and *BACE1* mRNA expression and ABCA1, apoA-I, and A $\beta$  oligomer protein levels were determined by RTQ-PCR and immunoblotting. *In vivo* effects on cerebrovascular endothelial cells were investigated using 3xTg AD and non-TG mice gavaged with 100 mg/kg Bex, 80 mg/kg Asx, or vehicle control (7 d).

**Results:** Cerebromicrovascular endothelial cells isolated from 3xTg AD mice treated with Bex, revealed elevated mRNA expression of apoE, ABCA1, and LRP1, whereas Asx treatment resulted in increased LRP1 mRNA expression. Both, Bex and Asx reduced BACE1 mRNA expression as compared to cells isolated from untreated and from non-Tg treated animals. Bex or Asx treatments dramatically reduced levels of soluble A $\beta$  oligomers in brain and mBCEC of 3xTg AD mice. Bex treatment of mice further revealed up-regulated ABCA1, apoE and LRP1, as well as down-regulated BACE1 mRNA expression detected in brain homogenates.

**Conclusions:** Our results strongly suggest that these two different nuclear receptor agonists exert beneficial effects on cholesterol and A $\beta$  metabolism in cerebrovascular endothelial cells.

## Stopping statins in the oldest old with dementia and severe dependency

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**Objectives:** To study the association between stopping statins and mortality rates during the following year in the oldest old — many of whom with dementia and severely dependent.

**Material and methods:** A historical prospective study. Included were all patients (n = 369) aged 80 years old or more (mean age 87.8 years), hospitalised in a single acute geriatrics department during one year. The study group included 140 patients in whom statins were stopped upon admission due to lack of indication, polypharmacy, malnutrition, etc. The control group included 229 patients who did not use statins in the first place. All-cause 1-year mortality rates were studied.

**Results:** Compared with the control group, patients in the study group were younger (87.1 vs 88.2 years,  $p = 0.044$ ), had higher prevalence of ischaemic heart disease (46.4 vs 18.8%,  $p0.001$ ), lower prevalence of pressure ulcers (0.7 vs 4.8%,  $p = 0.035$ ), less nursing-home residency rates (5.7 vs 19.7%,  $p0.001$ ), and lower incidence of hypoalbuminaemia (36.0 vs 57.8,  $p0.001$ ). Both groups had high, but comparable prevalence of dementia (42.1 vs 51.5%,  $p0.05$ ) and severe dependency (52.1 vs 60.7%,  $p0.05$ ). Still, there were no differences between the groups in terms of 1-year mortality rates in the crude analysis (31.4 vs 27.1%, HR 0.87,  $p = 0.438$ ), as well as following propensity score matching (27.7 vs 25.9%, HR 0.89,  $p = 0.680$ ).

**Conclusions:** Stopping statins in the oldest old, many of whom with dementia and severely dependent, is safe.

## Neurosyphilis combined with acute anterior thalamic infarction

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The most common presentations of neurosyphilis are neuropsychiatric manifestations. However, neurosyphilis can also cause a variety of neurological diseases, such as stroke or dementia. Here, we report on a patient who was diagnosed with neurosyphilis combined with acute anterior thalamic infarction. A 65-year-old right-handed man was brought to our memory disorder clinic by his wife, who reported that over the past 6 months, the patient had experienced personality changes such as apathy, abulia, and emotional lability. The patient's wife recalled him having fairly good memory; however, his memory had deteriorated dramatically over the prior two weeks. He could not remember the names of familiar people, and presented with reduced verbal fluency and word-finding difficulty. The patient was diagnosed with neurosyphilis based on the results of positive treponemal serology, lymphocytic CSF pleocytosis with elevated protein levels, and positive CSF VDRL reaction. However, his brain MRI demonstrated focal hyperintensities in the left anterior thalamus and right basal ganglia on diffusion-weighted imaging. The above lesions were confirmed to be acute ischaemic cerebral infarctions based on low signal intensity on the apparent diffusion coefficient map. After a 14-day treatment course with penicillin G, symptoms of apathy, abulia, emotional lability, disorientation to time and place, and reduced verbal fluency noticeably improved. However, the relatively recent symptoms of short-term memory impairment and word-finding difficulty persisted, suggesting thalamic amnesia remained. Considering neurosyphilis as a dementing illness, the mechanism of cognitive impairment may be direct invasion of brain parenchyma, as well as strategic infarction by meningovascular syphilis.

## Frontal cognitive dysfunction with apraxia of eyelid opening after traumatic brain injury: a slowly progressive delayed complication

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Apraxia of eyelid opening (AEO) has been suggested to be a dysfunction of the supranuclear control of the levator palpebrae superioris caused mainly by basal ganglial lesion. The hypometabolism of the medial frontal lobe may be a pathophysiologic mechanism in frontal lobe dysfunction and AEO. We report two patients who developed frontal cognitive dysfunction with AEO, as a delayed complication, 4–6 years after traumatic brain injury (TBI) progressively. Their MRI showed encephalomalacia with low signal intensity in medial frontal cortex, which suggests loss of cortico-spinal tract fibers in the medial frontal cortex, which was not shown in initial brain CT scans. Delayed pathologic changes after TBI may contribute to the development of frontal cognitive dysfunction and AEO in these cases. Therefore we need to make a close observation if the patients have TBI, especially severe enough to loss of consciousness even their brain imaging scans do not show abnormal finding initially.

## Analysis of TOMM40 rs2075650 polymorphism frequency in Polish Alzheimer's disease patients

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Alzheimer's disease (AD) is a progressive demented disorder with poorly understood pathogenesis. Currently, the variants in TOMM40 gene were shown to play an important role in developing AD. The poly-T variants (rs10524523) may influence age at onset of AD, while rs2075650 polymorphism is an AD risk factor. Both loci may be co-inherited with pathogenic APOE E4 allele. The aim of the study was the frequency analysis of TOMM40 rs2075650 polymorphism in Polish AD patients. The peripheral blood of 69 subjects with AD, 54 control volunteers (UC) and 48 control persons with family history of AD (RC) was collected for plasma and DNA isolation. The APOE and TOMM40 genotypes were determined by qPCR, HRM and capillary electrophoresis. The G allele of TOMM40 rs2075650 was significantly overrepresented in Polish AD patients as compared to UC and RC (OR = 6.94, 95%CI: 2.82–17.1, p0.0001 and OR = 2.86, 95%CI: 1.41–5.80, p = 0.0037 respectively), and was more specific than APOE E4 (OR = 5.15, 95%CI: 2.38–11.1, p0.0001; and OR = 1.90, 95%CI: 1.02–3.51, p = 0.05) as compared to UC and RC, respectively. Moreover, G/G genotype was accompanied with slightly earlier age at onset (69.8 vs 72.5 years, p = 0.508) and faster disease progression (5.06 vs 4.78 MMSE/year, p = 0.821), as compared to A/A variant. Subsequently, 24.6% of AD patients were carriers of both rs2075650 G and APOE E4 alleles, as compared to 3.70% of UC (OR = 8.83, 95%CI: 1.94–40.1, p = 0.0009). It seems that G allele of TOMM40 rs2075650 polymorphism is a significant risk factor for developing AD in Polish population, providing additional information to APOE genetic status.

## Preliminary results of screening of the mild cognitive impairment and dementia in Almaty

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Data on the prevalence of mild cognitive impairment (MCI) and dementia are absent in Central Asia, particularly in Kazakhstan. Moderate cognitive impairments, according to several authors are an intermediate stage between normal aging and dementia. The prevalence of MCI varies from 16% to 20%, indicating a high risk of transformation of MCI into dementia. Forty-six point eight million people worldwide suffer from dementia. Five point two per cent are people over the age of 60. The main aim of the work was to reveal the prevalence of MCI and dementia among people over 60 years old in Almaty. 236 respondents aged from 60 to 95 years took part in the screening (mean age of patients  $67.5 \pm 5.5$ ). The primary material was collected using the CHAMP Clinic Questionnaire and the MOCA test (cut point  $\leq 26$ ), based on the Almaty city hospital, which numbers are more than 60,000 people, 10,265 of them are over 60 years old (17.10%). We identified light cognitive impairment — 52.12% (123 respondents), mild cognitive impairment — 33.05% (78 respondents), normal cognitive function — 14.41% (34 respondents) and 0.42% (one respondent) with dementia. Numerical values indicate a high percentage of dementia syndrome development, from 1 to 5 years, in the absence of preventive care. Kazakhstan is a middle-income country and a growing trend of an aging population; we urgently need to conduct a screening of the population to identify MCI and dementia. This will reduce the risk of transition of moderate CI to dementia.

## Disrupted cholinergic transmission in mice with Alzheimer's disease-like tauopathy (AD) but not in mice with frontotemporal lobar degeneration-like tauopathy (FTLD)

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An important enzyme associated with the brain cholinergic system is acetylcholinesterase (AChE, E.C.3.1.1.7). The AChE staining in cortex and hippocampus coincides with much of the cholinergic innervation originating from the basal forebrain.

AChE activity in cortex and hippocampus was evaluated in 2 tauopathic mouse models: Line 1 (L1), with mild Alzheimer's disease-like tauopathy and Line 66 (L66) with severe frontotemporal lobar degeneration-like tauopathy (FTLD) relative to age-matched wild-type NMRI mice. Analysis was performed in 3 and 12.5-month-old mice to assess cortical and hippocampal cholinergic innervation originating from the basal forebrain. For AChE histochemistry, brain sections were stained with the method of Geneser-Jansen and Blackstad (1971). Computer image analysis system (NIS-Elements BR 4.30.00 Software) was used for quantitation of the intensity of staining (ROD, relative optical density) measured in the arbitrarily defined areas ( $75,000 \pm 500 \text{ mm}^2$ ) across the entire depth of cortical and hippocampal layers.

In cortex and hippocampus intensity of AChE staining was significantly lower in L1 in comparison with L66 and NMRI lines of both age groups. Additionally, in L1 mice a characteristic bilaminar pattern of laminar distribution of AChE-rich fibres in layers II and V was not clearly visible. AChE histochemical staining data suggest that there is an impairment of the basal forebrain cholinergic projection in L1 mice, what corresponds with observed lower intensity of ChAT and p75 immunohistochemical staining in basal forebrain neurons of these mice. Tauopathy of AD-type seems to be associated with destruction and disorganisation of the cholinergic projections extending to both cortex and hippocampus.

## Acute hypoxia induced an imbalanced M1/M2 activation of microglia through NF- $\kappa$ B signalling in Alzheimer's disease mice and wild-type littermates

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Alzheimer's disease (AD) is the most common neurodegenerative disease mainly caused by abnormal tau phosphorylation, amyloid  $\beta$  ( $A\beta$ ) deposition and neuroinflammation. As an important environmental factor, hypoxia has been reported to aggravate AD via exacerbating  $A\beta$  and tau pathologies. However, the link between hypoxia and neuroinflammation, especially the changes of pro-inflammatory M1 or anti-inflammation M2 microglia phenotypes in AD, is still far from being clearly investigated. Here, we evaluated the activation of microglia in the brains of APP<sup>swe</sup>/PS1<sup>dE9</sup> transgenic (Tg) mice and their wild type (Wt) littermates, after a single episode of acute hypoxia (24 hours) exposure. We found that acute hypoxia activated M1 microglia in both Tg and Wt mice as evidenced by the elevated M1 markers including cluster of differentiation 86 (CD86), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), C-C motif chemokine ligand 2 (CCL2) and CCL3. In addition, the markers of M2 microglia phenotype (arginase-1 [Arg-1], CD206, IL-4 and IL-10) were decreased after acute hypoxia exposure, suggesting an attenuated M2 phenotype of microglia. Moreover, the activation of microglia and the release of cytokines and chemokines were associated with Nuclear factor- $\kappa$ B (NF- $\kappa$ B) induction through toll-like receptor 4 (TLR4). In summary, our findings revealed that acute hypoxia modulated microglia M1/M2 subgroup profile, indicating the pathological role of hypoxia in the neuroinflammation of AD.

## Diagnostic prospects of early Alzheimer's disease based on blood microRNAs

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Alzheimer's disease (AD) is the most common cause of dementia in the elderly. One of the major challenges in the AD field is deciphering the molecular signatures, characteristic of early stages of the disease, in peripheral tissues in patients suffering from mild cognitive impairment (MCI) due to AD. In this study qRT-PCR was applied to evaluate microRNA (miRNA) profiles in blood plasma collected from 15 MCI-AD patients, whose diagnoses were confirmed by cerebrospinal fluid (CSF) biomarkers, 20 AD patients and 15 non-demented, age-matched individuals (CTR). 179 plasma miRNAs were compared between AD and CTR, and between MCI-AD and CTR. 23 differentially expressed miRNAs reported earlier as AD biomarker candidates in blood were confirmed in the current study and 26 novel differential miRNAs between AD and CTR were detected. TargetScan, MirTarBase and KEGG database analysis of 15 miRNAs that presented statistically significant differences in their expression indicated that these may regulate the expression of microtubule associated protein tau (MAPT), proteins involved in amyloid precursor protein (APP) processing and proteins regulating apoptosis. The potential of these 15 miRNAs to be used as biomarkers was further verified in independent AD, MCI-AD and CTR groups. Finally, 6 miRNAs (3 novel in AD context and 3 reported) were selected as the most promising biomarker candidates differentiating early AD from controls with the highest fold changes (from 1.32 to 14.72), consistent significance, specificities from 0.78 to 1 and sensitivities from 0.75 to 1, (patent pending, PCT/IB2016/052440). The miRNA panel is promising for diagnostics of early AD.

# Epilepsy

## Theory of mind deficits in two neuropsychiatric populations: patients with mesial temporal lobe epilepsy and schizophrenia

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**Introduction:** Patients with schizophrenia (SCZ) have been widely reported dysfunctional in their ability of emotion recognition as well as understanding of social signals. Interestingly, similar deficits have been found in population of patients with mesial temporal lobe epilepsy (MTLE). The common feature of both conditions is a dysfunction of limbic system network, which is believed to underlie emotional and social processing. The aim of the study was to compare these two clinical populations.

**Material and methods:** The study involved patients with MTLE (n = 31), schizophrenia (n = 48) and a healthy controls group (HC; n = 47). Groups were matched in terms of age, sex and education. The all subjects were examined with a Reading Mind in the Eyes Test (RMET), which evaluates emotion recognition and theory of mind. Patients with schizophrenia were additionally assessed with Positive And Negative Syndrome Scale (PANSS).

**Results:** Results showed, that RMET scores of both epilepsy (p0,001) and schizophrenia (p0,05) groups were lower than in HC, but similar to each other (p0,05). In the next step patients with schizophrenia were split into 2 groups with respect to the PANSS scores. The analysis showed that SCZ patients with high level of positive symptoms performed similar to MTLE (p0, 05) and worse than HC (p0, 05), while those with low level of positive symptoms performed similar to control group (p0,05) and better than MTLE (p0,05). No differences were found for the median-split with regard to negative symptoms.

**Conclusions:** MTLE patients present theory of mind dysfunctions similar to those found in the individuals with schizophrenia with high positive symptoms.

## Brain MRI post-processing with MAP07 in preoperative evaluation of patients with pharmaco-resistant epilepsy — our experience

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Epilepsy is a chronic disease of the central nervous system that affects 1% of the population. The large number of patients with the proper selection of antiepileptic drugs can achieve satisfactory seizure control, while the remaining 25–35% have pharmaco-resistant epilepsy and are considered as candidates for active neurosurgical treatment. Preoperative evaluation of patients with pharmaco-resistant epilepsy can be divided into two phases. Phase I includes non-invasive diagnostic procedures — EEG; continuous video-EEG polygraphic recording; preoperative neuropsychological testing; brain MRI (magnetic resonance imaging), preferentially 3T MRI, with specialised recording techniques including MRI spectroscopy, functional MRI and MRI hippocampal volumetry; post-processing of brain MRI; ictal brain SPECT (Single-Photon Emission Computed Tomography); PET (Positron Emission Tomography) and optionally MEG (magnetoencephalography) with MSI (“Magnetic Source Imaging”). Phase II en-

compasses invasive methods in carefully selected patients — Wada test; semi-invasive monitoring with sphenoidal electrodes; invasive monitoring (with subdural strip and grid electrodes, depth electrodes, and with cortical stimulation procedure). The most significant neuroradiological procedure in proper selection of candidates suitable for neurosurgery is MRI 3T. Post-processing of brain MRI with MAP07 (Morphometric Analysis Program) is a new sophisticated diagnostic procedure. The program offers a number of graphical post-processing methods (maps) and facilitates the detection and localisation of hippocampal sclerosis, focal cortical dysplasias and other types of cortical malformations, which cannot be easily detected by conventional neuroradiological methods. We present our experience with MAP07 software in the preoperative evaluation of patients with pharmacoresistant epilepsy and selection of candidates for neurosurgical treatment.

## Episodic amnesia — vascular or epileptic nature related to mild cognitive impairment

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**Objectives:** To evaluate the diagnosis and the assessment of therapeutic response of patients who presented transient, recurring amnesia states and developed mild neurocognitive disorder.

**Material and methods:** We have analysed and put under medical surveillance initially for 2 years long and after this assessment 3 years more ten patients with repeated amnesic states. We used clinical examination, repeated EEG brain scanner, echocardiography, Doppler cerebral, biochemical analysis and psychological test.

**Results:** All 10 patients underwent a standardised clinical interview, patients aged between 52–68 years, 3 men and 7 women all had vascular risk factors (hypertension, dyslipidaemia, smoking, obesity). Tests were performed cognitive and psychological (MMSE, MOCA), being excluded patients who had initially MCI or dementia. All 10 patients described attack with sudden onset, 8 to 50 minutes, of anterograde incomplete amnesia, repetitive questioning, and progressive recover. Neuroimaging recorders showed: 1 case with dural sinus thrombosis, 6 cases with ischaemic lacunae and 3 cases with normal brain image in computer tomography. Interictal surface EEG recording was performed with non-specific modification. All patients received vascular treatment for 5 years and only 4 anticonvulsant therapies. 6 of 10 patients were not presented attacks under vascular therapy and the other four after the introduction of anticonvulsant therapy. Psychological assessment after 5 years of evolution revealed in 8 cases mild neurocognitive disorders.

**Conclusions:** In some cases only therapeutic test can distinguish between transient global amnesia and transient epileptic amnesia, but ours patients developed minor neurocognitive deficit related probably to vascular risk factors.

## Prospects for the use of cannabinoids in the treatment of epilepsy

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There is a broad evidence on the protective activity of synthetic cannabinoid agonists against a variety of chemoconvulsants or electroconvulsions in rodents. The interactions between cannabinoid agonists (WIN 55,212-2 mesylate — non-selective CB<sub>1</sub> and CB<sub>2</sub> receptor agonist or ACEA — a selective CB<sub>1</sub> receptor agonist) and antiepileptic drugs (AEDs) have been evaluated. In the mouse maximal electroshock

model, ACEA (in subthreshold doses and always co-administered with a fatty-acid amide hydrolase inhibitor) potentiated the anticonvulsant action of conventional AEDs, valproate and phenobarbital and a newer AED, pregabalin. In no case, the adverse effects of AEDs (impairment of motor coordination, long-term memory and muscular strength) were enhanced by ACEA. As regards WIN 55,212–2 mesylate, it potentiated the anticonvulsant activity of carbamazepine, phenobarbital, phenytoin, valproate (classical AEDs) and that of lamotrigine, pregabalin and topiramate (newer AEDs). In all cases of the combinations with classical AEDs, profound neurotoxic effects were evident. Combinations with newer AEDs were free from pharmacokinetic mechanisms or neurotoxic effects. The initial clinical data on the add-on treatment with cannabidiol (a non-psychoactive cannabinoid) indicate that in 23 children and young adults with drug-resistant epilepsy, there was a 39% reduction in responder rate and 17% of patients were seizure free. The most frequent adverse effects included somnolence (57%), fatigue (57%) and increased concentrations of concomitant AEDs (22%). The experimental data point to the beneficial interactions of cannabinoid agonists with newer AEDs. More clinical data are required before reliable conclusions can be drawn on this issue.

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## Potential benefits of music for patients with epilepsy

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Human race has been living with music since ancient times. People listen to music, play music, and create music. The connection of musical sounds and the brain functions is a major challenge of modern neuroscience. It has long been proven that music has a psychological effect on human beings, including induction and modification of cognitive states, moods and emotions. It is possible that brain mechanisms involved in musical processing may be involved in the generation and propagation of seizures, manifesting with musical semiology. Hyperexcitable cortical areas may also become sensitised to specific musical triggers and may explain the basis of musicogenic epilepsy. On the other hand, anticonvulsant role of music has largely been explored in cognitive science. The cognitive effects of music are well documented in the literature, although these effects have been subject to scrutiny. In our review of available literature, we explored the potential of listening and playing music as a part of chronic anticonvulsant therapy. All of the collected data were distributed in three categories: music as a factor in reduction of the number of seizures, joint effect of music and pharmacotherapy, and the effect of music who underwent neurosurgical procedure. We have presented all our findings in infographics. In our review-study all the results clearly indicate that the music would be a powerful tool in the service of the neurological rehabilitation. Music activates many brain structures, increases cerebral circulation and stimulates the brain, but there is limited evidence of the anticonvulsant effect of music in epilepsy.

## Are the physical anthropological types associated with a presence of epilepsy?

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**Introduction:** A physical anthropological diversity of any human population is its stable and very important characteristic, which influences on various aspects of existence of this population, including epidemiological ones. For some neurological pathology an association was confirmed between

certain anthropological phenotypic variants (PhVs) and a presence of the disease, peculiarities of its symptoms and course.

**Material and methods:** To define specific PhVs, an integrated anthropological examination of 51 persons with epilepsy (G40), who formed the main group (MG), and 50 healthy persons, who represented a general population of Kharkiv Region (Ukraine) as a control group (CG), was performed.

**Results:** It was demonstrated that the presence of epilepsy was associated positively with Uralic (17.65% in MG vs 0.00% in CG;  $p < 0.05$ ) and Armenoid (11.76% vs 0.00%, respectively;  $p < 0.05$ ) PhVs. A tendency to be associated positively was indicated also for Atlanto-Baltic PhV (9.80% vs 6.00%, respectively). All these PhVs were few represented in the structure of the general population. Mediterranean (17.65% in MG vs 20.00% in CG), Dinaric (11.76% vs 12.00%, respectively) and East-Baltic (7.84% vs 8.00%, respectively) PhVs were neutrally associated with the presence of epilepsy. A negative association with the presence of epilepsy was found out for Alpine (13.73% in MG vs 32.00% in CG;  $p < 0.05$ ) and Paleo-European (9.80% vs 22.00%, respectively;  $p < 0.05$ ) PhVs.

**Conclusions:** Thus, it was shown definitely the existence of a specific phenotypic structure of the group of patients with epilepsy in comparison with general population and association between the presence of epilepsy and certain PhVs for Kharkiv Region.

## The role of serum prolactin in diagnosis of seizure disorders in children

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**Objectives:** The purpose of this study is to review the use of serum prolactin assay in epileptic seizure diagnosis and to differentiate between epileptic seizures from psychogenic non-epileptic seizures in children.

**Material and methods:** This study was conducted on 48 children aged 1–18 years of age, and comprised of four groups: Group 1 consisted of children with epilepsy, which was further subdivided into GTCS, CPS and SPS, Group 2 comprised of children suffering from non-epileptic paroxysmal events like breath holding spell, syncope and pseudoseizures. Group 3 comprised of children having febrile convulsions, Group 4 consisted of children who served as controls. Blood sample was collected within 2 hours of the event in all the groups, serum prolactin level was estimated by ELISA technique.

**Results:** In the present study, significant elevation of serum prolactin level was observed only in Group 1 ( $28.31 \pm 15.61$ ) as compared to controls ( $9.97 \pm 2.91$ ), and the highest levels were observed in children with GTCS and with status epilepticus, serial seizures. Maximum elevation of prolactin was seen within two hours post ictally, as the prolactin levels become normal after two hours of post ictal period, the test loses its significance.

**Conclusions:** Elevated serum prolactin assay, when measured in the appropriate clinical setting within 2 hours after a suspected event, is a useful adjunct for the differentiation of epileptic seizures from psychogenic non-epileptic seizure among children.

## Doctor–patient relationship and the art of communication

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Patients with epilepsy often experience poor emotional well-being. In one study it was determined that 38.4% of epilepsy patients showed symptoms of depression (Hecimovic, 2012). A good doctor-patient relationship has proved to be a central component, to both the physical and emotional health of the patient. Although various studies have looked at the impact that doctor–patient relationships has on

health, there are no studies specifically studying the impact it has on patients with epilepsy. The goal of this study was to compare neurologists and patient's perspective on how doctor-patient relationship impacts one's health. Online surveys were created and neurologists were identified with the US through pattern matching. A total of 65 patients and 255 neurologists participated in this study. After analysing the result from the two different surveys, it was discovered that, doctor-patient relationship plays a critical role in the emotional well-being of patients, from both the doctor's and the patient's perspective. Moreover, humour in care, was also seen by both the patients and neurologists as a significant factor in establishing communication and fostering better outcomes in care. The findings of this research emphasised the importance of doctor-patient relationships, specifically around the patient centred care and communication and health. A greater emphasis on doctor-patient communication should be broadened, covered throughout the spectrum of one's training, and covered using various modalities. The use of humour within the doctor-patient communication should also be further addressed, as it was an important factor in care.

## Arterial spin labelling in focal epilepsies

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**Introduction:** Arterial spin labelling (ASL) provides a non-invasive means of measuring cerebral blood flow (CBF). The technique uses magnetically labelled arterial blood water protons as endogenous tracer. The hypothesis is that ASL perfusion changes may occur peri-ictally in patients with focal epilepsy.

**Material and methods:** Patients with focal-onset seizures were studied for ASL perfusion changes in the peri-ictal period. Based on the MRI findings, the patients were grouped: Group A: MRI positive for the lesion; Group B: MRI positive for 2 lesions and Group C: MRI negative for lesion. Areas of hyper- or hypoperfusion were correlated with seizure semiology, inter-ictal EEG and MRI findings.

**Results:** During the study period, 27 patients (mean age: 39.3 years, range 10–73 years; M:F 9:18) with focal epilepsy were studied. The time interval between seizure and ASL study ranged 15'–72 hours, mean 21.28 hours. Group A: out of 19 patients, 15 (79%) had ASL changes (7 hypo-perfusion, 8 hyper-perfusion) correlating with MRI lesion. Group B: out of 4 patients, 3 had ALS perfusion of only 1 lesion. Group C: all the 4 patients had ASL perfusion abnormalities corresponding to the epileptogenic focus in the EEG. Time interval between seizure and ASL study: hyperfusion — mean 3 hours (range 0.25–7 hours); hypoperfusion — mean 17 hours (range 1–48 hours); and no ASL perfusion changes — mean 61 hours (range 52–72 hours).

**Conclusions:** Peri-ictal ASL helps in localising the possible epileptogenic focus in patients with focal epilepsy, even in MRI negative patients. The earlier the study, the higher the yield.

## Focal nonconvulsive status epilepticus manifested as an antegrade amnesia

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**Introduction:** Usual clinical feature of nonconvulsive status epilepticus (NCSE) includes confusion or aura continua. Limbic encephalitis predominantly involves hippocampal structures which have crucial role in memory registration. Memory impairment is common sequelae of limbic encephalitis. We report a woman who had persistent memory impairment as sole manifestation of NCSE.

**Material and methods:** A previously healthy 38-year-old woman presented with repeating generalised seizures and gradual impairment of consciousness into stuporous state. EEG demonstrated electrographic seizures in both temporal areas. Brain MRI showed signal increment in bilateral mesial

temporal lobes. CSF was positive with anti-NMDA receptor antibody. She was diagnosed as a status epilepticus with anti-NMDA receptor antibody encephalitis. Antiepileptic treatment including midazolam continuous infusion and immunomodulating therapy were undertaken. Midazolam continuous infusion was continued until when both electrographic seizures and periodic discharges disappeared. She recovered from the coma 18 days after the presentation. Her neurologic deficits were completely recovered except one. She suffered from persistent antegrade amnesia. Neurocognitive testing indicated significant impairment in the memory domain, while other domains were relatively preserved. A follow-up EEG and MRI were unremarkable. FDG-PET revealed focal hypermetabolism in the body of the right hippocampus. Antiepileptic drug treatment with higher intensity alleviated her antegrade amnesia. We concluded that the antegrade amnesia was a manifestation of persistent focal seizure activity.

**Conclusions:** Uncontrolled focal seizure activity can present as a memory impairment and can be mistaken for some sequelae of the limbic encephalitis. PET or SPECT could be helpful in discriminating these two conditions.

## Cognitive disorders associated with epilepsy screening by Addenbrooke's Cognitive Examination — revised

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**Introduction:** Addenbrooke's cognitive examination-revised (ACE-R) using for evaluating of the cognitive disorders associated with epilepsy (CDAWE) in general medical practice. Neuropsychological tools plays an important role in differentiation of CDAWE. All of it stipulates the necessity of application for general medical practice of simple and reliable psychometric instruments for early diagnostics of cognitive disorders. One of the methodologies worked out for these aims is modified Addenbrooke's Cognitive Examination — Revised — ACE-R.

**Material and methods:** The study was conducted in two steps at somatic hospitals and city polyclinics. It enrolled 31 patients (18 men and 13 women) with epilepsy spectrum disorders. Work did not include patients with mental backwardness, violations of physical development and chemical addictions. Diagnostics was conducted by doctors-psychiatrists. The psychometric characteristics of ACE-R and the possibilities of its use were estimated to detect CDAWE. The differences in the spectrum of cognitive impairments were analysed in patients with different types of CDAWE.

**Results:** ACE-R is shown to be an effective neuropsychological tool for the primary diagnosis detection and evaluation of CDAWE in the general medical network. The results of ACE-R use indicate that the spectrum of cognitive impairments has substantial differences in patients with different types of CDAWE.

**Conclusions:** ACE-R showed a high sensitiveness for patients with epilepsy. It can be used for estimation both clinically outlined organic and subclinical cognitive disorders.

## Antiepileptic treatment in patients with and without cardiovascular pathology

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We observed 50 patients with epilepsy and cardio-vascular diseases (CVD) and 50 patients without CVD, who were treated with carbamazepine (CMZ) 25%, valproic acid (VPA) 26%, lamotrigine (LTG)

24% and levetiracetam (LEV) 25%. Each patient had clinical neurological examination, ECG, EEG, lipidogram, heart ultrasound (Tei-index, M-Strain, Strain % evaluation), carotid arteries dopplerography. In patients on CMZ sinus bradycardia, sick sinus syndrome, ventricular and supraventricular arrhythmias, rise of total cholesterol and low density lipoprotein were reliably more often than in patients on VPA, LTG and LEV (p0,01). In patients on VPA rise of triglycerides, increase of intima-media thickness more than 0,7 mm were reliably more often than in patients on CMZ (p0,05), LTG and LEV (p0,01). Patients on VPA with CVD had lowest Tei-index and M-Strain (p0,01) compared with patients without CVD after six months of treatment (p0,05). That could be a predictor of diastolic heart dysfunction. We revealed heart rate and conductance disturbances in patients who were taking CMZ, VPA, LTG, increasing of cardiovascular risk parameters in patients taking CMZ, VPA. Patients on CMZ had more significant changes of lipidogram, but patients on VPA had worse results of carotid arteries dopplerography. Patients on VAL had negative inotropic effect that was more significant seen in patients with CVD (p0,01), so we can say that VAL administration requires careful heart function monitoring in patients with heart failure and CMZ — in patients with arrhythmias. Also lipidogram and intima-media thickness should be checked more often in patients on VAL and CMZ.

## Some aspects of difficulty in management of status epilepticus in patients with coma

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Status epilepticus (SE) is one of the most common neurological conditions, which needs an emergency assistance. In general, the management of SE is more difficult in patients with unknown coma. Under our observation there were 6 patients with different aetiologic factors of coma. 3 patients from them had immunologic disorder causing status epilepticus. In 4 of the cases, non-convulsive status epilepticus was identified. In three cases we have diagnosed progressive forms of main diseases, but we could not find out aetiologic factors of manifested immunological disorders. For the treatment, we have decided to use anticonvulsive drugs in combination with hormonotherapy and immunoglobulinotherapy. At the same time, all the patients were under the general anaesthesia including Ketamine. Despite of this, in two cases we could not control the SE development for a long period of time. In all of the cases, we have used EEG-monitoring and MRI study in dynamics. These observations showed that the lack of control was related to the exacerbation of the main disease or the processes. All in all, we have arrived at the conclusion that the acute disorder of the central nervous system and its development is very important in the SE management and the SE management itself defines the solution. It relates to both of the types of statuses: non-convulsive and convulsive. Moreover, timely diagnosis is significant in the management of the refractory SE.

## Cases of frontal epilepsy, revealed during EEG screening in a psychiatric consultation

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**Introduction:** Frontal epilepsy is a common and difficultly diagnosed disorder. It accounts for 1–2% of cases of primary detected epilepsy and 20–22% among recorded cases of focal epilepsy. Epileptogenic foci may be located in different departments of a highly differentiated frontal lobe. Depending on the

affected area, the main types of seizures are distinguished: Motor, Dorsolateral, Orbitofrontal, Frontal (front). With violation of mental functions: Zingular, Brake, Combined. The most difficult for diagnostics are seizures with violation of mental functions. They are virtually unidentified by neurologists, since patients are turning to psychiatrists and do not give cause for EEG research. According to our observations, the nature of the disorders is in the borderline spectrum. Here are 3 observations of our own.

**Material and methods:** The 1<sup>st</sup> case — a girl G., 19 years old, a student, who after experiencing a stressful situation, developed a state of affective excitation, confusion, insomnia. This condition has developed sharply. Received neuroleptic and lamotrigine during the appointment of a psychiatrist. Well came out of this state, but such attacks began to repeat with less significant stress. The use of only neuroleptics did not have an effect. In the EEG study, epileptic activity was detected in the anterior parts of the frontal area. MRT without pathology. The appointment of lamotrigine has stabilised the condition. The 2<sup>nd</sup> case is a woman of 42 years and the 3<sup>rd</sup> case, a woman of 52 years — EEG similar to the first case.

**Conclusions:** The epilepsy of the anterior part of the frontal lobe is clinically manifested by psychiatric symptoms: paroxysmal of states of control impairment, “the sense of automaticity” of their actions, “fog”, confusion, due to the disintegration of mental functions; depressive state is resistant to antidepressant treatment. These manifestations are very difficult to differentiate with depressive and psychotic episodes. Therefore, all patients with depressive states, disorganisation and/or automatism need to do an EEG study.

## Functional and structural differences between right and left unilateral mesial temporal lobe epilepsies

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Hippocampal sclerosis has been the most common aetiology of the mesial temporal lobe epilepsy (MTLE) and is regarded as the most crucial anatomical region. However, it is not just a focal disease and other cortical and subcortical areas seem to be affected in MTLE. Using resting functional MRI (fMRI) and voxel-based morphometry (VBM), we aimed to investigate the functional and structural changes in patients with unilateral MTLE with hippocampal sclerosis according to the each side. The study group consisted of ten MTLE patients associated with unilateral HS (right n = 6, left n = 4). All participants were right-handed and well-controlled, seizure-free state. We obtained T1 and T2\* weighted images from 3T MRI (Verio, Siemens, Germany). As a result, no characteristic difference was observed in the analysis of resting fMRI. Each patient showed individual, inconsistent functional connectivity pattern. However, decreased volumes in the widespread extra-hippocampal regions (bilateral insula, bilateral thalamus and contralateral hippocampus in the right MTLE and left insula, contralateral hippocampus in the left MTLE) were observed in the VBM analysis. These differences could not be attributed to a different present disease severity, epilepsy duration, or seizure frequency, since those factors did not differ significantly between the left and right-sided MTLE/HS subgroups. Due to lack of the number of patients, further study will be required for the concrete conclusion; however, these differences could be theoretically explained by different neuronal networks, connections among brain areas and structural changes may precede functional changes.

## Super-refractory status epilepticus of unknown aetiology with late onset and fatal outcome — case report

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**Introduction:** Super-refractory status epilepticus is defined as status epilepticus that continues or recurs 24 hours or more after the onset of anaesthetic therapy, including those cases where status epilepticus recurs on the reduction or withdrawal of anaesthesia. It is an uncommon but important clinical problem with high mortality and morbidity rates.

**Material and methods:** We are presenting the case of a 48-year-old patient, with no previous pathological history, no chronic treatment at home, that came to the Emergency Unit with altered state, GCS 8 points coma, and initial tonicoclonic convulsive seizures continuous. The patient was an alcohol abuser, and in an acute intoxicated state at the time of the arrival (0,5 g/L concentration). The patient was submitted to the Intensive Care Unit, where, according to the therapeutical protocol, she received treatment, yet she manifested tonicoclonic generalised seizures for over 24 hours. The laboratory tests, meaning recurrent cerebral CT, cerebral MRI with angioRM, lumbar puncture with biochemical CSF analysis, and all other biological examinations had not detected any pathological alterations. The general state unfortunately evolved unfavourably, leading to the patient's death, 15 days after the submission.

**Conclusions:** Epilepsy is not a singular disease, but a variety of disorders. An individual treatment pathway should be formulated for people who have super-refractory status epilepticus.

## Analysis of SCN1A and SCN2A gene polymorphisms in epilepsy patients

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Epilepsy is considered as a chronic neurological disorder, which requires long-lasting antiepileptic drugs (AEDs). The *SCN1A* and *SCN2A* genes encodes  $\alpha$  subunits of neuronal voltage-gated sodium channel, which are targets for different AEDs. It is thought that various genetic variants of these genes are involved in the pathogenesis and treatment effectiveness of epilepsy. The aim of the study was to analyse the frequency of c.3184 A → G polymorphism of *SCN1A* gene and c.56 G → A polymorphism of *SCN2A* gene in Polish epilepsy patients and the control group. There was taken into account kind of used treatment among epilepsy group. To this study we enrolled 46 epilepsy patients (aged 20–66) and 45 aged matches' controls (aged 23–66). Genetic study was conducted using HRM method. The study has showed that frequency of GG genotype of *SCN1A* 3184 A → G and AA *SCN2A* 56 A → G polymorphisms were higher in epilepsy patients than in the control group. AG genotype of *SCN1A* 3184 A → G polymorphism was less frequent in epilepsy group as compared to controls ( $p = 0,03$ ) and patients with this genotype were mostly treated with polytherapy consisting of newer and older AEDs. Two of three epilepsy patients (67%) with AA genotype of *SCN2A* 56 A → G polymorphism were treated with newer AEDs in monotherapy, despite of the duration of the disease more than 5 years. It seems that there is an association between the frequency of occurrence of *SCN1A* and *SCN2A* polymorphisms in epilepsy patients. Further study is needed to confirm the involvement of these genes in more personalised therapy.

## Autistic-like disorders in children with resistant forms of epilepsy caused by “forced EEG normalisation” (Landolt’s) syndrome

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**Introduction:** “Forced EEG normalisation” (Landolt’s) syndrome is a special type of behavioural disorder in the malignant forms of epilepsy in children. Autistic-like disorders cause by this phenomenon develop during decrease or regression of epileptic seizures with normal EEG. The presence of antagonism to folic acid in a number of AEDs increases the dopaminergic activity and aggravates these manifestations.

**Objectives:** To describe early EEG and behavioural disorders in children with “forced EEG normalisation” syndrome.

**Material and methods:** 18 children aged from 6 to 12 years with resistant symptomatic epilepsy were enrolled in the study. Main causes of epilepsy were focal cortical dysplasia (5 children), agenesis of corpus callosum (2 children), sclerosis of the hippocampus (3 children), hypoxic-ischaemic foci (8 children). Necessary clinical tests including AED serum concentration were carried out.

**Results:** 13 patients on AED therapy had marked psychomotor and autistic-like disorders with attention deficit and disinhibition (during 2–4 weeks), in absence of epileptic seizures and with normal EEG. Previously received AEDs were not cancelled, but enterosorbent, phenibut and bromides were assigned. Folic acid was prescribed, as an antagonist of dopaminergic activity. During a “forced EEG normalisation” episode, an increase in low-amplitude (up to 20 microvolts) high-frequency beta-rhythm and the predominance of theta and delta waves were noted on the EEG. The behavioural disorders were normalised in the interval from seven days to two months.

**Conclusions:** In the resistant forms of childhood epilepsy, temporary behavioural disorders may occur during the AED therapy and EEG normalisation. This may require mild tranquilisation and folate therapy.

## Influence of lacosamide, a third-generation antiepileptic drug on neuroprotection and hippocampal cell proliferation in a mouse brain

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Epilepsy, one of the most common diseases of the nervous system, belongs to a group of social illnesses. Lacosamide (LCM) is a novel third-generation antiepileptic drug (AED), which is recommended as add-on therapy in adult and adolescent patients with partial-onset seizures with or without secondary generalisation. LCM with its selective enhancement of slow inactivation of voltage-gated sodium channels stabilises neuronal membranes and thus, exerts its anticonvulsant properties. The aim of the study was to evaluate the impact of LCM on neuroprotection and neurogenesis in healthy mouse brain. All experiments were performed on adolescent male C57/BL mice. Animals were injected with LCM once a day (10 mg/kg) for ten days. The control mice were injected with 0,9% NaCl solution. Fluoro-Jade B (FJB) and TUNEL staining were performed to evaluate neurodegeneration and apoptosis of neural cells. Additionally, mice were given a BrDU injection for the last five days of the LCM and NaCl treatment to quantify the total amount of proliferating cells. Additionally, behavioural studies were conducted. FJB and TUNEL staining showed just single nerve cells degeneration or apoptosis in both LCM and

control group. No spatial learning and memory disturbances were observed in Morris water maze test. In turn, results obtained from BrDU staining showed, that LCM significantly decreased the total number of newborn cells compared to the control group. Overall, results demonstrated that chronic administration of LCM does not cause nerve cells degeneration; however it decreases hippocampal cell proliferation in mice brain.

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# Headache

## Efficacy and safety of two dose regimens of subcutaneous administration of fremanezumab versus placebo for the preventive treatment of episodic migraine

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Evaluate 2 subcutaneous dose regimens of fremanezumab for the preventive treatment of episodic migraine (EM). 16-week, multicentre, randomised, double-blind, placebo-controlled, parallel-group adult EM study. Daily diaries maintained during 28-day baseline period. Patient assigned to one of three treatment groups: (1) monthly: 225 mg fremanezumab at months 1, 2 and 3; (2) quarterly: 675 mg fremanezumab at month 1, followed by placebo injections at months 2 and 3; and (3) monthly administration of matching placebo. Primary efficacy endpoint, mean change from baseline to 12-week randomisation period in monthly average number of migraine days was analysed using an analysis of covariance method or the Wilcoxon rank sum test. The mean number of migraine days was 9.1 days during the 28-day baseline period. Fremanezumab-treated patients had significant reductions in the number of monthly migraine days during the 12-week period vs. Placebo (-2.2 days from baseline = 9.1 days), for both regimens (monthly -3.7 days from baseline = 9.2 days; quarterly [-3.4 days from baseline = 8.9 days]; p0.0001), and 4-weeks after 1<sup>st</sup> dose, for both regimens (p0.0001). Fremanezumab-treated patients had significant reductions in the number of monthly headache days of at least moderate severity (monthly [-2.9 days]; quarterly [-3.0 days]; vs placebo [-1.5 days]; p0.0001), and 4-weeks after 1st dose, for both regimens (p0.0001). Fremanezumab treatment resulted in statistically significant reductions in the number of monthly days of acute headache medication use (monthly [-3.0 days]; quarterly [-2.9 days]; p0.0001) vs placebo (-1.6 days). Most common adverse events were injection site reactions. These results confirm the efficacy, safety, tolerability, and flexible dosing profile of fremanezumab for the preventive treatment of episodic migraine.

## ID-Migraine is useful to detect cluster headache as well as migraine

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**Introduction:** The 3-item identification of migraine (ID-M) is a validated tool to screen migraine patients in primary care setting and is consisted with the items related to photophobia, nausea and disability. Cluster headache has several similar features with migraine and easily misdiagnosed as

migraine. We investigated the efficacy of ID-M in detecting cluster headache and differencing migraine from cluster headache.

**Material and methods:** The patients who visited clinic for headache were asked to administer ten questionnaires including three questionnaires from ID-M items. Sensitivity and specificity of ID-M in detecting migraine and cluster headache were evaluated among the patients with primary headache disorders. Two or more positive responses to three items is considered as positive ID-M.

**Results:** A total of 344 patients were enrolled: 42 patients with cluster headache, 211 patients with migraine, 73 patients with tension-type headache, and 18 with primary stabbing headache. Sensitivity of ID-M in detecting migraine and cluster headache were 75.3% and 81.0% and specificity was 60.2% and 40.7%. The proportion of all positive response to ID-M was 35.5% in migraine and 52.4% in cluster headache.

**Conclusions:** ID-M is useful to detect severe headache such as migraine or cluster headache. Although nausea and photophobia are considered as typical features of migraine, cluster headache should be differentiated before the diagnosis of migraine in patients with positive response to ID-M.

## Assessment of occupation in Korean cluster headache

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Cluster headache (CH) is a neurological disorder characterised by recurrent, severe headaches on one side of the head. The previous studies have shown that CH has a significant negative impact on quality of life. Although there are many studies on overall quality of life, studies on occupations in CH have not been investigated. The study was conducted in 17 headache clinics for patients diagnosed with CH. The control group consisted of patients with non-cluster headache, such as migraine or tension-type headache or healthy adults. Unemployed, students, and housewives were excluded. Occupational group, work behaviour and working time were also assessed. Survey of work experience and satisfaction with current job due to CH was investigated. A questionnaire was administered to 71 CH patients and 68 control subjects. Except for the unemployed, housewives, and students, the occupational evaluations were conducted for 57 subjects in each group. In the control group, 52 employees were employed, whereas in the CH group only 37 employees were employed. The remaining 18 were either employers or freelancers. 50 CH patients (87%) experienced job loss, lack of performance, voluntary resignation, and promotion disadvantage at work. However, only 26 of the control group (46%) had these experiences. Despite disadvantages in the occupation, job satisfaction was mostly above average. This study confirms that CH results in a decrease in the overall work life of patients. There is a need to improve the quality of life in the workplace by treating headache with active acute care and adequate preventive treatment.

## A tailor-made suit rather than one size fits all: why triptans are not the best choice for first line migraine attack treatment

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Triptans are an effective medication against migraine attack. This does not imply that they should be considered as the first line treatment. Triptans are only effective for 80% of patients. The effectiveness of particular triptan cannot be predicted. Therefore, a patient might have to try several different triptans before finding the effective one. Secondly, triptans have side effects. Most common are fatigue, dizziness, chest discomfort, somnolence and nausea. Due to their vasoconstrictive effect, triptans are proscribed in patients with cardiovascular diseases. They are also contraindicated during pregnancy or lactation. Triptans are more likely to induce a medication overuse headache than NSAIDs. On the other hand, NSAIDs are safe and effective solution for migraine attack recommended by AHS and EFNS. They present a high tolerability profile and a low risk of transformation from episodic to chronic migraine. A combination of sumatriptan with naproxen proved to be more effective and better tolerated than sumatriptan or naproxen alone. This leads to a conclusion that a multi-component medication may also be a good choice for the migraine attack treatment. Lamifiban, a 5HT<sub>1F</sub> receptor agonist has presented a good efficacy and safety in two clinical trials. Lasmiditan does not have a vasoconstrictive effect of triptans, while has all their benefits regarding efficacy. Choosing a first line treatment of a migraine attack it is important to take into consideration its severity, patient medical history and possible side effects. There is no solution that will be suitable for all patients.

## The impacts of migraine attacks on cognition in young Iranian chronic migraineurs in resting state

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**Introduction:** Chronic migraine disease as a repeated primary headache has multiple vasoconstrictions and vasodilatations, which can be gradually damaged to the structure of the human brain. We have not known the correlation between each characteristic of migraine attacks and various cognitive domains. The present study examines the impact of migraine characteristics on cognitive domains in young chronic migraine sufferers (CMs).

**Material and methods:** 150 young CMs without aura and 100 healthy controls assessed using Montreal Cognitive Assessment (MoCA), the Frontal Assessment Battery (FAB), and Migraine Disability Assessment Questionnaire (MIDAS) selected. Depression and anxiety rates evaluated using Hamilton tests. Scores combined for comparison of cognitive domains and analysis of test results using independent t-student, Spearman's correlation, logistic regression, and Bonferroni correction for the sub-test of batteries. The patients had to be migraine-free during the past three days.

**Results:** CMs had lower MoCA scores than controls (OR = 1.15; 95%CI 0/99\_1.33), even after the adjustment for depression, gender and educational level. CMs displayed visuospatial and attention impairments (P = 0.02, P = 0.001). Pain severity had no effect on the MoCA scores, FAB scores and MIDAS Grading (P0/05). CMs with a longer duration of migraines displayed a causal relationship with the FAB Scores and MOCA visuospatial sub score (P = 0.05). The frequency of attacks was also associated with disability in CMs (P = 0.04).

**Conclusion:** Cognitive performance reduction occurred in CMs. Visuospatial and attention mostly impaired in CMs. The duration of a migraine complains associated with the degree of impairment of FAB Scores, and MOCA visuospatial subtests, suggesting a correlation between cognition and the length of the disease.

## The positive impact of fremanezumab on work productivity and activity impairment in patients with chronic migraine

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Evaluate the effect of fremanezumab on work productivity loss and activity impairment in CM patients. A 16-week, multicentre, randomised double-blind, placebo-controlled, parallel-group adult CM study. Patient's assignments — 1:1:1 ratio to 1 of 3 treatment groups: monthly dosing: 675 mg fremanezumab followed by 225 mg of fremanezumab at months 2 and 3; quarterly dosing: fremanezumab 675 mg at month 1, followed by placebo injections at months 2 and 3; and monthly administration of matching placebo. Change in Work Productivity and Activity Impairment questionnaire (WPAI) scores from baseline to four weeks after last dose (weeks 9–12) was evaluated as an exploratory endpoint. Work productivity loss was assessed as the composite of absenteeism and impairment while working (presenteeism). Fremanezumab treatment led to larger reductions from baseline in overall work productivity loss from baseline to weeks 9–12 (quarterly:  $-16.6 \pm 2.1\%$ ,  $n = 375$ ; monthly:  $-15.9 \pm 2.0\%$ ,  $n = 375$ ) relative to placebo ( $-9.1 \pm 2.0\%$ ,  $n = 371$ ). Placebo subtracted differences favoured quarterly ( $-7.5 \pm 2.2\%$ ,  $P < 0.001$ ) and monthly:  $-6.8 \pm 2.3\%$ ,  $P = 0.003$ ). Similarly, changes from baseline in presenteeism were greater with fremanezumab (quarterly:  $-15.7 \pm 1.9\%$ ; monthly:  $-14.9 \pm 1.8\%$ ) than for placebo ( $-10.0 \pm 1.8\%$ ), resulting in significant treatment differences (quarterly:  $-5.7 \pm 2.0\%$ ,  $P = 0.005$ ; monthly:  $-4.9 \pm 2.1\%$ ,  $P = 0.02$ ). Fremanezumab also reduced impairment of activity outside of work in the quarterly dosing arm of the study relative to placebo ( $-15.0 \pm 1.7\%$  vs  $-11.0 \pm 1.7\%$ ; treatment difference:  $-4.0 \pm 1.9\%$ ,  $P = 0.03$ ). Fremanezumab treatment resulted in significant improvements in work productivity and activity impairment, demonstrating the positive impact of fremanezumab on the ability of CM patients to function both at and outside of work.

## Glyceryl trinitrate (GTN)-induced headache is affected by priming of trigeminal system

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**Introduction:** Infusion of glyceryl trinitrate (GTN) in migraine patients provokes an immediate headache, that often is followed by a delayed phase with characteristics of a migraine attack. However, in healthy volunteers, only an immediate headache that is less severe and shorter than migraine patients occurs following administration of GTN. The higher sensitivity of nervous system in migraine patients has been proposed to underlie their more intense and prolonged GTN-evoked headaches. We tested the hypothesis that in healthy humans, a priming pain stimulus would enhance or prolong GTN-evoked headache.

**Material and methods:** Three priming stimuli, chemical stimulation by capsaicin patch, mechanical stimulation by a custom-made headband, or a combination of the two, were used prior to administration of sublingual GTN (0.5 mg) to induce headache in healthy volunteers (N = 20; age:  $26.2 \pm 4.0$

years). Headache pain characteristics and responses to a battery of quantitative sensory tests were assessed. Statistical analysis was performed with STATA using the paneled regression model and post estimation tests.

**Results:** GTN-induced headache intensity was significantly higher (P0.0001) after the combined stimulation, when compared either chemical or mechanical stimulation alone. Combined stimulation also produced the largest pain area. Increased sensitivity to noxious mechanical and thermal stimulation was produced by the priming stimuli; however, administration of GTN did not further increase this sensitisation.

**Conclusions:** The findings confirm that pain sensitisation in healthy subject's increases the intensity of GTN-evoked headaches. This combined surrogate model of headband-capsaicin-GTN might be useful to study features of trigeminal sensitisation in humans that occurs in pathological craniofacial pain conditions.

## Episodic ataxia with intermittent headache, ataxia, and diplopia

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**Introduction:** Episodic ataxia (EA) is characterised by intermittent periods of headache, ataxia and visual problems of variable expression. We characterise the phenotypic spectrum and the genetic basis, using next generation sequencing (NGS), of familial EA presenting with episodic diplopia, ataxia and environmental triggers.

**Material and methods:** 3 affected brothers, with onset within the 3<sup>rd</sup> decade, their affected mother, the unaffected father and 4 offspring were recruited. All affected subjects and their offspring underwent full ophthalmology and neurological assessment including eye movement recordings and MRI. Using NGS we screened for candidate of known association with EA. The affected subjects were prescribed a trial of acetazolamide and 4-aminopyridine.

**Results:** The primary presentation of all three brothers was headache, vertical diplopia of variable severity and duration, which reversed throughout the day. The mother reported diplopia at the same age, although resolved during pregnancy. All affected subjects and offspring had abnormal vertical saccades, smooth pursuit and fixation. 2 subjects had endpoint nystagmus. MRI scans were normal. The eldest brother had dysarthria and ataxia prior to starting treatment. NGS excluded previously reported EA genes including *KCNA1*, *CACNA1A*, *CACNB4* and *SLC1A3* genes suggesting a potential novel gene within this family. Acetazolamide did not improve symptoms. 4-aminopyridine reduced the frequency of symptoms, including the headache, in the most affected subjects.

**Conclusions:** We report a dominantly inherited, aminopyridine responsive EA likely harboring a novel gene, possibly a channelopathy. The selection for possible causative gene mutations has been thus narrowed.

## Comorbidities and risk factors in a prospective chronic migraine registry: study in a series of 723 patients

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**Introduction:** Chronic migraine (CM) is a common and disabling evolution of migraine. We aimed to analyse clinical characteristics, including comorbidities and risk factors, in a prospective registry of CM patients.

**Material and methods:** Patients firstly attended in an outpatient headache unit in a tertiary hospital (January 2013–January 2018). They were referred from primary care or general neurology offices. We diagnosed CM accordingly to ICHD-2R and ICHD-3 criteria. We considered demographic and clinical data, previous symptomatic and preventive therapies, comorbidities, and risk factors.

**Results:** We included 723 patients (105 males, 618 females), with mean age at inclusion of  $40.1 \pm 13.7$  years (12–80), and age at onset of migraine of  $19.3 \pm 9.7$  years (3–65). In 349 patients (48.3%), we gathered any vascular risk factor, especially smoking in 222 (30.7%) and hormonal contraception (84, 13.6% of female cases). Other chronic pain conditions were present in 77 (10.7%), including discopathy (48, 6.6%) and fibromyalgia (15, 2.1%) symptomatic medication overuse in 497 (68.7%), and mood disorders in 94 (13%). Among precipitating factors, 237 patients (32.7%) described stressful events. Only 193 (26.7%) migraineurs had received triptans before the referral, and in 380 cases (52.6%) at least one oral preventative had been used.

**Conclusions:** In our MC population, medication overuse, mood disorders and stressful events are frequent risk factors. We consider that previous use of preventatives and triptans should be increased.

## Intracranial tumour as a challenge for multidisciplinary approach

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Clinical symptoms of brain tumours may be different. Sometimes are discreet, lasting for years, and sometimes worsen rapidly, even in a few weeks, days or even hours. The 59-year-old patient, previously untreated for chronic diseases, was admitted to the Department of Neurology with mild headache and acute vision loss in the left eye. Neurological examination revealed blurring and loss of vision in the low-side quadrant. Radiological imaging of the head revealed the presence of a pathological mass in the left sphenoid sinus with destruction of its walls and infiltration of the optic canal and the presence of extravasated blood. Consultations with numerous specialists did not bring the clear diagnosis. The patient was not qualified for neurosurgical operation due to the difficult access to the pathological mass. Despite symptomatic and supportive treatment, the patient's condition started to deteriorate three days after the admission to the hospital; there were disturbances of consciousness and weakness of the left limb and damage of the opthalmoplegia nerves. Respiratory distress and cardiac arrest occurred shortly after. Resuscitation was unsuccessful. Only post mortem examination established the final aetiology of the disease, which turned out to be quite surprising considering the symptoms and patient's medical history. This case shows how difficult it is sometimes to define the real cause of disease using conventional diagnostic methods. Different, also rare, aetiological causes may, in fact, entail the same clinical symptoms, thus they should be taken under consideration at all stages of diagnostics.

## Association between STX1A c.31-1811CT polymorphism and serotonin concentration in migraine patients

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Migraine is a primary headache disorder that affects 11% of adult population. It is divided into two clinical subtypes: migraine with aura (MA) and migraine without aura (MO). Migraine is multifactorial disease and may be a result of polymorphisms in numerous genes, e.g. STX1A c.31-1811CT polymorphism (rs941298) was associated with MO. The STX1A gene encodes syntaxin 1A, a presynaptic membrane protein which controls the synaptic vesicle exocytosis and functioning of ion channels. Syntaxin 1A is involved in the regulation of the serotonergic system by affecting the expression and location of the serotonin (5-HT) transporter. The reduced 5-HT concentration is a hallmark of migraine and may be caused by genetic changes. The aim of the study was to analyze STX1A c.31-1811CT polymorphism and 5-HT plasma concentration in migraine patients. The study included 90 migraine patients (MA: 39, MO: 51) and 90 controls. Mean age of participants was  $36 \pm 13$  years. The HRMA and sequencing were used for genotyping. 5-HT concentration was determined by HPLC/EC technique. T allele of STX1A c.31-1811CT was more frequent in migraine patients than controls, but there was no statistical difference. TT genotype in MO patients was associated with lower 5-HT concentrations ( $0.012 \mu\text{g/mL}$ ) as compared to controls ( $0.140 \mu\text{g/mL}$ ) and MA subjects ( $0.120 \mu\text{g/mL}$ ) with TT genotype ( $p = 0.0088$ ). STX1A c.31-1811CT polymorphism may alter the 5-HT concentration in MO patients. The functional studies would assess the effect of polymorphism on syntaxin 1A and 5-HT transporter relation. Analysis of STX1A polymorphisms and 5-HT concentration may be useful in optimisation of migraine pharmacotherapy.

## Headache is the predictor of lacunar strokes: data from the stroke registry sits — Kyrgyzstan

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**Objectives:** To characterise headache in patients with lacunar strokes, and to find a correlation between headache type, intensity and stroke outcome.

**Material and methods:** We studied a sample of 68 patients with acute lacunar infarction enrolled in SITS stroke registry, with confirmed lacunar lesion on DWI scans of MR. Fazekas scale was used for leucoareosis evaluation and NIHSS — for the stroke severity at the onset. All patients were interviewed on the presence of headache before and in the onset of stroke, its severity was estimated according to Visual Analogue Scale (VAS). In ten days after stroke, NIHSS and VAS were repeatedly measured and statistical correlation between them was described.

**Results:** Headache was present in 90% of observed patients at onset, strongly connected with arterial hypertension ( $p = 0.0001$ ). Systolic blood pressure higher than 156 mm was associated with increasing headache in sample ( $p = 0.01$ ). Headache was diffused and “pressure type” in 78% of all headache patients. Mean baseline NIHSS score in patients with headache was  $8 (\pm 1.8)$ , what is minor stroke, and mean VAS was  $6 (\pm 2)$ . There was no significant correlation between intensity of baseline headache and baseline NIHSS, and lacunar infarct localisation and headache intensity, but strong association of dull headache and infarcts with leucoareosis in 3<sup>rd</sup> stage. In 64% headache significantly decreased to 10th day of stroke ( $\text{VAS } 3 \pm 0.9$ ).

**Conclusions:** In patients with lacunar infarction, headache is moderate, diffuse and “pressure type”, not correlates with infarction site and NIHSS scale. Third stage of leucoareosis we found strongly associated with headache ( $p = 0.001$ ).

## Influence of accompanying symptoms on chronisation of migraine

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**Introduction:** Chronisation of the headache (HA) significantly impairs the quality of life. Thus, patients with chronic migraine compared with patients with episodic migraine, the quality of life is lower and they are forced to take much more analgesic drugs. Therefore, the important task is detection of predictors of chronic migraine.

**Objectives:** Identify the predictors of chronic migraine in patients with episodic migraine.

**Materials and methods:** The study involved 40 patients, 34 women and 9 men aged from 21 to 52 years, the average age —  $37.5 \pm 18.2$  years, suffering from migraine (criteria for the International Classification of Headache, 2013). All patients completed the following questionnaires: a diary of symptoms, accompanying headache (RHRS, 2009), an express questionnaire of vertigo, a pain questionnaire “PainDETECT”.

**Results:** Among the symptoms associated with HA, a high specific gravity of neck muscle tension was detected in 20 (66.7%) cases, imbalance in 19 (47.5%), sleepiness in 18 (60.0%) cases, vertigo in 30 (75.0%) cases. A high specific gravity of position-dependent system vertigo was found in 15 out of 30 cases (50%) and kinesia in 18 cases out of 25 (60%) ( $p 0,05$ ). Analysis of the indicators of the PainDETECT questionnaire revealed that 28 (70%) patients had a high probability of neuropathic pain component ( $p 0,05$ ).

**Conclusions:** The aggregate of painful and non-painful phenomena, such as vertigo, associated with HA, could have a significant impact on the perception of pain. These results point to a high risk of developing chronic migraine in patients with a migraine-associated vertigo.

## Medication overuse headache — prevalence, management and quality of life

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**Introduction:** Medication overuse headache (MOH) is frequent having a significant psychosocial, social and economic impact, affecting patient’s quality of life (QoL). It is the third most common type of headache, with a prevalence of 0,7–1,7%, caused by automedication and easy access to over the counter (OTC) medications recommended for headaches or other types of pain and secondary to excessive TV advertising.

**Material and methods:** A prospective study performed on 23 patients (19 women and 4 men), mean age 46 years, diagnosed with MOH answering a special questionnaire, completing headache diaries, RAND 36 item Health survey v. 10, Hamilton Anxiety and Depression scales and Visual Analogue Scale for headache intensity. The treatment was stopping the MOH inducing medication, associating prophylactic headache therapy or withdrawal therapy.

**Results:** The patients suffered from primary headache (73,91% migraine and 26,09 % tension type headache), 52% having a personal pathologic history of headache, 82,6% were women and 35% unemployed due to headache. Paracetamol and nonsteroidal anti-inflammatory drugs were used, in 39%

OTC and 52% automedication associated to medical prescriptions. 61% had lower education ( $\leq 12$  years). Stopping MOH inducing treatment was the first option. Prophylactic headache medication was preferred (52%), some patients needed withdrawal medication or hospitalisation. RAND 36 Item Health Survey v. 1.0 was a good prognostic predictor, 52, 17% of the patients having scores 60%.

**Conclusions:** MOH is more frequent than diagnosed. TV advertising for analgesics should be reduced. Prophylactic therapy should be used more frequently. A multidisciplinary team can reduce the time until withdrawal.

## Clinical case of familial hemiplegic migraine

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Migraine and epilepsy are co-morbid diseases. In some cases established its genetic causes. The man, 19 years old, since the age of 12 years experienced isolated episodes of numbness, paresthesias and weakness in right hand, sometimes accompanied by numbness in right leg, once — by dysphasia. One of the attacks was presented by isolated numbness and weakness in left leg. Some attacks were accompanied by headache. Regression of symptoms was after 20–40 minutes after sleep or rest. During seven years there were 5 attacks. Data of examination (including MRI of brain [3,0], doppler ultrasound) were normal. Slow activity in left temporal region was detected in EEG repeatedly. Long-term EEG monitoring (free-attack period): paroxysmal activity represented by bilateral high amplitude theta waves (predominantly in frontal regions) low index during wakefulness and sleep have been found. FHM is an uncommon type of migraine, frequently beginning in the first or second decade; frequency of attacks tends to decrease with age. Diagnostic criteria for FHM includes: criteria for migraine with aura; the aura includes some degree of hemiparesis and may be prolonged, but completely reversible; at least one first-degree relative also has such attacks. Headache usually lasts four to 72 hours, but may be completely absent. FHM is inherited in an autosomal dominant manner. Mutations in three genes (CACNA1A [FHM1], ATP1A2 [FHM2], and SCN1A [FHM3]) have been found to cause FHM. CACNA1A pathogenic variants commonly presenting with nystagmus and other cerebellar signs, ATP1A2 — with epilepsy.

# Multiple sclerosis

## Sexual dysfunction (SD) in multiple sclerosis (MS) population — incidence and management as it results from our experience

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**Introduction:** We consider that SD is a painful, but underreported and underdiagnosed symptom of the disease and can appear at any stage of the disease. SD is often unrecognised as patients and physicians are reluctant to discuss the problem. Our purpose is to share our experience regarding this significant problem, its incidence and the major impact of quality of life.

**Materials and methods:** We examined 110 patients, males (55) and females. They completed a questionnaire with multiple questions about their sexual life before and after they were diagnosed with multiple sclerosis.

**Results:** The most common symptom of SD in men with MS was erectile dysfunction (44%), reduced libido (40%), anorgasmia, ejaculatory issues (16%). The frequency of SD was higher in females (64.5%). Women reported most frequently reduced libido, difficulty in achieving orgasm.

**Conclusions:** Maintaining a healthy sexual life in patients with MS is a priority. The treatment of SD requires a multidisciplinary team and cooperation between different specialist, partners and society. Studies showed that up to 86% of men felt that MS affected their sexual life. We will present more results about SD and also the management of SD in MS population.

## Headache in patients with MS — causes and management — Colentina Clinical Hospital experience

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**Introduction:** The aim of this paper was to share with you the variables and causes of headache in patients with multiple sclerosis from our center, management and impact on quality of life. People with multiple sclerosis (MS) have an increased incidence of headaches. Some treatments used for MS have been demonstrated to exacerbate headaches, leading to a decreased quality of life and possible treatment nonadherence.

**Materials and methods:** We analysed a number of factors in relation to headache frequency in 140 of our patients with MS, focusing on headache history, pain description, modifying factors, social history, relation to disease. We observed headache characteristics in relation to MS diagnosis, disease exacerbations, and physiological conditions.

**Results:** More than half of patients reported the presence of headaches before the start of their MS symptoms. MS exacerbations caused a worsening of headaches for nearly two-thirds of our patients. Majority of our patients were females, with relapsing remitting MS and also secondary progressive and under an immunomodulatory treatment. Headache impact on daily life, measured by HIT-6 score and PHQ-9 score was very significant.

**Conclusions:** There are several hypotheses regarding how headache results from various forms of MS pathogenesis and we will present them in the extended paper. Thorough evaluation of headache in patients with MS is crucial to optimise patient management to help improve quality of life.

## Characteristics of multiple sclerosis relapses and factors affecting relapses frequency in patients with immunomodulatory therapy

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Our objective was to estimate the relapses of MS and the influence of seasonal and climate factors on patients in the Volyn region — the region with the highest MS morbidity in Ukraine. The study included 100 MS patients (27 males and 73 females) with relapsing-remitting course. The average age of patients was 38.59 ( $\sigma$ –8.8) years (20–57), the average time from diagnosis in these patients was 9.643 ( $\sigma$ –6.23) years, the average EDSS rate was 2.957 ( $\sigma$ –1.31). 46% of them were employed, 53% were unemployed, 76% were married, and 24% were not married. From the first symptoms prior to the diagnosis of MS on average passed 2227 days, if first symptoms began after 2010, time to diagnosis was reduced to 462 days. There were 243 relapses from 2012 to 2017. The average duration of the last relapse was 11,215 ( $\sigma$ –6,188) days. 19% of patients had visual, 82% — pyramidal, 50% — cerebellum, 32% — sensory, 36% — pelvic organs function disorders and 21% had cognitive impairment. The peak of relapses is in the beginning of spring (March — 30), then gradually decreases until the middle of summer (July — 14) and again it grows from the beginning of winter (December — 26). The amount of relapses was higher in the low-vitamin D period compared to the other two seasonal periods (99, 77,67 respectively). We found a significant strong correlation between the number of relapses and the radiation balance level (–, 998, \*p 0, 05). The lower radiation balance level correlates with the higher number of MS relapses.

## Evaluation of the long-term treatment effect of teriflunomide on cognitive outcomes and association with brain volume change: data from TEMSO and its extension study

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**Introduction:** In a blinded SIENA (Structural Image Evaluation using Normalisation of Atrophy) analysis of TEMSO (NCT00134563), teriflunomide significantly reduced brain volume loss (BVL) over 2 years vs placebo. Here, we explore the relationship between BVL and long-term changes in cognitive function in TEMSO and its extension (NCT00803049).

**Material and methods:** Effect of teriflunomide on cognitive function was assessed by change from baseline in Paced Auditory Serial Addition Test (PASAT)-3 scores in the TEMSO core (N = 1086) and extension (N = 740) studies. To evaluate change in PASAT-3 scores over five years, the TEMSO population was categorised into groups defined by percentage brain volume change from baseline to Year 2 (assessed by SIENA).

**Results:** Adjusted mean changes from baseline to Week (W)96 in PASAT-3 Z-score were -0.022 and 0.073 for placebo and teriflunomide 14 mg, respectively (difference vs placebo:  $P = 0.0435$ ). Over the long term, improvements in mean (SD) changes from baseline in PASAT-3 scores were observed with teriflunomide 14 mg treatment (Z-scores: W156, 0.194 [0.634]; W276, 0.200 [0.677]. Raw scores: W156,

2.36 [7.73]; W276, 2.43 [8.24]). In an association analysis, the group with least BVL from baseline to Year 2 demonstrated a significant improvement in PASAT-3 score with teriflunomide treatment over five years vs the group with most BVL.

**Conclusions:** Teriflunomide significantly improved PASAT-3 performance vs placebo over five years in the TEMSO core and extension studies. Significant association of early BVL with long-term cognitive changes was observed, suggesting that BVL earlier in the disease course predicts longer term cognitive function.

## Neurofibromatosis (NF1) and multiple sclerosis (MS) — a rare association

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**Introduction:** Neurofibromatosis 1 (NF1) is a genetic autosomal dominant neurocutaneous disorder. There are only a few cases of NF1 associated with multiple sclerosis (MS), 16.6% of the MS patients are carriers of the NF1 gene. The mutation in the oligodendrocyte myelin glycoprotein (OMG) gene is frequently associated with the primary progressive form of MS.

**Material and methods:** Our patient is a 30-years-old female diagnosed with NF1, with a family history of neurofibromatosis (mother and grandmother), who presented cafe'-au-lait patches, Crown sign, Lisch nodules and dermal neurofibromas. In the last 13 years she developed two episodes of self-limiting optic neuritis and a right cerebellar syndrome, for which she was admitted to our clinic. The brain MRI showed multiple T2-weighted areas of altered signal in both cerebral hemispheres suggestive for MS and the spinal MRI — same type of lesions at the C2–C3 and C4–C5 level. Cerebrospinal fluid examination showed high levels of oligoclonal bands and IgG index. The visual-evoked potentials were significantly bilaterally delayed. Other autoimmune and infectious diseases were excluded and OMG gene was absent. Her symptoms ceased under corticosteroid therapy. She underwent immunomodulatory treatment for relapsing-remitting MS with no exacerbations (3 years now — EDSS = 1.5 p).

**Conclusions:** The peculiarity of our case is the fact that NF1 usually goes along with primary progressive MS and no medullar lesions. Our patient has a relapsing-remitting form with a good response to immunomodulator treatment.

## Vaccines and multiple sclerosis: old dilemmas, new approaches

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**Introduction:** When discussing vaccinations in general and their possible adverse effects (including demyelination), the authors offer different opinions, and sources have sometimes warned against using a certain vaccine, such as the vaccine against the yellow fever that seems to exacerbate multiple sclerosis (MS). Vaccines generally are not accused to cause the onset or an exacerbation of MS; whereas tetanus vaccine might even have a protective effect in the clinical course of MS.

**Discussion:** Genetic and epidemiological studies have picked up populations at risk, such as those with Scandinavian or Scottish ancestry; HLA-DR2 haplotype has demonstrated linkage and association with susceptibility to multiple sclerosis. In Italy, there is a geographic region (Sardinia), where an unexpectedly high prevalence of MS has been found. Studies suggest that HLA-DR2 haplotype to be linked with demyelination after hepatitis B vaccination. Several sources underline the importance of

post-infectious and post-immunisation proinflammatory cascades in the pathogenesis of demyelination; molecular mimicry, re-infection and a “second-hit” immuno-inflammatory process are among the most elaborated models that explain satisfactorily the cascade of events.

**Conclusions:** We suggest that a control of HLA haplotype should be a logical and precautionary measure in subjects that due to several reasons must undergo an intense vaccination programme toward excluding remote albeit possible demyelinating complications.

## The role of advanced glycation of proteins in the aetiopathogenesis of multiple sclerosis

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**Introduction:** Advanced glycation end products (AGE) are involved in the pathogenesis of many diseases, including neurodegenerative diseases such as multiple sclerosis (MS). It is suggested that many xenobiotics may initiate abnormal immune response in individuals with certain genetic predispositions. Many of these compounds can also adversely affect the state of redox balance of the body, exacerbating radicalisation and reducing antioxidant defense mechanisms. This can be a bridge linking the aetiopathogenesis of MS to the processes of advanced glycation of proteins in the human body. The aim of the study was to evaluate the intensity of protein glycaemia in MS and their possible involvement in disease activity.

**Material and methods:** The study involved an authoritative questionnaire, which helped to survey a group of MS patients from the Upper Silesian region (n = 52; mean age — 37.9 ± 9.4 years); control blood samples came from healthy volunteers (n = 40; age — 41.1 ± 10.4 years). Concentrations of selected parameters of advanced glycation of proteins: AGE, carboxymethyllysine (CML), carboxyethylolysin (CEL), and their soluble receptor (RAGE) in sera of patients and controls were determined by immunoenzymatic method (ELISA), using commercially available kits.

**Results:** MS is accompanied by a statistically significant increase of protein glycaemia. The duration of the disease and the degree of motor impairment do not appear to affect the progression of the glycation processes. However, the disease process associated with MS alters the correlation between individual protein glycation products, particularly the correlation between CML and CEL concentrations.

**Conclusions:** Advanced glycation of proteins should be taken into account in the aetiopathogenesis of MS.

## Oligoclonal band multiple sclerosis presenting with sudden hearing loss

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**Material and methods:** A 33-year-old woman without significant medical history presented a first episode of neurological deficits with sudden left ear hearing loss, left facial palsy, left facial hypoaesthesia and left eye vision loss, lasting for a month. After 2 episodes of bowel incontinence, she developed a headache and a left eye vision loss and was admitted to our department. MRI revealed demyelinating

lesions in the left postero-lateral pons, anterior half of cervical spinal cord and deep white matter of the left temporal lobe. All laboratory findings were normal apart from low levels of vitamin D. CSF analysis was also normal. Visual evoked potentials revealed bilateral prolonged latencies, while auditory evoked potentials showed prolonged latencies on the left, thus confirming the left sensorineural hearing loss. Based on history and paraclinical assessment, diagnosis of relapsing-remissive multiple sclerosis was confirmed. Pulse-therapy was performed with symptom improvement, after which disease-modifying therapy was initiated.

**Discussion:** Lack of oligoclonal bands may suggest a different immunogenetic profile from other MS patients. In our case, the particularity resides in the predominant cranial nerve involvement and low lesion load on MRI. While sudden sensorineural hearing loss (SSHL) is more common in MS patients than in the general population, there have been only several cases described with SSHL at onset.

## Validation of MS-TEQ in Albanian

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**Introduction:** Disease-modifying therapies for the treatment of Multiple Sclerosis are the best strategy currently available to slow the natural course of MS, but on the other hand they are associated with inconvenient methods of administration, significant side effects, and low adherence rates. The MS Treatment Evaluation Questionnaire (MS-TEQ) is constructed to quantify and explore the barriers that get in the way of people taking their DMTs as prescribed.

**Material and methods:** As part of the validation process of this questionnaire in Albania, we translated it from English into Albanian language and then showed it to a small group of local MS patients to ensure it was easy for them to understand it. In December 2017 we asked 32 patients to complete the MS-TEQ.

**Results:** By analysing the data collected from the patients, we revealed that among the patients who missed the dose varied significantly by treatment between 9–12, 5% (p0.001), it was highest in IFB 1b sc, lowest in GA. It was observed that the time since the diagnosis was made was a significant evocator in MDR, lower in patient diagnosed in less than 18 months, compared to 3+ years of MS.

**Conclusions:** The results of MS-TEQ are very useful to MS patients and health care provider to come up with ways to make easier to take the treatment.

## Rapid disease progression following initiation treatment with dimethyl fumarate in patient with neuromyelitis optica spectrum disorders (NMOSDs)

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Neuromyelitis optica spectrum disorders (NMOSDs) are the group of aggressive autoimmune inflammatory demyelinating diseases of the central nervous system. NMOSDs manifest predominantly with attacks of optic neuritis and longitudinally extensive transverse myelitis. Correct diagnosis and adequate treatment is required to prevent morbidity and mortality. Corticosteroids used in relapses and immunosuppression with agents such as azathioprine, mycophenolate mofetil, rituximab is the mainstay of NMOSD's treatment. Disease-modifying drugs effective in multiple sclerosis (MS) might exacerbate NMOSDs. We present the case of NMOSD's patient diagnosed with MS after 2 relapses in the form of optic neuropathy and left hemiparesis with painful dysaesthesia with incomplete recovery

on intravenous methylprednisolone. Serum anti-AQP4 antibody tested with indirect immunofluorescence assay was negative. Interferon beta 1a treatment was started, but patient kept having relapses. Then the treatment was shifted to dimethyl fumarate. 3 months after new treatment initiation, the patient experienced a severe relapse characterised by spastic hemiplegia. Spine MRI showed extensive demyelination with cord swelling of the medulla extending down to Th1 vertebral level. Clinical and radiological symptoms were pathognomonic for NMOSDs. Serum anti-AQP4 was tested again using a cellular method and a positive result was obtained. Azathioprine treatment was started, dosed 50 mg twice a day. Exacerbation and even more severe relapses have been previously reported in NMOSD during the use of interferons, natalizumab, fingolimod and alemtuzumab, but there are few reports of such worsening using dimethyl fumarate.

## A case report of oligodendroglioma and multiple sclerosis: Occam's razor or Hickam's dictum?

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Tumefactive lesions on brain imaging can pose a diagnostic dilemma in patients with or without known multiple sclerosis (MS). It is important to differentiate tumefactive demyelinating lesions from intracranial neoplasms. Here we report on the case of a middle-aged man who presented with acute unilateral optic neuritis. Brain MRI showed enhancement of the right optic nerve, and multiple non-enhancing supratentorial white matter lesions including a three cm focal lesion in the right frontal lobe with adjacent gyral expansion. Cerebrospinal fluid (CSF) analysis showed more than 5 CSF-restricted oligoclonal bands and an elevated IgG index. The patient was treated with a short course of high dose intravenous methylprednisolone and started on glatiramer acetate for likely tumefactive MS. A follow-up brain MRI six months later showed no new or enlarging lesions, but persistence of the frontal gyral expansion. Brain biopsy led to the diagnosis of a grade II oligodendroglioma (with isocitrate dehydrogenase-1 mutation and 1p/19q co-deletion) managed with surgical resection and radiotherapy. A post-operative follow-up brain MRI showed a new enhancing periventricular lesion, making the choice of optimal disease modifying therapy for MS more challenging. This case highlights the possibility of co-existence of MS and oligodendroglioma in the absence of a preceding diagnosis of MS, emphasises the importance of a tissue diagnosis in the presence of atypical imaging features for MS, and underlines the challenges of choosing an appropriate disease modifying therapy when MS is concurrent with a brain tumour.

## Does the nature of nutrition affect the development and course of relapsing-remitting multiple sclerosis (RRMS)?

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**Introduction:** Considering the connection between microbiota and immune system, nutrition recommendations for patients with multiple sclerosis can lead to immune modulation and positive effect.

**Objectives:** Determine the main models of nutrition dominating among patients with RRMS with different activity.

**Material and methods:** 30 women with RRMS who did not change their dietary habits, and thirty healthy women at the age  $25.0 \pm 5.0$  and  $26.0 \pm 5.0$ , respectively, were examined. The diagnosis was established in accordance with the McDonald's criteria, EDSS = 2–3. The FFQ-based questionnaire was used, where nutrition products were grouped into clusters and five types of dietary models were derived.

**Results:** All 5 types of dietary patterns were identified in the examined patients: western, high-fat, vegetarian, lactovegetarian and traditional models. Most patients followed the western model (odds ratio [OR] = 1.97; 95% confidence interval CI: 1.61–2.92, P 0.005) and high-fat model ([OR] = 1.87; 95% CI: 1.61–2.92, P 0.005). Minority of the patients preferred the traditional ([OR] = 0.17; 95% [CI]: 0.05–0.20, P = 0.028), vegetarian ([OR] = 0.40; 95% ; [CI]: 0.17–0.78, P = 0.026) lactovegetarian diet ([OR] = 0.33; 95%; [CI]: 0.14–0.84, P = 0.018). During 6 months, the patients who followed the western model had 1–2 exacerbations with new periventricular Gd+ lesions on MRI, while patients on other diets did not have exacerbations.

**Conclusions:** The western and high-fat models dominate among the RRMS patients, which probably causes the bigger activity of the disease.

## Efficacy of a third course of alemtuzumab in patients with active relapsing-remitting multiple sclerosis who experienced disease activity after the initial two courses: pooled analysis of CARE-MS I and II

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**Introduction:** Alemtuzumab improved efficacy outcomes in 2-year (y), phase 3 trials vs SC IFNB-1a in RRMS patients (CARE-MS I: treatment-naïve [NCT00530348]; CARE-MS II: inadequate response to prior therapy [NCT00548405]). Patients continuing in an extension (NCT00930553) demonstrated durable 6-y efficacy; 27% (pooled CARE-MS I/II) received only one alemtuzumab retreatment (Course 3 [C3]) through Y6.

**Objectives:** Evaluate alemtuzumab retreatment efficacy in pooled CARE-MS I/II patients, who received C3.

**Material and methods:** Patients received 2 courses of alemtuzumab 12 mg/day (baseline: 5 days; Month 12: 3 days) in CARE-MS I/II, and could receive as-needed alemtuzumab retreatment (for relapse/MRI activity) or another DMT (investigator discretion) in the extension. Assessments: annualised relapse rate (ARR); mean EDSS change; improved/stable EDSS; 6-month confirmed disability improvement (CDI). Patients receiving > C3 or another DMT were excluded.

**Conclusions:** 3<sup>rd</sup> alemtuzumab course effectively reduced relapses and improved disability without further treatment. These data support administering C3 in patients with disease activity to achieve durable disease control.

## Serum levels of inflammatory cytokines after supplementation of vitamin D in patient with multiple sclerosis (MS) treated by interferon — $\beta$ (IFN $\beta$ )

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**Introduction:** In this study concerning IFN $\beta$  treated MS patients, the effect of vitamin D on the serum levels of inflammatory cytokines was evaluated.

**Materials and methods:** 33 IFN $\beta$  treated patients (age from 18 to 50) with relapsing-remitting MS, EDSS  $\leq$  4.0 were enrolled to the study. They received orally 1000 IU of vitamin D for 9 months. Serum concentrations of 25(OH)D, interleukin 10, 17a, TGF $\beta$  and IFN $\gamma$  were analysed before and after the supplementation of vitamin D.

**Results:** Under supplementation of vitamin D the increased level of 25(OH)D was noticed (relatively  $43.8 \pm 21.5$  before and  $106.7 \pm 41.1$  nmol/L after supplementation,  $p < 0.001$ ). Levels of anti-inflammatory cytokines TGF $\beta$  and IL10 measured at baseline (relatively  $75.2 \pm 23.1$ ,  $13 \pm 5.5$  pg/mL) in comparison to the results obtained after 9-month supplementation (relatively  $111 \pm 28.6$ ,  $17.5 \pm 5.6$  pg/mL) turned out significantly increased. In relation to the concentration of proinflammatory cytokine IL17a, a statistically significant difference was not observed when the results were compared before and after the supplementation of vitamin D ( $p = 0.3$ ). The levels of IFN $\gamma$  were increased (from  $3.35 \pm 6.2$  to  $4.51 \pm 7.1$  pg/mL relatively before and after supplementation) ( $p = 0.0005$ ).

**Conclusions:** Vitamin D application in dose of 1000 IU daily is sufficient to compensate vitamin D deficiency in MS patients. It is accompanied by the increased level in anti-inflammatory cytokines (IL10, TGF $\beta$ ). It may be assumed that the lack of endogenous IFN $\beta$  reduces the effect of vitamin D on IFN $\gamma$  production by T cells. Moreover, the increased level of IFN $\gamma$  in serum may result from a stable level of IL17a.

## Durable efficacy outcome improvements over six years in alemtuzumab-treated RRMS patients who relapsed between courses 1 and 2 (CARE-MS I)

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**Introduction:** In CARE-MS I (NCT00530348), 2 alemtuzumab courses (baseline: 5 days; Month 12: 3 days) improved efficacy outcomes vs SC IFNB-1a over 2 years in treatment-naive RRMS patients. Durable 6-year efficacy in the absence of continuous treatment was demonstrated in an extension (NCT00930553).

**Objectives:** Evaluate the 6-year alemtuzumab efficacy in CARE-MS I patients, who relapsed between Courses 1 and 2.

**Material and methods:** Assessments: annualised relapse rate (ARR); 6-month confirmed disability worsening (CDW) and disability improvement (CDI); MRI disease activity (gadolinium [Gd]-enhancing and new/enlarging T2 lesions); new T1 hypointense lesions; brain volume loss (BVL).

**Conclusions:** In patients, who relapsed between alemtuzumab Courses 1 and 2, clinical and MRI outcomes, including BVL measures, were favourable over six years. These data indicate that relapse after Course 1 is not indicative of subsequent limited treatment response and support administering the approved 2 alemtuzumab courses to achieve the optimal clinical benefit.

## Slowing of cortical gray matter atrophy with teriflunomide is associated with delayed conversion to clinically definite MS

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**Introduction:** In TOPIC (NCT00622700), teriflunomide significantly reduced risk of conversion to clinically definite MS (CDMS) vs placebo in patients with a first clinical episode suggestive of MS. Gray matter (GM) atrophy after a first clinical event is associated with conversion to CDMS and disability accumulation. Here, we explore the effect of cortical GM volume (CGMV) change on risk of conversion to CDMS in the TOPIC study.

**Material and methods:** Patients received placebo (n = 197) or teriflunomide 14 mg (n = 214) for ≤ 108 weeks. CGMV change was evaluated using the SIENAX-MTP (Structural Image Evaluation using Normalisation of Atrophy, Cross-sectional, multi-time-point) analysis. Data at Month (M)6, M12, M18, and M24, standardised for follow-up duration, were analysed relative to baseline. Statistical models were used to assess the treatment effects (nonparametric ANCOVA) and relationship of CGMV loss to CDMS conversion (Cox proportional hazards models).

**Results:** Teriflunomide 14 mg reduced CGMV change vs placebo by ≥40% (PP = 0.0052 for cumulative difference over two years). For every 1% decrease in CGMV, there was a 12.4% increased risk of conversion to CDMS at M12 (P = 0.0099), 14.2% at M18 (P = 0.0009), and 14.5% at M24 (P = 0.0005). Teriflunomide 14 mg also reduced risk of CDMS vs placebo: 46.3% (P = 0.0220) at M12, 42.1% (P = 0.0260) at M18, and 46.6% (P = 0.0085) at M24.

**Conclusions:** Consistent effects of teriflunomide on reducing CGMV loss, together with the correlation between conversion to CDMS and CGMV loss indicate how teriflunomide may favourably impact early inflammatory and neurodegenerative components of MS.

# NEUROIMMUNOLOGY

## Targeting key signaling factors as a way to control microglial activation and induction of neuroinflammation

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Neuroinflammation is co-occurring phenomenon during pathological processes in the nervous system. Key player in this process is microglia. As moderate activation of microglia is beneficial, excessive one however, leads to more severe degeneration of tissue and inhibition of its endogenous regeneration. One way to prevent this situation is to modulate or inhibit microglia activation. The aim of this study was to use gene silencing technique to influence microglial activation. By targeting key proteins — NF- $\kappa$ B, MyD-88 and TRIF, we intended to decrease inflammatory signaling network. Gene silencing was optimised on stable murine microglia BV-2 cell line. Before stimulation with lipopolysaccharide (LPS), the cells were transfected with designed siRNA sequences. Efficacy of transfection was assessed by evaluating expression of NF- $\kappa$ B, MyD-88, TRIF, as well as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , TREM1, TREM2 at mRNA and protein level. Optimised sequences of siRNA were then used on primary microglia. Our results showed that siRNA can successfully inhibit activation of microglia *in vitro* after stimulation with LPS. Significant decrease was observed in expression of signaling proteins. However, depending on targeted factor, different decrease patterns were observed for IL-1 $\beta$ , IL-6 and TNF- $\alpha$ . Thus, a mixture of siRNA was combined to achieve most successful effect. Our results provide a new method to successfully limit microglia activation with siRNA technique. This approach will be further used *in vivo*, in our models of Parkinson's disease and hypoxia-ischaemia encephalopathy, in which severe inflammation is observed.

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## Demyelinating disease during anti-tumour necrosis factor $\alpha$ therapy — case report

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Tumour necrosis factor alpha (TNF $\alpha$ ) is a cytokine that plays a key role in inflammatory response in various autoimmune diseases also in the central nervous system (CNS). This potent agent with pleiotropic actions can be present both as a transmembrane protein as well as soluble cytokine. Biological effects of both forms are mediated through interaction with receptors TNFR1 and TNFR2 with distinct functions. Multiple sclerosis (MS) is a chronic and progressive disease of the CNS with a complex aetiology. Its main pathological features include neuroinflammation, demyelination and axonal loss. There is a strong evidence of role of tumour necrosis factor alpha (TNF $\alpha$ ) in pathogenesis of the disease. Despite data suggesting that TNF- $\alpha$  intrinsically causes primary demyelination, apoptosis and neurological damage, previous attempts of treatment of MS with TNF $\alpha$  antagonists led to an increase of disease activity. Moreover, neurological adverse events have been reported among the patients which received anti-TNF $\alpha$  treatment for other autoimmune and inflammatory diseases. Here we present a case of patient suffering from rheumatoid arthritis treated with recombinant monoclonal human anti-TNF $\alpha$  antibody (adalimumab). During therapy, neurological symptoms developed suggestive of the CNS demyelination. Neurological deficits correlated with magnetic resonance imaging showing hyperintensities on T2-weighted images without gadolinium enhancement. Cerebro-spinal fluid analysis supported hypothesis of present neuroinflammation with positive oligoclonal bands, however with

normal IgG index. In this study we also discuss dualistic role of TNF $\alpha$  in the process of CNS myelin damage and repair with emphasis on different roles of TNFR1 and TNFR2.

## Stiff person syndrome as initial manifestation of systemic lupus erythaematosus: a case report

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**Introduction:** Stiff person syndrome (SPS) is a rare, but disabling neurological syndrome, associated with various autoimmune pathologies.

**Objectives:** This is a case-report of possible SPS, manifesting a year before the full-clinic of systemic lupus (SLE).

**Material and methods:** 67-year-old Caucasian female patient admitted to the clinic in February 2016 with acute gaze apraxia and unilateral blepharospasm. She had a history of hypertension and no autoimmune pathology. EMG showed periorbicular dystonia. MRI revealed vascular foci in the right frontal lobe. Symptoms regressed after few weeks. After 6 months the condition suddenly deteriorated. The patient had painful stiffness of her legs, and she was restricted to the wheelchair. EMG revealed dystonia of lower extremities. There was CRP elevation to 22 mg/l, CSF protein 0.56 g/l, positive ANA 1:100. Paraneoplastic antibodies were negative. There was no opportunity to test GAD-antibodies, but due to the suspicion of SPS, an immunotherapy was performed — methylprednisolone 500 mg IV, then per os intake from 32 mg. There was a dramatical improvement — the functions of lower extremities recovered completely. Her condition remained normal for a year. The exacerbation developed acutely in autumn 2017 after hyperinsolation with photodermatitis, legs rash, arthritis, heart failure, and painful legs stiffness. Carditis, atrial fibrillation, pneumonitis, nephritis, anaemia, ESR 60 mm/h, CRP 56 mg/L, ANA 1:320 were revealed. SLE was diagnosed based on SLICC criteria. The patient received methylprednisolone 24 mg, hydroxychloroquine 200 mg, gabapentin with positive somatic and neurological dynamics.

**Conclusions:** This case supports that SPS can outpace other symptoms of systemic autoimmune diseases.

## Haptenic diseases

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**Introduction:** This study was undertaken to verify the hypothesis on toxic interactions of humans through water-soluble antigens, also called haptens: A, B, H, Lea and Le, which are present in secretions and odour of the human body.

**Material and methods:** Subjects showing pathologic symptoms when inhaling the odour of some persons were studied. Knowledge of haptens, present in saliva, sweat, urine, milk and semen was obtained from contemporary scientific literature. The haptens were analysed in multiple sclerosis, epilepsy, depression, headache, sudden death and some other conditions. The study methods were modified and improved over time. The patients were visited in their environment. Blood and saliva samples were collected from the patients and persons staying often with them. The results served to determine persons interacting toxically through haptens. Altogether, 213 subjects were studied, including 83 patients with multiple sclerosis.

**Results:** The hypothesis on toxic interactions of humans through water-soluble antigens, called haptens: A, B, H, Lea and Le was explanatory in approximately 80% of cases of multiple sclerosis and other diseases.

**Conclusions:** On the basis of tests of blood and saliva it is possible to predict the onset and potency of human–human interactions caused by haptens. Multiple sclerosis and other neurological diseases can be foreseen, prevented, arrested in their progression, and causally treated by avoiding toxic haptens. The results of the present and similar studies deserve greater attention of physicians and scientists.

## Fungal infections: complication of immunosuppressive therapy of myasthenia gravis

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Myasthenia gravis is an agent-mediated autoimmune disease. In its most severe form, the life-threatening myasthenic crisis is accompanied by a respiratory failure. In addition to the symptomatic treatment with pyridostymin, immunosuppressive therapy using glucocorticosteroids and azathioprine is therapy of choice. The typical side effects of immunosuppressive therapy are infections, although very rare in their occurrence, particularly opportunistic infections are a severe, undiagnosed complication of the therapy of myasthenia gravis. A consistent risk management is necessary to prevent them.

## Neuroinflammatory markers in dementia with Lewy bodies and dementia in Parkinson's disease

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**Introduction:** Investigation of inflammation reactions in dementias of neurodegenerative genesis and detection of their biological markers are considered to be urgent. According to the current conceptions, Parkinson's disease with dementia (PDD) is a part of DLB spectrum.

**Objectives:** The aim of the study was to determine the values of peripheral markers of neuroinflammation in blood plasma of DLB and PDD patients compared to healthy controls.

**Material and methods:** Blood samples of 7 DLB patients ( $74,4 \pm 8,8$  years) and 10 PDD patients ( $73,6 \pm 7,6$  years). The patients were diagnosed according to DLB and PDD diagnostic criteria (Miller B.L., Boeve B.F. 2017; Budson A.E., Solomon P.R.B 2016). 42 healthy subjects of the same age were included in the control group. Enzymatic activity of leucocyte elastase (LE) and functional activity of  $\alpha$ 1-proteinase inhibitor ( $\alpha$ 1-PI) were determined by spectrophotometric method. Concentration of IL-6 and the level of AAB to neurospecific myelin basic protein (MBP) were measured by using immune-enzyme method.

**Results:** Significant increase in activity of  $\alpha$ 1-PI and IL-6 level in DLB and PDD compared to control ( $p = 0.0001$ ,  $p0.05$  resp.) was revealed, while LE activity and the level of AAB to MBP reduced ( $p = 0.01$ ,  $p0.01$  resp.).

**Conclusions:** The increase in the level of anti-inflammatory cytokines of the acute phase of inflammation in DLB and PDD confirms involvement of neuroinflammation in the pathogenesis. Reduction of LE activity may be due to decrease in degranulation activity of neutrophils. Identification of inflammatory markers will make it possible to improve reliability of diagnostics and laboratory monitoring of the disease progression.

## Implication of autoantibodies against lactosylceramide in a neuroinflammatory disorder, EMRN

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Previous studies have shown that encephalomyeloradiculoneuropathy (EMRN) involves both central and peripheral nervous systems. The detailed molecular mechanisms of this disorder, however, still remain to be elucidated. Our previous study has demonstrated that EMRN patients exhibit autoantibodies against neutral glycosphingolipids, especially lactosylceramide (LacCer) in the acute phase of the disease and these autoantibodies disappeared after extensive immunomodulatory therapies, suggesting these autoantibodies can be an excellent biomarker for EMRN (Neurology, 2014). Intriguingly, a recent report indicated that astrocytes in plaque lesions of MS model mice extensively produce LacCer and its content was significantly upregulated in the lesions of both mice model and MS patients (Nat Med, 2014). In the present study, with LC/MS/MS analyses of cerebrospinal fluid (CSF), we found statistically significant increase of LacCer levels in CSF from EMRN patients than neurologically free individuals. Moreover, anti-LacCer antibodies induced the upregulation of inflammatory cytokines mRNA expression from cultured astrocytes. These data strongly suggest the same story as recently reported by Grabowsky's group on Gaucher's disease also hold on EMRN, where they demonstrated that increased amount of glucosylceramide induced the production of autoantibodies against glucosylceramide and these autoantibodies in turn induce neuroinflammatory reactions (Nature, 2017). Thus, there should be some abnormalities in neutral glycosphingolipids metabolism, especially LacCer in EMRN patients and these abnormalities result in an alteration of the tuning in immune system of the patients, provoking neuroinflammatory reactions.

## Immune response against neural antigens and paraneoplastic neurological syndromes in endometrial cancer patients

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**Introduction:** The purpose of this study was to analyse the spectrum of paraneoplastic neurological syndromes and onconeural/antineural antibodies and antibodies against nucleoplasm in women with endometrial cancer and breast cancer.

**Materials and methods:** The study included 75 patients with endometrial cancer and 22 patients with breast cancer. Onconeural, antineural antibodies and antibodies against nucleoplasm in serum were assessed with the use of indirect immunofluorescence. Western blotting was performed as a confirmation test for the presence of onconeural antibodies in patients' sera.

**Results:** Antineural antibodies (12 patients, 16,1%) and antibodies against nucleoplasm (14 patients, 18,7%) were the most frequent. Onconeural antibodies were detected in two cases (2,6%). The neuropathy/polyneuropathy predominate in endometrial cancer patients. Autoantibodies were present in 16 patients with breast cancer and neurological symptoms. Sensory neuropathy and subacute cerebellar syndrome were the most frequent. The presence of antineural, onconeural or antibodies against nucleoplasm antigens did not depend on grading or staging of endometrial cancer. All antibodies were the most frequent among endometrial cancer patients with low grading (mainly in the course of endometrial adenocarcinoma). Neurological deficit is associated with low clinical stage and high grade.

**Conclusions:** The detection of antineural antibodies and anti-nucleosome antibodies in a woman with

peripheral nervous system deficit should be an indication for gynaecological neoplasm screening. In a patient with already diagnosed endometrial cancer and coexisting neuropathy/polyneuropathy, the detection of autoantibodies can be helpful in the decision on immunomodulating treatment.

## A case of localised variant of Guillain-Carré syndrome associated with IGM anti- $\beta$ 2-GPI antibodies

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Facial diplegia and paresthesias (FDP) is a rare localised subtype of Guillain-Barré Syndrome (GBS), which is characterised by simultaneous facial diplegia, distal paresthesias and minimal or no motor weakness. We report a patient who presented with simultaneous weakness of bilateral facial nerve and paresthesias. A 73-year-old man presented with acute bilateral facial palsy and paresthesias in distal extremities preceded by flu-like symptoms. Extensive investigations were performed to evaluate the cause of his symptoms. Nerve conduction study (NCS) of upper and lower limbs showed sensory-motor polyneuropathy, which was both axonal and demyelinating. In addition, facial NCS revealed absent of compound muscle and sensory nerve action potentials. Considering his clinical manifestation and relevant investigations, a diagnosis of FDP, a localised variant of GBS, was made. Interestingly, the patient was found to have serum IgM anti- $\beta$ 2-GPI antibodies, although other anti-ganglioside antibodies were all normal. Intravenous immunoglobulin was started at a dose of 0.4 g/kg/day for five days. After ten weeks of treatment, his facial diplegia improved with mild residual facial weakness. Anti- $\beta$ 2-GPI antibodies are the main antiphospholipid antibodies, along with anticardiolipin and lupus anticoagulant, that characterise the autoimmune disease antiphospholipid syndrome (APS). Although APS was known to be associated with a variety of neurological manifestations, including stroke, multiple sclerosis, and transverse myelitis, its association with GBS and variants of GBS was not well studied. We report a rare case of anti- $\beta$ 2-GPI antibody detected in a patient, who complied with the typical clinical features of FDP, a localised variant of GBS.

## Olfactory deficits in mice with experimental autoimmune encepharomyelitis, a model of human multiple sclerosis

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Olfactory deficits are commonly recognised in a variety of human neuro-inflammatory diseases, including multiple sclerosis (MS). The relationship between autoimmune CNS disease multiple sclerosis and olfactory deficits is under debate. To address this question in human MS, we induced experimental autoimmune encephalomyelitis (EAE) in mice, as an animal model of human MS, and compared the behavioural performance of food searching, and neuropathologically examined olfactory bulbs, which are one of central tissues of odour processing. Neuro-inflammatory lesions, including the infiltration of inflammatory cells and activation of glial cells were found in the olfactory bulbs of EAE-affected mice, as do in the spinal cords. Some inflammatory cells were found along the olfactory nerves and in the submucosa of olfactory mucosa. Analysis of differentially expressed genes revealed that olfaction related genes including olfactory marker protein were significantly down-regulated in the olfactory bulbs of EAE. Behaviourally, the searching time for a bait pellet was significantly delayed in EAE mice. These findings all together suggest that neuro-inflammation in the olfactory bulbs in EAE-mice would be related with olfactory deficits as far as mice EAE is concerned. This research was supported by the National Research Foundation of Korea.

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## OTHER

### Ultrasonography may be more valuable to localise ulnar nerve entrapment without conduction block in electrodiagnosis

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Ulnar neuropathy at the elbow (UNE) is thought to most often occur from compression of the nerve within the cubital tunnel. The sensitivity of electrodiagnosis for UNE is much lower than for median mononeuropathy at the wrist. The reasons for false-negative electrodiagnostic results are not always known, but may include improper elbow position and early or mild ulnar nerve involvement. Ultrasound (US) is an emerging tool for the evaluation of neuromuscular conditions. US findings in patients with UNE and no conduction block have been rarely reported. We describe electrodiagnosis and US findings in a 23-year-old man with pain and numbness in his left 4<sup>th</sup> and 5<sup>th</sup> fingers. There was no definite weakness. His symptoms had begun three months ago, when he exercised heavily for several months. Nerve conduction study (NCS) revealed reduced amplitude of left dorsal ulnar cutaneous nerve and distal ulnar sensory nerve without definite conduction block in inching study at the elbow. Electromyography showed mild denervation potentials in left adductor digiti minimi and first dorsal interossei muscle. US showed increased cross sectional area of ulnar nerve below the elbow. He received surgical treatment and his symptoms nearly fully recovered four months after surgery. This indicates that ultrasound may be a useful tool for assessing an entrapment site in UNE symptoms without exact localisation in electrodiagnosis.

### Polycythaemia vera a potential cause of spinal cord infarction — case report

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**Introduction:** Polycythaemia vera (PV) is a myeloproliferative disorder that results in an excess of RBC in the bloodstream, and thus increased blood viscosity and platelet activation, leading to an increased risk for vase-occlusive events. Spinal cord ischaemia is a very rare complication, considering the large anastomotic net of spinal cord blood vessels.

**Material and method:** A 62-year-old woman presented in the emergency room with complaints of proximal muscle weakness of the lower extremities with subacute onset, four weeks following a benign gastrointestinal illness. The deep tendon reflexes were absent and there was a level of sensibility T12, with urinary retention. A thoraco-lumbar MRI study performed in the first day of hospitalisation was unremarkable. Blood work showed a high RBC and haemoglobin levels. All the other blood laboratory tests and cerebrospinal fluid analysis, total body CT scan, were unremarkable. In the 6<sup>th</sup> day of hospitalisation the situation was complicated with DVT of the right leg. Two days after, the motor deficits worsened, and the patient became paraplegic. A repeated thoracolumbar MRI study revealed spinal cord the presence of acute infarction in T12-L4 levels. The bone marrow biopsy and myelogram confirmed the presence mutations in JAK2V617F blood test analysis, compatible with PV diagnosis.

**Conclusions:** Although this is a rare haematological disorder, PV should be considered when dealing with acute myelopathies or classical spinal cord syndromes. Physicians should be more alert on this possible disorder, which can be easily identified by a simple blood test analysis.

## Angioblastoma in the cervical segment of the spinal cord in a 50-year-old patient with peripheral symptoms — case report

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**Introduction:** CNS imaging examinations with the use of the electromagnetic field in patients with a cardiac pacemaker still generate controversies in Poland, though these examinations are routinely performed in the USA.

**Material and methods:** The report presents a 50-year-old female patient with an implanted cardiac pacemaker, with a 1-year history of aggravation of symptoms seemingly linked to peripheral nervous system injury. In accordance with procedures foreseen for CIED patients, an MRI was performed. The MRI revealed the presence of a tumour in the cervical region of the spinal cord — angioblastoma.

**Conclusions:** Angioblastoma is a rare, slowly growing benign tumour developing usually in the posterior cranial cavity and spinal cord. The patient's case shows what variable an array of symptoms and signs intraspinal changes angioblastoma can generate, what great a role MRI can play in the diagnostic procedure and in planning a surgical intervention, also in the growing number of CIED patients.

## Transverse myelitis as a first symptom of lupus erythaematosus

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**Introduction:** Lupus erythaematosus (SLE) represents the prototype of autoimmune diseases, and can lead to neurological manifestations. Transverse myelitis is a rare (1–2%) and severe complication of SLE and it usually appears in the later stages of this disease. Our patient presented transverse myelitis as a first symptom.

**Material and methods:** Our patient is a 29-year-old female, who, since childhood, presented photosensitivity. She was hospitalised for interstitial pneumonia and left pleural effusion. Soon after that, her left leg became warm, erythaematous, oedematous and painful. Two weeks later, she was paraplegic, with sensory impairment and urinary incontinence. On admittance in our neurological department she presented: paraplegia, lower limb reflexes were absent, superficial sensory impairment with T8–T9 level, urinary incontinence. Biological tests showed: mild anaemia, thrombocytopenia, inflammatory syndrome, nephritic syndrome, ANA and ANDdc antibodies were positive, C3 was low and the lupic anticoagulant factor was positive. Doppler echography presented ileofemoral thrombosis. A medullar MRI showed multiple hyperintense areas in T2-weighted sequences in the whole cervical and thoracic segment. We tested for infections (viral, bacterial and parasitic), tumours, other autoimmune diseases, EMG and cerebral MRI were performed and everything was within normal parameters. At this moment, we established the SLE diagnosis with secondary SAFL, and cortisone therapy was initiated. The patient mildly recovered: the sensory impairment and urinary incontinence were remitted and the motor deficit was ameliorated.

**Conclusions:** In conclusion, we cannot disregard SLE when confronted with a transverse myelitis just because this is a rare manifestation of the disease.

## BDNF level in vascular depression and the therapeutic role of Actovegin

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**Introduction:** The BDNF deficit in organic brain insufficiency and depression is actively discussed. The aim was to analyse the possibility of enhancing the outcome by Actovegin similar in some aspects of structure to BDNF.

**Material and methods:** 30 patients (age —  $71.6 \pm 3,9$  years) with vascular depression observed. Main group (n = 15) received antidepressants (SSRI) and Actovegin 400 mg in intravenous infusions daily for ten days followed by oral treatment 600 mg per day during three weeks. Control group (n = 15) received antidepressants only. Clinical data and BDNF concentration assessed at the beginning and on the 30<sup>th</sup> day. Cornell and CGI scale were used. Statistics included Fisher (F) and Mann-Whitney (U) tests.

**Results:** Significant improvement (assessed by CGI) noted in 65.7% of the main group compared to 44.1% in the controls (F = 2.4; p0.05). More prominent effect concerned feeling of sorrow, every-day activity, inhibition and diurnal variation of affect (p0,05). Median BDNF level among all patients increased from  $92,1 \pm 5,7$  to  $124,1 \pm 7,1$  (U = 135,8; p0,05). No statistical difference found in BDNF concentration between highlighted groups at both stages of the study.

**Conclusions:** Results of vascular depression therapy can be augmented by Actovegin. It is possibly related to neuroplasticity activation significant in depression (especially organic) regress. Underlying neurochemical mechanisms are complex and not only BDNF-dependent.

## A retrospective two-year analysis of the diagnosis of paraplegia made in the emergency room

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**Introduction:** The presenting of paraplegia in the emergency room is an occurrence of extreme severity. However, a consistent number of cases although treated as peripheral nervous system injuries, have another background diagnosis. Such a diagnosis might be difficult to clarify in the emergency conditions; however the medical first responders should bear in mind the diagnostic diversity.

**Material and methods:** We have controlled the admission files on the ER of “Mother Teresa” UHC of Tirana for 2015 and 2016 with the diagnosis “paraplegia”. Notes were made on the gender and age profile of the patients, with a special focus on the final (discharge) diagnosis.

**Results:** 88 cases (47 males) were registered during the year 2015 and 77 cases (38 males) during 2016 with admission diagnosis “paraplegia”. The gender profile was clearly in equilibrium; with the month of May registering the largest number of cases presenting with paraplegia for both consecutive years. A minority of cases (total 28/165) had a diagnosis of Guillain-Barré syndrome or myelitis. 41 cases represented a tumoural condition, with the majority of those having the characteristic of metastatic processes. Few cases were diagnosed during hospitalisation and treated duly as stroke-like occurrences.

**Conclusions:** In spite of the fact that paraplegia needs a careful diagnostic workup of the peripheral nervous system, remote causes should be hold in mind and included in the differential diagnoses. Several imaging and electrophysiological methods are available for ensuring a high accuracy, that cannot however be warranted always and simply in ER.

## Serum lactate and pyruvate in relation to clinical severity rate in paediatric facial nerve neuropathy

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The assessment of lactate and pyruvate in paediatric facial nerve neuropathy would be advisable, as these markers of hypoxia reflect changes in decrease of tissue oxygenation. Trials have demonstrated the prognostic value of lactate and pyruvate levels in many pathological conditions, including cystic fibrosis, acute bleeding and pancreatitis, intestinal obstruction, septic shock. The aim of the study was to find the correlation of lactate and pyruvate in children with facial nerve neuropathy with severity of the dysfunction of the “facial nerve — facial muscles” according to the House-Brackmann scale. The study involved 122 children with acute facial nerve neuropathy. According to the severity of the defeat of the “facial nerve — facial muscles” in 12 children (9.8%) was observed the 3<sup>rd</sup> degree, 97 children (79.5%) had the 4th degree and 13 children (10.7%) had 5th degree by House-Brackmann scale. We found a direct correlation between the severity of facial palsy and lactate level (Pearson’s coefficient + 0.35): the level of lactate in the blood of patients with facial nerve neuropathy at baseline was increased and most pronounced in case of 5th degree by House-Brackmann scale. In all patients with severe facial palsy was observed a significant reduction of pyruvate (Pearson’s coefficient + 0.82). Correlations between biochemical changes and clinical severity rate indicate a significant role of violation of redox processes in the dynamics of the disease and provide a suggestion that correction of redox processes can improve the outcomes of treatment.

## Neurological aspects in a case of amyloidosis transthyretin type variant Glu54Gln

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Transthyretin hereditary amyloidosis is a rare disease and, so far, this has considered limited to certain geographical areas. Recently, with the intensification of genetic screening possibilities, new cases, new mutation and endemic areas (e.g. the Balkan area in Europe) have been found — this shows that this disease is more widespread than was believed, so doctors need to be warned and think more often about this disease. We present the case of a 51-year-old male patient that had a sister, who died at the age of 49 from a cardiac disease and his mother died at the age of 50. The onset of his disease was in 2012 with diarrhea of unknown cause (rectum biopsy — Congo Red negative). Afterwards, in 2014, he presented paresthesias and muscle weakness in the lower limbs. In March 2016 he was admitted to the Neurology Clinic-Fundeni and the EMG established the diagnosis of sensorimotor axonal polyneuropathy. The patient was then admitted to the Haematology Clinic with peripheral oedema, painful lower limb paresthesias that progressed to knee-level, orthostatic hypotension, bowel disorders and cachexia. It was established to be familial amyloidosis transthyretin type (Glu54Gln) with systemic involvement: cardiac (restrictive cardiomyopathy), SNP (sensorimotor axonal polyneuropathy), SNV (orthostatic hypotension). Familial amyloidosis transthyretine type is an incurable disease, with a median survival of 7–10 years after the onset of symptoms. Liver transplantation is the standard therapy for eligible patients, because it stops the synthesis of the mutant TTR. Tafimidis and other transthyretin stabilisers are new agents, still under investigation.

## Posterior reversible encephalopathy syndrome in rapid progressive glomerulonephritis

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Posterior reversible encephalopathy syndrome (PRES) is a disease that developed reversible vasogenic oedema on brain. Although the pathophysiology of PRES is not fully understood, several clinical conditions are related with the development of PRES, for example renal failure, use of cytotoxic drugs or eclampsia, which associated with endothelial dysfunction. Here we report a case of PRES related with rapid progressive glomerulonephritis (RPGN), that associated with P-ANCA. A 66-year-old woman with history of P-ANCA related RPGN was consulted for generalised seizure. She admitted on nephrology because of AKI and was taking immunosuppressive agents. Brain MRI demonstrated high signal intensity, which suggested vasogenic oedema on T2 weighted image in both frontoparietal lobes, posterior temporal and occipital lobes and right cerebellum. EEG suggested diffuse cortical dysfunction. Follow up brain MRI revealed improved vasogenic oedema. PRES is a benign and reversible when the causative factor can be treatable. In this case, improvement of renal failure and discontinuation of immunosuppressive agents seem to have improved PRES.

## Brain atrophy correlates with optic nerve atrophy in LHON with MS-like disease — Harding's syndrome — case report

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**Introduction:** Leber's hereditary optic neuropathy (LHON) is maternally inherited mitochondrial optic nerve degeneration with bilateral optic atrophy that very rare is associated with multiple sclerosis-like disease.

**Objectives:** To report on an optic nerve atrophy coexist with severe brain atrophy in case of a young female with multiple sclerosis (MS-like) disease with LHON confirmed by genetic testing with m.117778GA mutation.

**Material and methods:** 22-year-old female experienced two episodes of right and left painless progressive decrease of visual acuity with subsequent bilateral profound optic nerve atrophy with pale discs on ophthalmoscopy and two recovered, steroid response exacerbation of numbness in right arm, left lower limb and weakness of lower limbs. Harding's syndrome was diagnosed by typical MS brain and thoracic spinal cord lesions, positive CSF with oligoclonal bands and m.117778GA mutation. Brain MRI after ten years of first symptoms (visual) appearing showed significant brain atrophy in addition to the patient's age and gender information estimated by percentile generation program of CorTechs Labs.

**Results:** Results showed advanced brain atrophy with loss whole and regional volume: whole brain and thalami volume in 1<sup>st</sup> percentile for age with lateral ventricles, inferior lateral ventricles and 3<sup>rd</sup> ventricle volume in 99<sup>th</sup> percentile. Cerebral white matter volume was in 61<sup>st</sup> percentile with high cerebral white hypointensities volume in 99<sup>th</sup> percentile.

**Conclusions:** Optic nerve atrophy correlates with advanced whole and regional brain atrophy in LHON with MS-like disease.

## Diagnostic pitfalls in Creutzfeldt-Jakob disease

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**Introduction:** Creutzfeldt-Jakob disease (CJD) is a very rare neurodegenerative disease of the brain. One of the main characteristics of CJD is the rapidly progressive dementia. The clinical tableau consists in: rapidly progressive dementia, myoclonic jerks and a variety of neurological abnormalities. The particularity of our case is the lack of dementia, which raised the difficulty level in establishing a diagnosis.

**Material and methods:** Our patient is a 55-year-old female who suddenly presented gait disturbance and left limb ataxia. She was hospitalised for what was supposed to be a stroke, performed a CT without any abnormalities. Almost immediately she developed myoclonic contractions on her left limb. We found: paraparesis, myoclonia on her left limbs, bilateral horizontal nystagmus, dysmetria, dysarthria and bilateral Noica sign and all her intellectual functions were preserved. The laboratory tests were normal, the cerebral MRI showed a hyperintensity in T2 and FLAIR -weighted images of the basal ganglia and right occipital cortex. The EEG was suggestive for CJD. The spinal fluid was positive for the "14-3-3" protein. At this point the diagnosis of CJD was established. The seizures gradually became generalised in spite of the maximal antiepileptic treatment. She became comatose due to this state, was intubated and died within two months since onset.

**Conclusions:** Till the moment on which our patient became comatose, she did not present any signs of dementia. We should not disregard the CJD diagnosis in the absence of cognitive impairment.

## Wernicke's encephalopathy in a young man as a complication of Crohn's disease — case report

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**Introduction:** Wernicke's encephalopathy (WE) is a medical emergency characterised by ataxia, confusion, nystagmus and ophthalmoplegia resulting from thiamine deficiency. Alcoholism is the common cause for this disease. WE may be present in the general population with a prevalence of around 2%.

**Material and methods:** A young patient (21 years old) was admitted to the Department of Neurology with the pertaining of balance disorders and double vision. The patient had suffered from Crohn's disease (CD) from childhood. A month before his admission to the hospital he had an increase in Crohn's disease activity. On admission to the department he presented ataxia of the lower limbs, horizontal and vertical nystagmus and memory loss. At the admission, the MRI of the brain scan result was normal. The EMG excluded polyneuropathy. Due to the suspicion of Miller-Fisher syndrome, he had triple plasmapheresis, but without any improvement. Memory loss symptoms exacerbated. The follow-up MRI revealed symmetric lesions involving bilateral tegmentum of the pons and periaqueductal area, mammillary bodies and the medial thalamus. The WE was suspected. Vitamin B1 was administered parenterally. After a week, the follow-up MRI was concluded with the lesions eliminated. Neurological symptoms were substantially reduced. By the end of the patient's stay in the department, deep vein thrombosis was observed and subsequently treated with anticoagulant therapy. On day five of the ongoing anticoagulant therapy, the patient suffered massive pulmonary embolism, which led to his death. Despite the rapid reversal of WE the patient died due to another complication of CD.

## Prevalence of diabetes sensory neuropathy by a questionnaire interview in a cohort of Taiwanese diabetes patients

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A cohort of 1403 Taiwanese diabetes patients were screened for diabetes sensory neuropathy by questionnaire interview based on 3 categories of abnormal sensation, i.e.: 1) numbness or tingling pain; 2) electric shock; and 3) skin thickness sensation. 7 sites on each upper limb (i.e., finger tips, finger, palm, dorsum of hand, wrist, lower arm and upper arm) and 6 sites on each lower limb (toe tips, toe, plantar surface of foot, dorsum of foot, lower leg and thigh) were recorded for the respective symptoms. At the beginning of the screening, the questionnaire did not discern the right and left sides (Cohort I, n = 680), but at a later time, the questionnaire was revised to separate the right and left sides (Cohort II, n = 723). Results showed that 47.9% of the patients in Cohort I and 59.6% in Cohort II had any one of the symptoms on any limb. The questionnaires with and without discerning the right and left sides were then combined together (i.e., combining Cohort I and Cohort II) and diabetes sensory neuropathy was defined by using different definitions. The prevalence of diabetes sensory neuropathy was 54.0% if it was defined as “any positive symptoms on one or more sites”. It was 41.7% if the definition was “any positive symptom on at least one site involving the lower limb”. In conclusion, Taiwanese diabetes patients may have a high prevalence of diabetes sensory neuropathy if a structured questionnaire is used for screening.

## Neuroimaging features of structural changes in the brain and their relationship with different forms of the cerebral palsy in children

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**Introduction:** Cerebral palsy (CP) is one of the most disabling diseases of childhood, but its pathogenesis is still controversial.

**Objectives:** To compare various forms of CP with location and type of brain lesions.

**Material and methods:** Under our supervision, there were 134 children (boys — 80, girls — 54) at the age 3–10 years with different forms of CP: 1<sup>st</sup> group with double hemiplegia — 55 patients (41.5%), 2<sup>nd</sup> group with spastic diplegia — 43 patients (32%), 3<sup>rd</sup> group with hemiparetic form — 21 patients (15.6%), 4<sup>th</sup> group with atonic-astatic form — 15 patients (11.1%).

**Results:** The following MRI abnormalities were detected: in the 1<sup>st</sup> group: cystic degeneration — 17 patients (12.6%); microcephaly — 6 patients (4.4%); polymicrogyria — 5 patients (3.7%), focal cortical dysplasia — 3 patients (2.2%). In the 2<sup>nd</sup> group periventricular leucomalacia was detected predominantly — 38 patients (28.3%). In the 3<sup>rd</sup> group haemiatrophy of the brain was detected in 6 cases (4.4%), cystic degeneration in 6 cases (4.4%), schizencephaly in 2 cases (1.49%) and pachygyria in 6 cases (4.4%). In the 4<sup>th</sup> group, cerebellar hypoplasia was revealed in 5 cases (3.7%) and in 4 children (2.9%) Dandy-Walker anomaly was detected. In 36 patients (26.9%) MRI did not reveal any detectable brain changes, despite the reliable diagnosis of CP.

**Conclusions:** Periventricular leucomalacia was the most frequent MRI abnormality and it was associated with a diplegic form of CP. Apparently, for each form of CP, there is the most vulnerable “critical” zone in the process of neuroontogenesis, which requires further investigation.

## Post-traumatic cervical dystonia in a patient with neurofibromatosis type 1

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A 6-year-old boy without any past medical history visited to our hospital, complaining of spasmodic torticollis. The symptom has come suddenly after he slipped down in bathroom. Although three months of treatment with soft collar apply and halter traction, the patient's symptom did not improve. On neurological examination, we could not find any focal neurological sign except spasmodic torticollis. Cervical spine x-ray and computed tomography scans revealed atlantoaxial rotatory subluxation. MRI of the cervical spine demonstrated extensive intramedullary hyperintensities without enhancement at the C1–C4 levels on sagittal T2-weighted image. Cerebrospinal fluid analysis was within normal range and anti-aquaporin-4 antibody test was also negative. Brain MRI demonstrated multifocal hyperintensities in the bilateral basal ganglia and left cerebellar peduncle on T2-weighted and fluid-attenuated inversion recovery images, suggesting neurofibromatosis-associated multiple gliomas. The patient has 7 cafe-au-lait spots on his abdomen, back, and hip. In addition, NF1 gene mutation was found by genetic testing. Any abnormality or trauma of the cervical spine can present with spasmodic torticollis. Trauma, including minor trauma (sprains/strains), fractures, dislocations, and subluxations, often result in spasms of cervical musculature. It has been known that most cases of post-traumatic cervical dystonia are self-limited, and symptoms resolve in 1–2 weeks. However, our patient's symptom lasted more than three months without improvement. We assume that not only minor trauma, but also NF contributed to the development of acute cervical dystonia in this case, since pathologic and neuroradiologic studies revealed focal lesions involving the basal ganglia, suggesting a pathogenic mechanism of focal dystonia.

## Changing vertical nystagmus in the opposite direction: is the transition from upbeat to downbeat nystagmus a diagnostic clue for Wernicke's encephalopathy?

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**Introduction:** Changes of vertical nystagmus in the opposite direction are very rarely reported. This study aimed to report an unusual case of Wernicke's encephalopathy (WE) presenting with a transition from upbeat nystagmus (UN) to downbeat nystagmus (DN) and to investigate the clinical pattern of changing vertical nystagmus in the opposite direction reported in the literature.

**Material and methods:** We present a WE patient with primary position UN that changed to DN with an upward or horizontal lateral gaze. Additionally, we review previously reported cases and analyse the clinical patterns of changing vertical nystagmus in the opposite direction.

**Results:** Among ten cases, including our case, the most common type of changing vertical nystagmus in the opposite direction was a transition from UN to DN (n = 9, 90%). The most common diagnosis was WE, which is accompanied by changes in vertical nystagmus from UN to DN (n = 6, 60%). The most commonly associated neuro-radiological localisations for the changing of vertical nystagmus were the brainstem and the cerebellum.

**Conclusions:** The results of this clinical investigation may provide support for the diagnosis of WE. In addition, if young or middle-aged patients exhibit transitions from UN to DN with brainstem or cerebellar signs, a diagnosis of WE should be considered. Furthermore, clonazepam and thiamine might be helpful for improving nystagmus symptoms.

# PARKINSON'S DISEASES AND OTHER MOVEMENT DISORDERS

## Frequency and associations of Tardive Dyskinesia in a cohort of patients with chronic mental disorders in North West Ireland

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**Introduction:** Tardive dyskinesia (TD) is a form of abnormal involuntary muscle movements. TD is an antipsychotics medication-induced movement disorder that can be developed after long-term use, reduction, or discontinuation of antipsychotics. It affects the social functioning of patients and their compliance with treatment.

**Objectives:** The aim was to evaluate TD in a cohort of patients with Chronic Mental Illness (Schizophrenia, Schizoaffective or Bipolar) who are in a long time on antipsychotic medications.

**Material and methods:** Consecutive patients attending outpatient clinics. Data were collected regarding demographics, diagnosis, medications and the abnormal movements were evaluated with the Abnormal Involuntary Movement Scale (AIMS).

**Results:** A 122 participants, mean age 55.03 (SD: 12.74), 74 (60.7%) males. 88 (73%) had a diagnosis in the F20 ICD-10 category, 27 (22.1%) in F30 and 6 (4.9%) in others. A new generation antipsychotic was prescribed in 100 (82%) and an old one in 22 (18%), 36 (29.5%) had 2 antipsychotics and the rest were on monotherapy. AIMS was 0 on 59 (48.4%) participants while 63 (51.6%) had identified with TD. TD was significantly more often to those with more than one antipsychotic and to those who taken the old ones ( $t = 3.055$ ,  $df:120$ ,  $p = 0.003$ ,  $x^2 = 25.136$ ,  $df:1$ ,  $p = 0.001$  respectively). Significantly more likely to develop TD those on Zuclopenthixol, Risperdal, Fluphenazine and Flupenthixol and less likely those on Olanzapine and Amisulpride ( $x^2 = 43.802$ ,  $df:9$ ,  $p = 0.001$ ).

**Conclusions:** It was expected that new generation antipsychotics are less likely to cause TD, but in long term some of them can still cause TD.

## Parkinson's disease: network analysis of publications' activity

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Work of any researcher involves a continuous need to obtain information on research topics over the world. It is important to understand what has already been done and what is most relevant in the research thematic area. Such kind of information can be obtained using huge knowledge bases, however, new approaches to their analysis are required. The presented models of network analysis of publications on various aspects of Parkinson's disease allow to reveal the links between research clusters, rank its importance and track changes. Recently developed network analysis algorithms, including new centrality indices have been applied for publications databases on different aspects of Parkinson's disease. Articles with keywords "Parkinson's disease" were analysed. Data were taken from Web of Science publications database and consist of more than 75 000 articles dated from 1980 to 2017. Networks of publications are modeled as graphs, where the nodes are identification numbers

(and other information, which can be received from the database), and the edges of the graph carry the information about the citations between them. New approaches and methods of centrality analysis are used to identify pivotal works. The key advantage of these approaches with comparison to existing methods is that we consider long-distance connections as well as special attributes of papers and group influence on them. This allows to detect hidden key publications: while classical measures detect explicit powerful works, our methods also detect works that influence other papers in groups.

## **Newly diagnosed extrapyramidal and movement disorders in Croatia throughout eleven years (2006–2016)**

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Movement disorders collectively affect approximately ten million people in Europe, Parkinson's disease, essential tremor and primary dystonia being the three most common of these. They are considered to affect primarily older generation, although there are cases across all age groups. We intended to analyse the number of newly discovered cases of extrapyramidal and movement disorders in Croatia by age groups since 2006 to 2016. Thus we conducted a research of Croatian health statistics yearbook editions since 2006 to 2016. The ICD-10 version codes G20–G26 were taken into consideration. The population was distributed in four groups so as to be comparable to GBD; group 1 (0–6 yr.), group 2 (7–19 yr.), group 3 (20–64 yr.), group 4 (65+ yr.). Since 2006 to 2016 the total of newly discovered cases of extrapyramidal and movement disorders was 186 309, with an average of 16 937 cases for each year. When distributed across age groups, the greatest trend of increase in incidence can be seen in group 4 (65+ yr.), the least increasing trend is shown by the group 1 (0–6 yr.). The other two groups (2 and 3) also show a steady increase of new cases. The findings of this research are in correlation with other developed countries, and European yearbooks.

## 27-hydroxycholesterol increases $\alpha$ -synuclein protein levels through proteasomal inhibition in human dopaminergic neurons

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Accumulation of the  $\alpha$ -synuclein ( $\alpha$ -syn) protein is a hallmark of a group of brain disorders collectively known as synucleinopathies. The mechanisms responsible for  $\alpha$ -syn accumulation are not well understood. Several studies suggest a link between synucleinopathies and the cholesterol metabolite 27-hydroxycholesterol (27-OHC). 27-OHC is the major cholesterol metabolite in the blood that crosses the blood-brain barrier, and its levels can increase following hypercholesterolaemia, aging, and oxidative stress, which are all factors for increased synucleinopathy risk. In this study, we determined the extent to which 27-OHC regulates  $\alpha$ -syn levels in human dopaminergic neurons, the cell type in which  $\alpha$ -syn accumulates in PD, a major synucleinopathy disorder. Our results show that 27-OHC significantly increases the protein levels, not the mRNA expression of  $\alpha$ -syn. The effects of 27-OHC appear to be independent of an action through liver X receptors (LXR), its cognate receptors, as the LXR agonist, GW3965, or the LXR antagonist ECHS did not affect  $\alpha$ -syn protein or mRNA levels. Furthermore, our data strongly suggest that the 27-OHC-induced increase in  $\alpha$ -syn protein levels emanates from inhibition of the proteasomal degradation of this protein and a decrease in the heat shock protein 70 (HSP70). Identifying 27-OHC as a factor that can increase  $\alpha$ -syn levels and the inhibition of the proteasomal function and reduction in HSP70 levels as potential cellular mechanisms involved in regulation of  $\alpha$ -syn. This may help in targeting the correct degradation of  $\alpha$ -syn as a potential avenue to preclude  $\alpha$ -syn accumulation.

## Metabolism of lipids in Parkinson's disease

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Studies of recent years show the possibility of hyper- and hypocholesterolaemia effects on both development and progression of Parkinson's disease (PD). The mechanism of lipid effects remains insufficiently studied, but recent researches point to a tendency towards a decrease in lipid metabolism in patients with PD. The purpose of this study was to evaluate the association of the lipid spectrum with the clinical features of the PD. Two hundred and fifty-five patients with PD were examined. The control group was 30 healthy people. The mean level of total cholesterol (TC) in the control group was  $5.4 \pm 1.2$  mmol/L, triglycerides (TG) was  $1.7 \pm 0.8$  mmol/L. Patients with PD showed a tendency to decrease these data in comparison with the control group (PD stage 1: TC —  $5.2 \pm 1.1$  mmol/L, TG —  $1.0 \pm 0.2$  mmol/L; PD stage 1.5: TC —  $5.0 \pm 1.1$  mmol/L, TG —  $1.2 \pm 0.4$  mmol/L; PD stage 2: TC —  $5.1 \pm 1.0$  mmol/L, TG —  $1.5 \pm 0.6$  mmol/L, PD stage 2.5: TC —  $4.9 \pm 0.9$  mmol/L, TG —  $1.0 \pm 0.2$  mmol/L). More pronounced changes were observed at stages 3 and 4 of the disease. The level of TC in patients with disease stage 3 significantly decreased compared with the control group to  $4.5 \pm 0.8$  mmol/L, TG to  $0.9 \pm 0.3$  mmol/L ( $p < 0.05$ ), in patients with PD stage 4 TC decreased to  $4.5 \pm 0.8$  mmol/L, TG to  $0.9 \pm 0.3$  mmol/L ( $p < 0.05$ ). Thus, we confirmed the hypothesis of a decrease in lipid metabolism in patients with PD and it was shown, that in more severe stages hypocholesterolaemia increases.

## Changing the game for treating Parkinson's disease dementia

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Ceftriaxone (CEF) has long been used as antibiotic and has recently been shown to increase expression of glutamate transporter-1. Glutamatergic hyper-activity is involved in neuronal loss in Parkinson's disease (PD). By treating PD rats with CEF, we demonstrated that CEF improve motor and cognitive functions. In addition, our histological, electrical, and MRI data showed that CEF increases neuronal density and activity in the hippocampus and dopaminergic system. Interestingly, elevation of neurogenesis in the above areas was also observed. Moreover, receiving CEF treatment, PD patient earned motor, emotion, cognitive, and neuronal benefits. Except dopamine agonist, for example, L-dopa, treatment effect being not satisfied, there is a lack of medicine for treating PD. Our data support that CEF may has potential for effectively treating dementia in PD.

**Keywords:** Parkinson's disease, dementia, glutamate

## Patient with Essential Palatal Tremor and coexisting bipolar disorder successfully treated with botulinum toxin injection — case report

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**Introduction:** Palatal tremor is an abnormal movement of the soft palate, classified into two subtypes, “symptomatic form”, and an “essential form”. There is a small, but growing body of evidence suggesting that botulinum toxin may be useful for treatment of depression.

**Material and method:** F. M. 30 years-old-male, complained of click sounds in both ears and abnormal movements in palate; 3 years later — psychiatric symptoms — diagnosed as bipolar disorder. At our Movement Disorder Clinic — MRI Brain done to exclude secondary causes — diagnosed as “Essential Palatal Tremor” (EPT). A total of 11 U of BoTX type A was injected (on each side) in the tensor veli palatini muscle without any local anaesthetic. Follow-up — decreased severity and frequency of palatal tremor and click sound in the ear. Patient developed nasal tonation and nasal regurgitation, but no dysphagia; 6 weeks later — marked improvement with no bulbar symptoms.

**Discussion:** At present no specific treatment has been established, although successful treatment by botulinum has recently been reported. BoTX injection showed antidepressant effect both when used as an ancillary treatment and by itself. BoTX treatment of the face can impact on mood and affect. There has been no known aetiological correlation between EPT and bipolar disorder. The rarity of palatal tremor and its coexistence with bipolar mood disorder with psychotic features, resulted in misdiagnosis of the sound as an auditory hallucination. Thus, injection of BoTX not only improved palatal tremor but also improved comorbid psychiatric disorder.

## Anodal transcranial direct current stimulation prevents methyl-4-phenyl-1,2,3,6-tetrahydropyridine induced neurotoxicity as a *in vivo* mouse model of Parkinson's disease through autophagy modulation

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**Introduction:** Parkinson's disease (PD) is a neurodegenerative disorder characterised by accumulation of protein inclusions and loss of dopaminergic neurons. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that has demonstrated promising results in clinical studies of PD. Despite accumulating evidence have proved the protective effect of tDCS, the mechanism of action is still unknown. Autophagy is thought to be one of the important mechanism in the development of PD, and recent studies have demonstrated dysregulation of the autophagy pathway in the PD patients and animal PD models. In the present study, we firstly investigated the neuroprotective effect of tDCS in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced PD mouse model, and then evaluated the effect of tDCS on autophagy pathway.

**Material and methods:** Mice were stimulated for consecutive five days with MPTP treatment. After observation of behavioural alteration using Rota-rod test, mice were sacrificed for the measurement of the PD and autophagy-related protein levels in substantia nigra.

**Results:** tDCS improved the behavioural alteration and tyrosine hydroxylase protein level and suppressed  $\alpha$ -synuclein protein level in MPTP-treated mice. MPTP-treated mice with tDCS also decreased the level of autophagy-related protein, such as microtubule-associated protein 1 light chain 3 and AMP-activated protein kinase and increased the level of mechanistic target of rapamycin and p62. In addition, the protein level of phosphoinositide 3-kinase and brain derived neurotrophic factor were enhanced and unc-51-like kinase 1 was suppressed by tDCS in MPTP-treated mice.

**Conclusions:** Our findings suggested that tDCS protects against MPTP-induced PD mouse model through modulation of autophagy.

## Can miglustat halt the progression of Niemann-Pick disease type C?

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Miglustat has been known the only medical treatment to improve or halt the neurological symptoms in Niemann-Pick type C (NP-C). The efficacy of miglustat was evaluated for the first two Korean patients. Case 1 developed delusion and abnormal posturing on both hands at the age of 18. All symptoms were gradually aggravated. At 24, he became completely dependent on caregivers and wheelchair bound. Case 2 was the younger sister of case 1. Her symptoms began with dystonia in the right hand at 19 years old and were milder than her brother. Both patients were evaluated for dystonia and ataxia using the Dystonia Movement Scale (DMS, maximum score 120) and Scale for the assessment and rating of ataxia (SARA, maximum score 37) before and 18 months after the administration of miglustat. 600 mg of miglustat a day was given to both patients. The baseline scores of DMS were 74 and 29 for case 1 and 2, respectively. They changed to 96 and 27 after the administration of miglustat for 18 months. The baseline scores of SARA were 26.5 and 13. They changed to 39 and 14. After miglustat therapy, case 1 worsened for both dystonia and ataxia. However, case 2 demonstrated stabilisation of her symptoms. Our results show that miglustat treatment can halt the disease progression at least for a period of time in the early stage of the illness. The earlier detection of the condition seemed to be important for the better efficacy of miglustat in NP-C.

## Fatigue in idiopathic Parkinson's disease: clinical characteristics and risk factors

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**Introduction:** Fatigue is a common nonmotor symptom in patients with Parkinson's disease (PD). Although it develops in every stage of PD and has a major impact on quality of life, fatigue is not fully studied.

**Objectives:** The purpose of this study was to elucidate the characteristics and risk factors of fatigue in PD.

**Material and methods:** We studied 148 patients at an average of 3.6 years after the diagnosis of PD. The presence of fatigue was assessed using Parkinson Fatigue scale. A cut-off point of 3.3 was used for diagnosis of fatigue. The presence of other nonmotor symptoms, including depression, was also identified. The relationship among demographic characteristics, clinical features and fatigue was evaluated.

**Results:** Fatigue was observed in 99 patients (66.9%). In univariate analysis, diabetes, history of stroke, disease duration, Hoehn-Yahr stage, presence of depression and constipation were significantly associated with fatigue. Multivariate analyses showed that history of stroke ( $P = 0.044$ , OR 2.35) and presence of depression ( $P = 0.012$ , OR = 2.88) were independent factors related to fatigue.

**Conclusions:** Fatigue is a fairly common nonmotor symptom in patients with PD. The presence of depression is the most important factor related to fatigue, followed by history of stroke. Strategies to improve the fatigue should be individualised according to the associated factors.

## A qualitative assessment of dynamic balance reactions in patients with Parkinson's disease

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**Introduction:** To evaluate balance disorders in Parkinson's Disease (PD) many tools can be used, however the majority of them does not take into account the dynamic balance reactions (DBR). The aim of this study was a qualitative assessment of DBR in patients with PD, thus authors proposed two functional tests.

**Materials and methods:** A study group consisted of 19 PD patients was compared to a control group — 19 healthy subjects. In this study new methods — a trial on a balance platform (rocker board) and a reach-to-side test (RST) — were proposed and compared to the Activities-Specific Balance Confidence (ABC) Scale. Study on the balance platform assessed postural control mechanisms in a standing position; RST completed this evaluation in sitting.

**Results:** In the test on the balance platform, the average results achieved by the study group (55%) was statistically significantly different ( $p < 0.05$ ) than in the control group (91.25%). In RST, the average result in the study group was 62.5%, whereas in the control group was 87.5%. In both functional tests, the correct order of DBR in PD patients was significantly less frequent ( $p < 0.05$ ). Comparing the average results of functional tests with ABC scale there is no statistically significant correlation.

**Conclusions:** The ABC scale provides information about the patient's subjective assessment, which is not always confirmed during motor tasks. It can be concluded that this scale is only good complement for motor tests. Both proposed methods are based on simple instruments and could be used in every consulting room.

## Autosomal dominant spinocerebellar ataxia type 40 caused by mutations in the **CCDC88C** gene — report of the first European family

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Autosomal dominant spinocerebellar ataxias form a group of clinically and genetically diverse disorders. There has been only one report of the spinocerebellar ataxia 40 in a Chinese family. We identify four-generation Polish family with tremor, cerebellar ataxia, Parkinsonism and dementia history. The proband is a 59-year-old man with a 10-year history of asymmetric upper limb tremor as a prevailing symptom. Neurological examination also indicates negligible: ataxia, dysidiadochokinesia, bradykinesia, hyperreflexia and mild cognition function impairment. MRI of the proband's brain is normal. The whole exome sequencing analysis was done in four individuals of this family, including three affected and one unaffected. The mutations in genes associated with Parkinson's disease and Wilson's disease were not confirmed. The genes associated with tremor and ataxia were analysed. The analysis revealed missense mutation in the **CCDC88C** gene. Bioinformatic analysis shows that the Asp43Asn mutation of **CCDC88C** is pathogenic. Cosegregation analysis was done and the mutation cosegregates with the phenotype. Referring to OMIM database, this mutation is related with SCA 40.

## Encephalitis lethargica syndrome: clinical features and management of two cases

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**Introduction:** Lethargic encephalitis (LE) (Economo's disease) — enigma of 20<sup>th</sup> century, caused pandemic observed from 1915 to 1927, since then occurs sporadically. Despite numerous researches, so far true nature (virus) of LE is unknown. Autoimmune nature of LE with lesions in basal ganglia and subthalamic area was revealed in many researches. Acute oculolethargic form of LE is mostly known. Postencephalitic Parkinsonism and other extrapyramidal forms (choreoathetosis) are mostly often in chronic LE.

**Material and methods:** We observed two patients (25-year-old male and 31-year-old female) with subacute onset with moderate infectious symptoms, pharyngalgia, followed by diplopia and hypersomnia. Gradually focal neurological symptoms, disturbances of the endocrine and autonomic functions appeared. In first case, this were hemiparkinsonism corresponded with focal subcortical lesions on MRI, moderate lymphocytic pleocytosis, suddenly formed sweating, obesity and priapism. In second case after pharyngalgias, subfebrile fever and acute diplopia, hypersomnia, cachexia and choreoathetosis appeared. CSF analysis revealed mild inflammatory changes. Focal encephalitis in deep brain structures was confirmed on MRI. Screening investigations did not find actual viral infections. Pathogenetic role of *S. aureus* was established in both cases.

**Results:** After etiotropic, immunosuppressive and neuroprotective treatment both patients noted significant improvement.

**Conclusions:** Oculolethargic syndrome appeared after bacterial infection, focal lesions of deep brain structures, inflammatory changes in CSF followed by extrapyramidal disturbances; improvement after complex therapy permit us to make conclusion of LE- syndrome autoimmune nature induced by *S. aureus*.

## Glucose transporter type 1 (GLUT-1) Deficiency Syndrome — delayed diagnosis and treatment — case report

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Glucose transporter type 1 deficiency syndrome (GLUT1-DS) is a treatable metabolic disorder caused by a mutation in SLC2A1 gene. The most severe classic phenotype comprises infantile-onset epileptic encephalopathy associated with delayed development, acquired microcephaly, motor coordination disturbances, and spasticity. There are also observed the less severe clinical features, associated with paroxysmal exercise-induced dystonia with or without epileptic seizures. We describe the woman, who was diagnosed as epileptic patient and treated for years with different antiepileptic drugs with no clinical effect. She had the only two generalised tonic clonic seizures in her life. Instead of them, she suffered from increasing frequency of the paroxysmal involuntary movements of lower limbs, leading to gait disturbances and falls, which were wrongly diagnosed as epileptic seizures, too. The jerks of the head and limbs were observed for the first months of her life. The symptoms were provoked by stress and exertion. Additionally, slight mental retardation was observed during her growth. Due to similarity of seizures symptomatology, as well as paroxysmal dystonic movements, related to them status epilepticus and dystonic status, clinical differentiation may be difficult. The lumbar puncture was performed, then low glucose concentrations in cerebrospinal fluid was set. The results of genetic tests revealed the missense mutation of protein p.Arg333Trp, and confirmed the diagnosis of GLUT-1-DS1 syndrome. Delayed diagnosis caused the great problems with acceptance of the ketogenic diet, which is suggested as the treatment of choice in GLUT-1 deficiency syndrome.

## De novo ADCY5 mutation in patient who showed early onset dystonia and paroxysmal choreoathetosis in Korea

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**Introduction:** Adenylyl cyclase 5 (ADCY5) mutations are associated with heterogenous hyperkinetic movement disorders: familial dyskinesia, paroxysmal chorea and dystonia; autosomal-dominant chorea and dystonia; and benign hereditary chorea. We observed a patient, who identified ADCY5 mutation for the first time in Korea.

**Material and methods:** This 20-year-old man presented motor milestone delaying since nine month of age. He had difficulty in sitting, grab and standing, and walking difficulty in his 17 month of age. Psychomotor development was normal. The plasma amino acid, urine organic acid, X-ray and brain magnetic resonance image (MRI) was checked, but specific findings did not observed. At 2-year-old age, he had difficulty in supporting his neck, and he maintained head dropped posture. He had no pre- and postpartum injury, but diagnosed athetoid cerebral palsy at that time. He was hospitalised for comprehensive rehabilitation at the age of 20 years and cooperated with neurologist. Neurological examination confirmed axial hypotonia (neck) and mild dystonic posture of the four limbs. Gait is unsteady or nearly impossible because of the head drop. He showed hyperreflexia and episodic, paroxysmal choreoathetosis during sleep and when he fall asleep. The laboratory tests, EEG, EP, cognition test and follow up brain MRI were normal. De novo ADCY5 gene mutation (c.2088+1GT) was found by trio exome sequencing, and he was treated with clonazepam and clobazam.

**Conclusions:** ADCY5 genetic analyses may be relevant in the diagnostic workup of early-onset dystonia and hyperkinetic movement disorders.

## Doctor, researcher or a friend?

**T. Rogalski**

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Journey on the other side of the mirror — is it worth to endure the hardships of traveling through “terra incognita” to limit the destructive influence of stereotypes? I was taken by PD Travel Agency for a package tour as I was diagnosed with Parkinson’s disease eight years ago. An educated patient can help neurologists if they are equipped to allow it. This is an invitation to discuss on how to effectively do doctor–patient communication while we are out on our journey. Patient, through a long travel with Mr. PD, had to get to know his habits and whims, as well as the increasingly rude behaviour of this stowaway passenger. How can they recognise what is just a symptoms fluctuation of disease, and what is a real response to medications? Do patients understand well what the neurologist recommended to them? Do they have the inner conviction about the implementation of the recommended strategy, and are aware of the limitations and expected effects? What a patient can do to select relevant information to report changes in an efficient manner and not omitting important information about their state? Clinical trial procedures define individual roles and responsibilities, like in a theater script. Is it enough for each of team members to learn how to play our roles in order to ensure reliable results? If you are ready to accept an invitation to a discussion, we might find something beneficial to everyone involved. Let me put you in a PD patient shoes.

## COPPADIS-2015: an ongoing global Parkinson’s disease project about disease progression with more than 700 patients included. Preliminary results of baseline evaluations

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**Introduction:** To describe preliminary results of baseline evaluations of a Spanish ongoing global Parkinson’s disease (PD) Project, COPPADIS-2015 (Cohort of Patient’s with Parkinson’s Disease in Spain, 2015).

**Material and methods:** Observational, descriptive, non-interventional, 5-year follow-up, national (Spain), multicenter, evaluation study (Santos-Garcia D et al. BMC Neurol, 2016). PD patients, principal caregivers and controls will be assessed in detail during follow-up. Here, we presented general preliminary results about baseline visits.

**Results:** A total of 717 PD patients (59.8% males;  $62.8 \pm 9$  years old), 302 caregivers and 209 controls (49.5% males;  $61.2 \pm 8.5$  years old) were included in the study between January, 2016 and October, 2017. The mean disease duration was  $5.5 \pm 4.4$  years. Hoehn and Yahr stage was 1 or 2 in 88.9% (Unified Parkinson's Disease Rating Scale-part III  $22.7 \pm 11.5$ ) of the patients, while 28.1% and 17.5% of them presented with motor fluctuations and dyskinesias, respectively. Mean Non-Motor Symptoms Scale (NMSS) total score was  $45.5 \pm 38$  and 25.9% of the patients presented cognitive impairment, 14.1% major depression, 19.8% impulse control disorder and 56.5% pain. Compared to the control group, PD patients presented a significant higher burden of non-motor symptoms and a worse quality of life. More than 340 subjects have undergone complementary studies (serum biomarkers, genetic and neuroimaging) so far.

**Conclusions:** COPPADIS-2015 would have to provide important knowledge about PD progression. Currently, we have extensive information about the baseline visits (cross-sectional study), that will be analysed in detail in the short-term future.

## Neuromodulatory role of subthalamic nucleus deep brain stimulation (STN-DBS) in Parkinson's disease (PD) patients

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**Introduction:** STN-DBS has been claimed to change progression symptoms in animal models of PD, but there are lacking information about the possible neuromodulatory role of STN-DBS in humans.

**Objectives:** The aim of the study was to evaluate the impact of STN-DBS on the motor disabilities and cognitive alterations in PD patients in comparison to Medical-Therapy-only (MED) and Post-Operative-Patient (POP) groups.

**Material and methods:** DBS-group consisted of 20 PD patients (7F, 13M) who underwent bilateral STN-DBS. POP-group consisted of 15 post-DBS PD patients (6F, 9M) in median 24 month-time after surgery. Control group (MED-group) consisted of 24 patients (13F, 11M). UPDRS III scale and RS (reflexive saccades) parameters (latency, amplitude, duration, peak of velocity) were measured during three visits in  $9 \pm 3$ -months periods (V1, V2, V3) in total OFF phase. Cognitive assessment was performed during each visit in ON phase.

**Results:** The comparable UPDRS III OFF gain in V3/V2/V1 visits ( $p < 0.05$ ) in both MED-group and POP-group was observed. UPDRS III OFF results in DBS-group revealed significant UPDRS III OFF worsening in V2/V1 DBS-group visits ( $p < 0.05$ ) with no UPDRS III OFF change in V3/V2 DBS-group visit. Similar general relations were observed in the increase of RS latencies in V2 compared to V1 DBS-group ( $p < 0.05$ ), but no change in the latency was observed in V3/V2 DBS-group and V3/V2/V1 visits in MED-group and POP-group. Cognitive assessment revealed significant V3/V1 changes between DBS-group and MED-group in verbal fluency tests ( $p < 0.05$ ).

**Conclusions:** The impact of STN-DBS on UPDRS III OFF, RS latency and cognitive changes can suggest its neuromodulative role, mainly during first 6–12 months after surgery.

## Levodopa: prescription errors in the use of antiparkinsonian drugs

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**Introduction:** The introduction of levodopa (LD) in 1960 revolutionised the management of Parkinson's disease (PD). As it is a drug with few indications (PD, dystonia, and other movement disorders), it facilitates identification of associated prescription mistakes, which are frequent in general practice. No study has analysed levodopa prescription errors, but drug warning letters have been reported since 1971.

**Material and methods:** A cross-sectional study was conducted using de-identified administrative data of two Colombian Health Maintenance Organisations (HMO). 4 306 042 subjects were included from a 2 year period (2014–2015). To identify PD patients, a filter using ICD-10 (G20X,G258,G259,F023) and levodopa ATC codes (N04BA01,N04BA02,N04BA03) was applied. All subjects with at least one code were included. A descriptive analysis of the drug prescription relevance was carried out.

**Results:** 4 952 PD patients were included. The age median was 72 years (IQR: 62–80). Ninety point thirty-three per cent of the sample were 50 years or older. Three thousand six hundred and twenty-seven subjects had Levodopa prescription, of these 58.7% had at least one inclusion diagnosis associated and 0.77% had dystonia (ICD-10:G24). These prescriptions were considered “adequate”. 692 patients (13.79%) with levodopa, but without ICD-10 code diagnosis were considered as “inadequately prescribed”. The most common diagnoses associated with levodopa misprescription were: non-specific diagnosis (ICD-10: R688, R69, Z) 64.60%, hypertension 10.84%, other neurological disorders 9.54%. Formulation errors were more frequent in women (15.7% vs 13.44%) and patients younger than 50 years (50.24% vs 18.03%), 4 pregnant patients were misprescribed instead of methyl dopa.

**Conclusions:** A high proportion of patients receive levodopa without having an adequate ICD-10 diagnosis that justifies the prescription.

## Immobilisation test as an assessment of the treatment effectiveness in patients with restless legs syndrome on the basis of diabetic polyneuropathy

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**Introduction:** Restless legs syndrome (RLS) is characterised by unpleasant sensations and motor disturbances in the lower extremities. The aim of the study was to examine the efficacy of pramipexole in patients with RLS on the basis of diabetic polyneuropathy (DPN) with the use of immobilisation test (IT).

**Material and methods:** The study involved 76 patients with type 2 diabetes mellitus complicated with DPN. In 19 (25%) patients RLS was found. All patients received the standard therapy of DPN and pramipexole 0.750 mg once a day and were examined with IT before and 30 days after treatment.

**Results:** The following data received: on the basis of treatment average movement index (MI) decreased from  $47.2 \pm 1.5$  to  $19.6 \pm 1.2$  ( $p = 0.04$ ). After the treatment, decrease in the number of PLM (-72%) was noted more in the first 30 minutes of the test, as opposed to the last 30 minutes (-28%). Treatment with pramipexole increased the average interval between movements in seconds ( $p = 0,035$ ). According to the MI, two (10.4%) patients had a mild form of RLS, four (21.1%) patients — severe and 13 (68.5%) patients — moderate form of RLS. After 30 days of therapy, 6 (31.5%) patients had mild, 9 (47.4%) — moderate stage of RLS, in 4 (21.1%) patients number of PLM was less than 10 per 1 hour.

**Conclusions:** Our research showed the efficacy of pramipexole in patients with RLS on the basis of DPN, which was proven by IT, as a reliable and probable test for determining the severity of RLS and the response to treatment.

## Ghrelin reduces A-type potassium channels in nigral dopaminergic neurons via PKC but not PKA pathway

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**Introduction:** The excitability of dopaminergic neurons in the substantia nigra pars compacta (SNc), that supplies the striatum with dopamine, determines the function of nigrostriatal system for motor coordination. Our previous studies showed that the brain-gut peptide ghrelin could enhance pacemaker firing of nigral dopaminergic neurons by inhibiting voltage-gated potassium Kv7/KCNQ/M-channels. However, whether the other potassium channels are also involved in the ghrelin-induced excitability of dopaminergic neurons still remains unclear. In this study, we focus on A-type potassium channels ( $I_A$ ), which has a wide expression on dopaminergic neurons and play a key role in pacemaker control.

**Material and methods:** Brain slices of the SNc were prepared from C57BL/6 mice of postnatal 15–20 days. The effects of ghrelin on discharge frequency and IA current of dopaminergic neurons were observed by whole cell patch clamp technique.

**Results:** Ghrelin (100 nM) can significantly increase the discharge frequency of dopaminergic neurons and inhibit the amplitude of IA current. Application of either PKA selective inhibitor H89 or PKC inhibitor GF109203X alone had no effect on IA; However, GF109203X abolished ghrelin-induced inhibition of IA. In addition, GF109203X and the IA specific blocker 4-AP could occlude the excitatory effects of ghrelin.

**Conclusions:** These results demonstrated that inhibition of IA may contribute to the ghrelin-induced excitation of dopaminergic neurons. Ghrelin reduces IA by activation of PKC but not PKA pathway.

## Lactoferrin shows protective effects in a MPTP-induced mouse model of Parkinson's disease

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**Introduction:** Lactoferrin (Lf), and the lactoferrin receptor (Lfr), regulate cell membrane iron transport, are synthesised in the brain by activated microglia, and their expression is increased in dopaminergic neurons in Parkinson's disease (PD). We investigated the effects of iron-free Lf (apo-Lf) and iron-saturated Lf (holo-Lf) in a mouse model of PD and hypothesised that Lf protects against PD through altered iron metabolism.

**Material and methods:** We examined the effect of daily intragastric doses of apo-Lf and holo-Lf for 7 days in an experimental 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine(MPTP)-induced mouse model of PD.

**Results:** Apo-Lf and holo-Lf antagonised MPTP-induced symptoms including shortening pole climbing time, reducing weight loss, preventing tyrosine hydroxylase immunoreactive (TH-ir) neuron loss in the substantianigra (SN), and restoring dopamine in the striatum. Lf increased SOD1 and Bcl-2 expression, and decreased cleaved caspase-3 expression in the SN. Lf treatment down-regulated iron import protein divalent metal transporter (DMT1) and up-regulated iron export protein ferroportin1 (FPN1) normalising MPTP-induced accumulation of nigral iron. Lf alleviated MPTP-induced increases

in serum iron and ferritin, and decreased serum TIBC, spleen weight, and spleen iron content. Liver iron routine blood test remained unchanged.

**Conclusions:** Apo-Lf and holo-Lf have a protective effect against MPTP-induced PD, with apo-Lf showing greater efficacy. Therefore, Lf is a new potential treatment for PD. More importantly, we put forward a hypothesis that spleen weight loss and lower spleen iron levels might be the original source of iron overload in SN.

## Comparison of gait parameters between drug-naïve patients with multiple system atrophy with predominant parkinsonism and Parkinson's disease

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Even though more gait symptoms present from early stage in the patients with multiple system atrophy with predominant parkinsonism (MSA-P) compared to those with Parkinson's disease (PD), the gait patterns of MSA-P were not clearly elucidated yet. We enrolled drug-naïve 34 PD patients and 26 MSA-P patients at the Movement Disorders Clinic, Samsung Medical Center. Parkinsonism was evaluated with Unified Parkinson's disease rating scale (UPDRS) part III and cognition with mini-mental status exam (MMSE). All enrolled subjects underwent DIERS Pedoscan and GAITRite to measure postural instability and gait. We compared the results of posturography and gait analysis between MSA-P and PD patients, and performed correlation analysis with UPDRS part III and MMSE scores. Although there was no difference in demographic and clinical variables between two groups, MSA-P patients showed larger total anterior-posterior and lateral movement of center of pressure (COP) than PD patients. In terms of gait analysis, MSA-P group had slower velocity, decreased step/stride length, and increased base compared with PD patients. In correlation analysis, MMSE score was correlated with step/stride length and single/double support time in PD patients after controlling age, sex, height, body weight, education year, disease duration, and UPDRS part III score. Even from early stage, MSA-P patients demonstrated more involvement of postural instability and gait disturbance compared with PD patients. Particularly, because of more severe postural instability in MSA-P patients, MSA-P patients showed larger movement of COP and wide base during gait than PD patients.

# REHABILITATION

## Nucleo CMP forte in the treatment of patients with radiculopathy: clinical and neurophysiologic studies

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**Introduction:** Nucleo CMP forte, which is an external source of pyrimidine nucleotides (PN) necessary for reparation of a nerve tissue, is widely used in the treatment of peripheral neuropathy, in particular, vertebrogenic radiculopathies (VR). Purpose: to study the effects of Nucleo CMP forte for patients with VR.

**Material and methods:** 60 patients were involved in the study. They were divided into two groups. The patients in the first group (40 persons) received interference therapy (IT) with intramuscular injection of Nucleo CMP forte during 15 days, afterwards they received capsules of the same medicine orally (twice in a day each time one capsule) for one month period. The patients in the second group (20 persons) were treated with IT for 15 days. Neurophysiologic studies were conducted before, on the 15th day and at the end of the treatment. Neurophysiologic studies included evaluation of impulse conduction velocity (ICVeff) and the parameters of F-wave on motor fibers of peripheral nerves, ICVaff on sural nerve, also, amplitudes of motor and sensory responses.

**Results:** As a result of the treatment, no statistically significant changes were observed in the indicators of M-response and sensory responses were not found. In the group, which received Nucleo CMP forte, significant increase of ICVeff was observed on motor fibers of fibular and tibial nerves ( $p < 0,05$  and  $p < 0,01$ ), also ICVaff on sural nerves by the end of the second step of the treatment.

**Conclusions:** The use of Nucleo CMP forte with IT contributes to the improvement of neurophysiologic indicators of peripheral nerves.

## Protective effect of agomelatine on traumatic brain injury induced cognitive deficit in rats: possible role of neurotransmitters

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Traumatic brain injury (TBI) is the leading cause of death and disability among children and young adults worldwide. These patients often have short and long term cognitive, behavioural and emotional impairments. The 5-HT<sub>2C</sub> and melatonin receptors are known to have involvement in memory functions. The aim of the present study is to find the beneficial effect of agomelatine (selective 5HT<sub>2C</sub> antagonist and melatonin receptor agonist) against weight drop induced traumatic brain injury in rats. The weight-drop model closely mimics the real life TBI. The injury was induced by dropping a weight of 450 gm from a height of one metre through a hollow metallic tube onto the exposed skull of rats under anaesthesia. After 14 days of TBI, the agomelatine (10, 20, and 40 mg/kg p.o. daily) treatment was given for next 14 days (i.e. till 28th day). The cognitive impairment was observed in Morris water maze (from 24<sup>th</sup> to 28<sup>th</sup> day) and novel object recognition (on 27<sup>th</sup> and 28<sup>th</sup> day) test. Immediately after behavioural parameters animals were sacrificed and hippocampus and cortex were isolated for biochemical (LPO, nitrite, GSH, AChE), neuroinflammatory (TNF- $\alpha$ , IL-1 $\beta$ , IL-6) and neurochemical (serotonin, DA, NA and their metabolites) estimation. The weight drop model significantly induced

memory impairment in TBI rats that has been assessed by Morris water maze and object recognition task. A significant rise in acetylcholinesterase activity, neuroinflammatory markers, oxidative stress (lipid peroxidation and nitrite, GSH) was found in both cortex and hippocampal regions of traumatised rat brain, while agomelatine treated rats has been shown to reverse the injury effects and significant increase in serotonin, dopamine and norepinephrine levels in TBI rat brain. Agomelatine has shown to possess memory-enhancing effects, that might be due to involvement of MT1/MT2 and 5-HT<sub>2C</sub> receptors. Hence agomelatine represents a promising new neuroprotective drug for cognitive enhancing effects.

## Cognitive interventions and cognitive training in adults with HIV: a state of the science

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**Introduction:** Combination antiretroviral therapies hinder HIV viral replication, allowing people to age with HIV. With over 50% of adults with HIV over 50+, this challenges the concept of successful neurocognitive aging. Unfortunately, over 50% of HIV+ adults experience HIV-Associated Neurocognitive Disorder ranging from milder forms (i.e., Asymptomatic Neurocognitive Impairment or Mild Neurocognitive Disorder) to a more severe form (i.e., HIV-Associated Dementia). Yet, even such milder neurocognitive impairments can interfere with financial and medication management, driving, and other instrumental activities of daily living that impact quality of life and survival. As this clinical population continues to age well into late adulthood, these milder forms of neurocognitive impairment may be accelerated or accentuated resulting in more severe neurocognitive and functional loss.

**Objectives:** Researchers and clinicians need to identify medical and lifestyle factors that facilitate positive and negative neuroplasticity in this population in order to promote cognitive reserve.

**Material and methods:** In an ongoing review of the literature, factors that promote positive neuroplasticity include good sleep hygiene, physical exercise, good nutrition, social engagement, and cognitive stimulation. Factors that promote negative neuroplasticity include comorbidities (i.e., diabetes, cardiovascular disease), substance abuse, trauma and stress, social isolation, and loneliness. In this presentation, current research to improve positive neuroplasticity in older adults with HIV emphasises the use of computerised speed of processing, transcranial direct current stimulation, and their combined use.

**Conclusions:** Emerging insights from the first large longitudinal study (The Think Fast Study) investigating a cognitive training protocol in older adults (40+) with HIV are provided as an exemplar.

# SLEEP

## A case of restless legs syndrome in patient with neurogenic sciatic nerve tumour

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Restless legs syndrome (RLS) is chronic neurological disorder, in which the primary symptoms is unpleasant and disturbing sensation accompanied by urge to move in multiple body parts, especially in legs. RLS may present in distinct phenotypes, often described as “primary” vs “secondary”. Secondary RLS can arise from aetiologies such as iron deficiency, pregnancy, peripheral neuropathy, and end-stage renal disease. We report a rare case of RLS associated with neurogenic tumour of the sciatic nerve. A 72-year-old man complained of recurrent and worsening RLS symptoms in his right lower extremity, despite medical treatment. The patient showed no signs of any neurological deficit. Interestingly, we found a nodular lesion (about 2.2 cm in diameter) at the right greater sciatic notch region on hip magnetic resonance imaging (MRI). Even if patients fulfill with the diagnostic criteria for typical RLS, if the progression is different from typical course and the secondary cause is not completely excluded, extensive work-up including MRI may be required to confirm the structural lesion of lower limbs. We report a rare case of secondary RLS, which is thought to be neurogenic tumour invasion of sciatic nerve.

# STROKE

## Diagnostic of rare form of acute stroke (venous stroke) in early postpartum period

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**Objectives:** To improve the diagnosis and treatment of acute stroke in women in the early postpartum as a rare, but possible cause of maternal mortality and disability.

**Material and methods:** Observation, diagnosis and treatment of two cases of acute stroke rare form — a venous stroke (VS) as a thrombosis of Trolard vein (the frequency is 0.1% to 3–5%) in women in early postpartum. In our observations postpartum women, delivered by CS under general anaesthesia, complained only of general weakness and diffuse unexpressed headache during first hours of disease. After 5 hours, the 27-year-old (G1P1) postpartum woman had a nausea, vomiting, numbness of the hand. After examination of neurologist, CT neuroimaging was performed, and patient was transferred to the stroke unit with a diagnosis of haemorrhagic transformation of ischaemic stroke. In the second case, the 32-year-old (G1P1) postpartum woman continued to stay in the obstetric hospital for another 24 hours. After generalised convulsive attack, with suspicion of acute viral encephalitis (according to the conclusion of CT), she was transferred to the neurological department.

**Conclusions:** In both cases there were a late referral to neurologist, which is most likely due to vagueness of clinical symptoms of the disease. Women of young age with risk factors for hypercoagulation are at risk. VS causes difficulties in diagnosis due to prevalence of general symptoms over local manifestation. Haemorrhagic transformation and development of epilepsy are frequent complications of VS. Given these facts and the early postpartum period, anticoagulant therapy should be discussed.

## Spinal cord infarction or acute myelitis? Fibrocartilaginous embolisation as a rare cause of spinal cord infarction

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Fibrocartilaginous embolisation (FCE) is an extremely rare cause of spinal cord infarction, however it should be considered in a diagnostic process. The mechanism results from the expulsion of fibrocartilaginous nucleus pulposus material to the vessels that supply the spinal cord. We would like to present two cases of spinal cord infarction. The 1<sup>st</sup> patient with a hemiparesis and lesion in dorsal spinal cord at C4 level in magnetic resonance and second one with tetraparesis due to anterior spinal artery occlusion with typical owl's eye sign in magnetic resonance. In both cases, the features of discopathy at level of lesions in spinal cord were described. Both of patients developed symptoms after hard physical work and had only one risk factor of stroke. During diagnostic process, we excluded central nervous system infection, demyelinating diseases, autoimmune diseases and other spinal cord inflammation. Clinically suspected FCE was recognised in our patients mostly based on the exclusion of other diseases mimicking transverse myelitis of the spinal cord and presence of a disc disease. Based on the diagnostic process of our patients we would like to propose the containing criteria that increase the probability of FCE.

## Nuclear abnormalities as a manifestation of mitotic instability of vascular myocytes in cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL)

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**Introduction:** Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a stroke and dementia syndrome with degeneration and loss of vascular smooth muscle cells (VSMC). The disease is associated with mutations in the *NOTCH3* gene playing a role in VSMC differentiation, proliferation and apoptosis. Since one of the possible pathomechanism of CADASIL may involve alterations in cell proliferation that are governed by the activity of the Notch-3 receptor-signaling pathway, to verify that hypothesis we performed morphological studies of VSMC.

**Material and methods:** In autopsy and skin-muscle biopsy material of patients with CADASIL diagnosis, assessment of VSMC in arterial vessels at the level of light and electron microscopy was performed. Proliferative activity of VSMC was evaluated in immune reactions to proliferative markers: PCNA, and cyclins B1 and D.

**Results:** In CADASIL, a part of VSMC revealed abnormal nuclear morphology. The affected myocytes showed variability in nuclear size, irregularity in nuclear shape, and abnormal chromatin appearance. Frequently, double nuclei of equal size or micronuclei were observed. Sometimes, even multinucleated myocytes were found. In some VSMC nuclei, the immune reactions to PCNA and studied cyclins were positive.

**Conclusions:** Aberrant structure and number of VSMC nuclei, as well as their immunoreactivity to proliferative markers suggest mitotic instability of vascular myocytes in CADASIL. Mutated *NOTCH 3* gene, which is unable to control properly VSMC proliferation, may be responsible for their premature or inappropriate entry of into mitosis, irreversible arrest of the cell cycle, senescence or degeneration and loss.

## Clinical correlates of post-stroke apathy

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Post-stroke emotional disorders are widely discussed during the recent decade, but the post-stroke apathy remains the least studied among them. One hundred and forty-seven patients in the early recovery period of first-ever atherothrombotic anterior circulation ischaemic stroke and 30 healthy individuals (control group [CG]) were examined. Neuropsychological examination of cognitive and emotional status, sonography of extra- and intracranial vessels and non-parametric data analysis (Statistica 8.0) were used. The mean apathy level in Starkstein Apathy Scale (SAS) score was 12 (9; 16) compared to 5 (4; 7) in CG (p0.05); patients with right-hemispheric stroke (RHS) manifested significantly higher SAS score of 13 (11; 19) (p0.05) compared to 10 (9; 13) in patients with left-hemispheric stroke (LHS). Comorbidity of apathy and depression was observed in 14.9% of RHS patients and exceeded the LHS indices (2.5%) (p0.05). SAS score correlated with the degree of stroke severity on the Scandinavian Stroke Scale (r = -0.34; p = 0.027), cognitive functioning on MMSE (r = -0.34; p = 0.048), FAB (r = -0.49; p = 0.036) and MoCA (r = -0.41; p = 0.0068), and the depression severity according to HADS (r = 0.61; p0.001) and ZSDS (r = 0.6; p0.001). Increase of SAS score was also associated with ipsilateral internal carotid artery stenosis (r = 0.32; p = 0.027) and decrease of peak velocity in the middle

cerebral artery ( $r = -0.31$ ;  $p = 0.036$ ). These results allow suggesting that patients after RHS are more predisposed to post-stroke apathy. At the same time, apathy was associated with cognitive dysfunction, that may be a result of some common links of underlying pathogenesis chain of these neuropsychological syndromes.

## Insufficient physical activity among population of Azerbaijan

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**Introduction:** Lack of physical activity has clearly been shown to be a risk factor for stroke. Less active and less fit people have a greater risk of developing high blood pressure.

**Material and methods:** In the offered article by means of International Physical Activity Questionnaire it was studied prevalence of insufficient physical activity among 40–49 years old population of the Guba-Khachmas economic region of Azerbaijan Republic during 2008–2010. In the study participated 1821 persons (3% of 40–49 years old population). From them 1164 (575 women, 589 men) lived in rural settlements, 657 (348 women, 309 men) in the city. Also, we studied other most common stroke risk factors among these persons.

**Results:** Among risk factors, an insufficient physical activity met more often —  $37.3 \pm 1.1\%$ . It was revealed, that men ( $68.0 \pm 1.9\%$ ) conduct more physically an active way of life, than women ( $57.5 \pm 1.6\%$ ). The country people conduct an active way of life ( $76.4 \pm 1.3\%$ ) on comparison with city ( $38.5 \pm 1.9\%$ ).

**Conclusions:** The prevalence of insufficient physical activity increases according to the level of income. High income countries had more than double the prevalence compared to low income countries for both men and women, with 41% of men and 48% of women being insufficiently physically active in high income countries as compared to 18% of men and 21% of women in low income countries. In conclusion we found, that on average, in Guba-Khachmaz region the prevalence of insufficient physical activity in Azerbaijan falls at the middle level in comparison with other countries.

## Post-stroke care systems — comparison of organisation, changes and tendencies in Poland and New Zealand

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**Introduction:** Stroke is a major health problem worldwide. Stroke mortality steadily declines in developed countries with the development of specialised units and early diagnosis and interventions. However, people who survived a stroke often have significant morbidity and live with the effects of the stroke. Patients need access to effective rehabilitation services that aim to enhance quality of life by improvement of participation in society and functional activities.

**Material and methods:** Authors compared structure and accessibility of stroke services in two health systems (Poland and New Zealand) in the light of current guidelines. The available statistical data were compared including trends over last five years in prevention, morbidity and mortality.

**Conclusions:** Prevention, early diagnosis, early treatment and effective, widely accessible rehabilitation are crucial to improve chances of surviving and recovering from stroke. Different medical systems offer similar approaches and similar trends are observed over last 5 years. New Zealand experience

shows that further improvement in outcomes for stroke patients depends on developing increased awareness of prevention (minimising risk factors) and engaging all services, including primary care and non-governmental organisations.

## Case of Hashimoto's encephalopathy under mask of another diagnosis

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**Introduction:** Demonstration of the importance of “orphan alertness” in everyday medical practice in the diagnosis of orphan diseases. In recent years, the frequency of diagnosis of Hashimoto's encephalopathy had begun to increase due to awareness of doctors.

**Material and methods:** Under our supervision was the female of 1986 birth. From the anamnesis it was known that during the last few years she had repeated ischaemic strokes with good clinical recovery. She was treated in three clinics in Ukraine and in one clinic in Germany with the diagnosis: “antiphospholipid syndrome”, but in Germany this diagnosis was with a question mark.

**Results:** As a result of our in-depth study of anamnestic data, it was found that the patient during recent years had been treated by endocrinologist with diagnosis: “autoimmune thyroiditis”, her levels of antibodies to thyroperoxidase had been increased from hundreds of times at the onset of the disease till ten times at the time of our assessment. The levels of thyroid hormones were within normal limits and so that the treatment of autoimmune thyroiditis had been stopped by endocrinologist. As a result of detailed study of medical records and exclusion of other possible diagnoses had been diagnosed Hashimoto's encephalopathy.

**Conclusions:** 1. In the everyday medical practice there should be “orphan alertness” for the timely diagnosis of orphan diseases, which often masked under other diagnoses. 2. There should be closer cooperation between specialists for diagnosis of rare diseases.

## An unusual case of stroke in young adult after motor vehicle accident without evidence of dissection

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Isolated midbrain infarctions in young adults are rare and poorly studied. Blunt cerebrovascular injuries with cerebrovascular dissection have been identified as a cause of stroke after trauma in young adults. Little is known about the aetiology of stroke following blunt cerebrovascular injury when dissection is not discovered. We report an isolated stroke in the posterior midbrain of a young woman following motor vehicle accident with unclear aetiology. A 28-year-old previously healthy female presented to the hospital after low-speed motor vehicle accident. She was evaluated and released. She returned to hospital hours later with acute onset the decreased visual acuity in right eye with dilated pupil and painless paresthesias on the right half of her tongue. On physical exam, associated decreased superior and inferior gaze, and decreased adduction were noted. CTA of the neck and repeat CT head were unremarkable. MRI/MRA of the brain was significant for subacute right posterior midbrain infarct and axonal injury with intact anterior and posterior circulation. Extensive blood work up did not reveal any abnormalities. Midbrain cerebrovascular accidents in young patients in the absence of dissection are rare. There is a correlation between blunt head trauma leading to dissection, which can cause stroke. In the presented case, there was no evidence of dissection, following blunt trauma. Identification of cerebrovascular dissection following blunt head trauma is important as anti-coagulation

has been shown to be beneficial in this setting. Cerebral infarction in the setting of blunt trauma may not always be due to vessel dissection.

## Clinical and radiological factors associated with unfavourable outcome after intravenous thrombolysis in patients with mild ischaemic stroke

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**Introduction:** A significant proportion of patients with mild ischaemic stroke become disabled despite receiving intravenous thrombolytic therapy. The purpose of this study was to assess factors associated with unfavourable outcomes in patients with minor ischaemic stroke that received intravenous recombinant tissue plasminogen activator (rt-PA) therapy.

**Material and methods:** We identified anterior circulation stroke patients with initial NIHSS scores  $\leq 5$  who received intravenous thrombolysis within 4.5 hours of stroke onset and had pretreatment magnetic resonance (MR)/MR angiography using our prospective stroke database. Logistic regression was used to determine independent predictors of unfavourable outcomes.

**Results:** Among 121 patients (85 men; mean age,  $63.4 \pm 11.3$  years) included in this study, 46 (38%) had unfavourable outcomes at 90 days and diffusion-weighted imaging (DWI) lesion patterns showing infarction in the deep middle cerebral artery (MCA) territory involving the perforating artery area was observed in 47 (38.8%) patients. On multivariable analysis, unfavourable outcomes at 90 days were associated with diabetes (odds ratio [OR], 3.41; 95% confidence interval [CI], 1.06–10.9;  $P = 0.039$ ), NIHSS score on admission (OR, 2.11; 95% CI, 1.35–3.30;  $P = 0.001$ ), and infarction in the deep MCA territory on DWI (OR, 4.19; 95% CI, 1.63–10.8;  $P = 0.003$ ). Lesions in the deep MCA territory was independently associated with early neurological deterioration ( $P = 0.032$ ). The patients without deep MCA territory infarction had a higher prevalence of cardiac embolism ( $P = 0.009$ ).

**Conclusions:** Higher NIHSS scores, diabetes, and deep MCA territory infarction may be useful for predicting unfavourable outcomes in patients with minor stroke treated with intravenous rt-PA therapy.

## The number of endovascular thrombectomy attempt is related to clinical outcomes in large artery occlusion in patients with acute ischaemic stroke

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**Introduction:** It is not well known how many attempts for recanalisation it would be advisable. We evaluated the relationship of the number of EVT attempt and clinical outcome.

**Materials and methods:** Patients who treated with EVT for large artery occlusion in anterior circulation and within 24 hours from last seen normal time were included. Age, sex, comorbidities, admission NIHSS score, modified Thrombolysis in Cerebral Ischaemia score, time intervals from the puncture to recanalisation, number of EVT attempt and three months modified Rankin Scale score were analysed.

**Results:** 207 patients receiving EVT for AIS in January 2012 to September 2017 were included. Successful recanalisation was achieved in 156 (75.3%) after EVT. As the number of EVT attempt increased, the rate of favourable outcome (mRS 0–2) was significantly lowered. The clinical outcome of patients with one to three EVT attempt was more favourable than patients without successful recanalisation, the clinical outcome of patients with more than four EVT attempt was not better.

**Conclusions:** This study showed that an increased number of EVT attempt to achieve a good recanalisation is related with worse outcomes. Even though successful recanalisation is necessary to have good clinical outcomes, more than four EVT attempt could be futile.

## Anxiety traits as predictor of stroke in general population in Russia/Siberia: gender features. WHO program MONICA-psychosocial study

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**Introduction:** To evaluate the influence of personal anxiety on risk stroke in general population of Russia/Siberia.

**Material and methods:** In frame of the third screening WHO programme “MONICA-psychosocial” a random representative sample of the population aged 25–64 in Novosibirsk in 1994 (men n = 657, women n = 870) was surveyed. The programme included: registration of socio-demographic data; personal anxiety was studied with Spielberger test. Over 16-year period, cases of stroke incidence in women and men were identified (35 and 22, respectively). Cox regression model was used for relative risk assessment (HR).

**Results:** Over 16 years, the risk of stroke in women with high anxiety level (HLA) was 3.5-fold higher compared to those with lower anxiety levels. HR was 4.43-fold higher in men. After adjustment for age and social parameters, HR risk of stroke was 3.5 and 3.2-fold higher for women and men with HLA, respectively. The greatest risk of stroke in presence of high anxiety was in divorced (HR = 5.017) and widowed men (HR = 3.848), aged 55–64 years (HR = 5.8).

**Conclusions:** Anxiety is the most potent psychosocial risk factor for stroke in general population. The risk of stroke was higher in men over 16-years period in spite attenuated associations after adjustment.

## Implication of calpain-mediated beta-secretase up-regulation for neurodegeneration in the postischaemic basal ganglia

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Brain hypoperfusion may be related to the development of Alzheimer’s disease (AD), which was shown in some neocortex studies. However, the basal ganglia, such as putamen, caudate nucleus and thalamus have received less attention. Although some brain imaging studies revealed diminished volumes of these structures in the various neurodegenerative diseases, including AD, it still remains unknown how brain ischaemia affects basal ganglia. In the present study, we focused on the implication of brain ischaemia to elucidate the pathogenesis of sporadic AD, using the monkey experimental paradigm. As hallmarks of neurodegeneration induced by cerebral hypoperfusion, microtubule-associated protein 2 (MAP2) and glial fibrillary acidic protein (GFAP) were studied by immunohistochemistry in the monkey brain undergoing 20min whole brain ischaemia followed by reperfusion. This showed, that immunoreactivity of MAP2 was decreased, while that of GFAP was increased in the basal ganglia and thalamus. Cerebral ischaemia/reperfusion also induced amyloid precursor protein (APP) processing due to  $\mu$ -calpain activation, which was represented by both up-regulations of  $\beta$ -Site APP-cleaving enzyme 1 (BACE1) and C-terminal fragment of 99 amino acid ( $\beta$ -CTF) protein levels. Moreover, decreases of the cAMP response element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF) were seen in postischaemic basal ganglia and thalamus. These results suggest that brain ischaemia plays an

important role in the development of neurodegeneration in the basal ganglia. The  $\mu$ -calpain-induced overexpression of BACE1 in the postischaemic basal ganglia of monkeys may suggest implication of brain ischaemia for the development of AD.

## Carotid “web-like” stenosis as a complication of endarterectomy

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**Introduction:** Carotid endarterectomy is the treatment of choice for extracranial carotid atherosclerotic disease. However, there is an associated potential for restenosis, which implies increased risk of stroke. The main pathogenesis is still unclear, but two main mechanisms are proposed: intimal hyperplasia and smooth muscle cell growth (early stage) and atherosclerotic process (later stage).

**Material and methods:** We report a case of an 80-year-old man with multiple vascular risk factors and a left endarterectomy for symptomatic stenosis. Afterwards, annual imaging screening with carotid Doppler-Ultrasound (CDU) revealed a severe bilateral carotid disease, with left residual stenosis. The patient was later re-admitted in our hospital with an acute right ischaemic stroke. Diagnostic workup was performed: cranial CT scan revealed an acute right frontal ischaemic lesion; CDU showed significant left internal carotid artery (ICA) stenosis and right ICA atherosclerotic occlusion; digital subtraction angiography revealed recurrence of left carotid stenosis and confirmed right occlusion. After multidisciplinary discussion, endovascular repair (angioplasty with stent insertion) of the left ICA was performed. CDU confirmed reperfusion of the artery. He was started on double anti-aggregation and high-dose statin and, during the follow-up period, there were no recurring neurologic events.

**Conclusions:** Currently, there is no consensus regarding the best approach of carotid restenosis following carotid revascularisation (surgical therapy vs carotid stenting). There is now a trend to choose endovascular approach. In our case, it was effective and without complications.

## Carotid stenosis cause cognitive decline

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Studies have found that cerebrovascular disease could play an important role on cognitive decline or dementia in patients without an obvious history of stroke. Recent studies have highlighted the role of carotid atherosclerosis, not only as a primary cause of cognitive impairment, but also adjuvant to the expression dementia caused by other factors, including Alzheimer’s disease and other neurodegenerative pathology. Carotid intima-media thickness could predict accelerated cognitive decline, particularly in the domain of verbal and nonverbal memory, as well as a test of semantic association fluency and executive function. Carotid plaque biology and serologic biomarkers of vulnerability can be used to predict the risk of cognitive impairment. Patients with bilateral carotid stenoses have worse performance on the tests for executive function, attention, and memory than unilateral carotid stenosis. The difference in cognitive function between patients with left and right carotid artery stenosis was not significant in high stenosis grade, while in lower stenosis grade, badly cognitive function was observed in patients with left carotid stenosis than patients with right carotid stenosis. As carotid atherosclerosis always overlap with neurodegenerative pathology, the relationship between them still needs to be investigated in more studies due to multiplicity of underlying pathology.

## Stent deployment as a treatment for stent retriever failure in acute ischaemic stroke: an evidence-based case report

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**Introduction:** Stent retriever has been approved as definitive therapy for acute ischaemic stroke, but it has various failure rates ranging from < 1%–30%. Deploying self-expandable stent can be considered in patients refractory to conventional management. A patient sustains acute ischaemic stroke with stenosis in middle cerebral artery, M1 & M2. After 3 attempts of stent retriever, there was no recanalisation. Then, the stent is deployed and TICI 2b/3 was achieved. This study aims to identify the outcome of stent deployment as a treatment for stent retriever failure in acute ischaemic stroke.

**Material and methods:** Literature searching was performed in three databases: PubMed®, Cochrane®, and ScienceDirect® using keywords: stenting, failure, acute ischemic stroke, and modified Rankin Scale score with their acronym or abbreviations. Two articles were generated using inclusion and exclusion criteria. Critical appraisal was performed using validity, importance, and applicability criteria.

**Results:** The randomised control trial (RCT) showed lower modified Rankin Scale score (mRS score 0–2, 35.3%) and cerebral herniation (11.8%) in stenting group compared to non-stenting group (mRS score 0–2 7.1%; cerebral herniation 42.9%). In a cohort study, stent deployment results good outcome (mRS score 0–2) in 42% patients and moderate disability (mRS score 3) in 21% patient.

**Discussion:** In atherosclerosis stenosis, the self-expandable stent minimise barotrauma to the vessel, more flexible to reach distal lesions, and have various sizes. Besides, it has lower acute/periprocedural complications with no instances of procedural stroke, vessel rupture, or stent migration. Therefore, deployment of stent-expandable stent in acute ischaemic stroke can be used in stent retriever failure.

## Homeotic genes expression profile of peripheral blood leucocytes in transient ischaemic attacks and cerebral ischaemic strokes

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The aim of the study was to identify homeotic genes expression profile of peripheral blood leucocytes in patients diagnosed with transient ischaemic attacks (TIA) and cerebral ischaemic strokes in order to select “gene candidates” useful in predicting the risk of subsequent ischaemic incidents in this group of patients. The study group included 51 subjects diagnosed with TIA (n = 24) or ischaemic stroke (n = 27). RNA was extracted from peripheral blood leucocytes and the panel of 168 genes belonging to homeotic genes family was evaluated using SABiosciences PCR Arrays (PAHS-083Z and PAHS-0501Z). The obtained results were then elaborated using bioinformatic tools involving heat maps, gene set enrichment and association studies, as well as clinical analyses. Potential genes indicating the risk of recurrent ischaemic episode in patients diagnosed with transient ischaemic attack were DMBX1, PROX1, GATA1, GATA6 and HAND1. In case of DMBX1 and PROX1, the risk of subsequent ischaemic attack correlated with increased expression of these genes. On the other hand, decreased expressions of GATA1, GATA6 and HAND1 indicated the probability of another episode of cerebral ischaemia. According to clinical evaluation, the most promising genes, strongly correlating with established factors of the cerebral ischaemia, were GATA1 and GATA6 (p0,0001; r = 0,8). They indicate, however, the risk of a recurrent cerebral ischaemic episode exclusively in patients diagnosed with TIA. No genes have been shown as the potential factors indicating the risk of re-ischaemia in patients initially diagnosed with cerebral ischaemic stroke.

## Cerebral venous sinus thrombosis in pregnancy

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Cerebral venous sinus thrombosis is a rare, multi symptomatic and a very serious complication in pregnancy. About 0,5–1% of all strokes are cerebral venous sinus thrombosis. Women are at three times higher risk of having a cerebral venous sinus thrombosis than men. In addition to that, it occurs 5,5 to 6 times more often during pregnancy than in general population of women. The most frequent symptoms and signs are headache (74%), focal seizures with or without secondary generalisation (50%), impairment of muscle strength (38%), disturbance of consciousness (45%), visual impairment. Magnetic Resonance Venography (MRV) is a key method to investigate for venous thrombosis in pregnancy. The first line treatment for cerebral venous sinus thrombosis in pregnancy is body-weight-adjusted subcutaneous low-molecular weight heparin. When CVT occurs during pregnancy, anti-thrombolysis treatment should be considered as soon as the diagnosis has been confirmed, until at least six weeks after the delivery. The shortest accepted time of treatment are three months. The presence of CVT in the health history is not a contraindication for next pregnancy, but only on the condition that anti-thrombolysis treatment is provided. That treatment consists of body-weight-adjusted subcutaneous low-molecular weight heparin from the time of conception till six to eight weeks after the delivery. The prognosis is auspicious.

## Clinical case: how to treat venous stroke in women in early postpartum period?

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**Introduction:** Venous stroke (VS) is a rare form of stroke due thrombosis of Trolard's and Labbe's veins (the frequency is from 0.1% to 3–5%). The important risk factors of the VS are pregnancy and the postpartum period in young women. Differential diagnosis and treatment of the VS cause certain difficulties.

**Material and methods:** A 27-year-old postpartum woman was admitted to our clinic complaining of nausea, vomiting, numbness and jerking movements of the left limbs. 5 hours before she had general weakness and diffuse headache. Neurological examination revealed left-sided hemiparesis and Jacksonian seizures in the left hand. After CT and MRI, neuroimaging was performed, and the patient was transferred to the stroke unit with a diagnosis of haemorrhagic transformation of ischaemic stroke (focal lesion of the right parietal lobe). Analysis of the cerebrospinal fluid was normal. EEG was registered convulsive readiness. CT angiogram showed VS due total thrombosis of the anastomotic vein of the right parietal lobe. She received carbamazepine, enoxaparin. After the treatment, there was a clinical improvement.

**Results:** Verification of VS is difficult due to the following features: a later appeal to the neurologist, which is most possibly due to the vagueness of the clinical symptoms of the disease, necessity to do detailed follow-up examination by a skilled neuroradiologist.

**Conclusions:** Venous stroke causes difficulties in diagnosis due to the prevalence of general symptoms of the focal symptoms. Haemorrhagic transformation and development of epilepsy are frequent complications of the venous stroke. Can we use thrombolytic therapy by VS?

## Does the spleen play a role in acute neurological injuries?

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**Introduction:** A wealth of pre-clinical animal studies suggest that the spleen contributes to peripheral immune responses to injury in stroke, brain haemorrhage, and traumatic brain injury. The spleen has been shown to promote the migration of inflammatory cells to the brain, leading to secondary injury and propagating BBB disruption and CNS inflammation. We present a review of our published studies on spleen responses in patients with acute neurological disorders and define whether the spleen contributes to inflammatory responses and clinical outcomes.

**Material and methods:** Over 100 patients with acute ischaemic stroke and brain haemorrhage have been prospectively studied with splenic ultrasounds, brain imaging, neurological exams and blood studies. Serum inflammatory cytokines and the systemic inflammatory response have been measured in a subset of patients.

**Results:** Using nomograms of splenic volumes derived from healthy volunteers, we find that the spleen reduces in size in nearly half of studied patients. African-Americans, older patients, and patients with prior stroke have higher odds of splenic reduction. Spleen reduction is associated with elevations in specific inflammatory cytokines. In a subset of patients, longitudinal analyses show that the spleen contracts within six hours of symptom onset and re-expands after three days.

**Conclusions:** The spleen may play an important biological role in patients with acute neurological disorders, raising the possibility for the development of new therapeutic targets to modulate inflammatory responses and improve outcomes.

## Search for the embolic source: a patient with two consecutive stroke episodes

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**Introduction:** 70-year-old male patient was seen in the emergency room with left hemi hypoaesthesia, ataxia and cerebellar dysarthria and the cranial imaging showed right cerebellar acute lacunar infarct. Hypertension, hyperlipidaemia and diabetes mellitus were present in the medical history of the patient. There was no significant stenosis in the carotid-vertebral arterial system. Electrocardiogram (EKG) and transthoracic echocardiography (TTE) revealed no significant pathology. Acetylsalicylic acid (ASA) 300 mg once a day was prescribed during the externation of the patient. One month later he was seen at the emergency department again with acute onset ataxia and the cranial imaging revealed a new lacunar infarct at the right side of the pons while under ASA treatment. Doppler, EKG and TTE were repeated, but they revealed no significant pathology. We decided to perform transoesophageal echocardiography (TEE) to reveal any cardioembolic source. The report of the TEE showed grade V atheroma at the aortic arch. Clopidogrel combined with ASA was prescribed for the patient.

**Discussion:** Atheroma of the aorta is a well-known risk factor for stroke and it increases the risk four times. In our case, routine work-up and two separate TTE could not detect such a high grade atheroma at the arch and we were unable to detect the plaque until TEE was performed. In this poster we would like to discuss if it was possible to detect the atheroma with TTE or another technique in the first place and when and how should we expand our work-up to detect aortic atheroma.

## Factors associated with concomitant asymptomatic intracranial artery stenosis in patients with atherothrombotic brain infarction attributable to intracranial artery stenotic lesion

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**Introduction:** The purpose of this study was to identify factors associated with concomitant asymptomatic intracranial artery stenotic lesion (ICAS) in patients with atherothrombotic brain infarction (ATBI) attributable to ICAS.

**Material and methods:** Subjects of this study were 54 patients (37 men; mean age,  $71.0 \pm 12.9$  years) with symptomatic ICAS, who were admitted to our department within seven days of the onset of ATBI, between April 2013 and August 2017. Significant ICAS was defined by the presence of  $\geq 50\%$  stenosis or occlusion of intracranial arteries, as detected by MR angiography.

**Results:** 26 patients (48.1%) had concomitant asymptomatic ICAS. Patients with asymptomatic ICAS was significantly older ( $74.9 \pm 2.4$  vs  $67.3 \pm 2.4$  years,  $p = 0.029$ ) and more likely to have a history of ischaemic heart disease (IHD) (23.1% vs 3.6%,  $p = 0.033$ ), compared to those without. The prevalence of current smoking habit was significantly lower in patients with asymptomatic ICAS than in those without (11.5% vs 35.7%,  $p = 0.038$ ). Multiple logistic regression analysis showed that advanced age (Odd ratio [OR], 1.83; 95% confidence interval [CI], 1.04–3.53;  $p = 0.034$ , for every 10 years) and a history of IHD (OR, 11.5; 95% CI, 1.42–265.5;  $p = 0.020$ ) were associated with concomitant asymptomatic ICAS.

**Conclusions:** Our results suggested that patients with ATBI attributable to ICAS who had concomitant asymptomatic ICAS were older and prone to have a history of IHD.

## Mechanical thrombectomy for the posterior circulation stroke: analysis of outcomes and comparison to anterior circulation large vessel occlusion treatment

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**Introduction:** Mechanical thrombectomy (MT) is now well-established method for anterior circulation large vessel occlusion (LVO) treatment. There is, however, no solid evidence of its efficacy in the setting of posterior circulation LVO. We present the comparison of treatment outcomes and periprocedural complication rates in both groups.

**Material and methods:** We reviewed the Clinical Regional Hospital No. 2 in Rzeszów local MT-treatment database. The baseline characteristics, site of occlusion, procedural times, and presence of successful reperfusion, procedural complications, outcomes and mortality at three months were analysed.

**Results:** 77 patients (48% woman, median age 70, IQR 61–79) were treated with MT (Solitaire FR or Penumbra system) between January 2013 and December 2016. 14 (18%) had posterior and 63 (82%) anterior circulation LVO. There was no significant difference in age and baseline National Institutes of Health Stroke Scale (NIHSS) score in the posterior circulation cohort ( $p < 0.05$ ). The median time to treatment was significantly longer than anterior circulation LVO group (median (IQR) 283 min (225–360) vs 220 min (180–288),  $p = 0.008$ ). There was none symptomatic intracerebral haemorrhage (sICH) identified (0% vs 8%,  $p = 0.58$ ). The posterior group showed tendency to higher reperfusion rates (85.7% vs 66.7%,  $p = 0.21$ ) and better outcomes (mRS = 0–2) at 3 months (57.1% vs 37.7%,  $p = 0.23$ ). Mortality rates were similar in both groups (28.6% vs 27.9%,  $p = 1$ ).

**Conclusions:** MT for the posterior circulation LVO stroke is not associated with higher complication rates and mortality than anterior occlusion treatment. High reperfusion and good outcome rates could be achieved.

## Repeated thrombectomy of middle cerebral artery

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We present a case of 79-year-old male with occlusion right middle cerebral artery (MCA), treated with thrombectomy and after ten months retreated because of reocclusion of the same artery. The patient developed the symptoms of acute ischaemic stroke of right hemisphere on 4<sup>th</sup> January 2017 with left side central facial palsy, hemianopia, hemiparesis, hemianaesthesia, hemineglect and conjugated gaze partial palsy to the left side. Total NIHSS was 16. In history, the patient had permanent atrial fibrillation, arterial hypertension and neoplastic process under control (carcinoma of bladder and prostate with bilateral ureterocutaneostomy). The occlusion of right MCA was found and thrombectomy was performed with complete recanalisation. On control CT, the infarction without haemorrhagic transformation (HT) in the right hemisphere was seen. The patient was discharged home with 5 points in NIHSS, mRS after 30 days rehabilitation was scored 1. On 6<sup>th</sup> November 2017, the patient developed the symptoms of new acute ischaemic stroke of right hemisphere and the NIHSS was scored 16. The occlusion of right side M1 MCA was found and thrombectomy was performed (despite the residual old infarcted area in the territory of the operated MCA), with complete recanalisation. On 24<sup>h</sup> control CT a new infarct, next to the old one, was seen with small HT2. The patient functionally improved and was discharged to rehabilitation unit with 10 point in NIHSS. 30 day mRS was scored 2 (functionally independent). This is the first report on repeated thrombectomy on the same artery, with good clinical effect.

## Isolated choroid plexus infarction presenting as acute-onset Parkinsonism

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An isolated choroid plexus infarction presenting as acute-onset Parkinsonism has never been reported. A 70-year-old woman with a history of hypertension and hyperlipidaemia visited our clinic complaining of sudden gait disturbance and bradykinesia, which started ten days prior. On neurological examination, the patient's gait showed a decrease in step height and walking speed. Symmetrical bradykinesia of the upper and lower limbs was also observed. Secondary Parkinsonism was suspected, and a laboratory and imaging diagnostic workup was performed. Interestingly, her brain MRI demonstrated a focal hyperintense lesion in the right choroid plexus on diffusion-weighted imaging. The above lesion was confirmed to be an acute ischaemic stroke based on low signal intensity on the apparent diffusion coefficient map. To differentiate the patient's symptoms of acute-onset Parkinsonism from CSF circulation disorders or underlying cerebral dopamine depletion, a diagnostic lumbar puncture and 18F-FP-CIT PET scan were performed. Opening CSF pressure was 56 mm H<sub>2</sub>O, which was lower than normal range. A 18F-FP-CIT PET scan revealed normal dopamine transporter binding. Seven weeks after the onset of symptoms, she had noticeable recovery with no symptoms of Parkinsonism. Follow-up lumbar puncture revealed a normal opening pressure. We speculated that acute-onset Parkinsonism

in this case might be related with low CSF pressure syndromes, such as intracranial hypotension. Considering the course of recovery for seven weeks after the onset of symptoms, we suggested that the patient's Parkinsonism was due to choroid plexus infarction. Clinicians should be aware of this unique condition as a rare cause of secondary Parkinsonism.

## Predictive values of neutrophil to lymphocyte and platelet to lymphocyte ratios in outcomes of patients with stroke

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**Introduction:** The systematic and local inflammation plays a key role in physiopathology of stroke. The aim of our study is to examine the prognostic utility in short term of neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) measured in the admission of the patients with stroke.

**Material and methods:** 70 patients admitted in the service of neurology from March to December 2017. Neutrophil, lymphocyte and platelet counts were obtained using Coulter ADVIA 2120i. NLR and PLR were then calculated and a questionnaire was completed. Patients were contacted six months later for research of possible recurrence. At first, a descriptive analysis was realised. Secondly, a Kaplan Meier survival curves and a *Cox* regression analysis are established, as well as the determination of the value of threshold for predicting recurrence by *ROC*.

**Results:** There is a statistically significant difference of the mean age between men and women ( $p = 0,035$ ). The Kaplan Meier survival curves are significantly different between categories low NLR and high NLR ( $p = 0,004$ ) also for PLR ( $p = 0,0001$ ). The *Cox* model reveals that the NLR (HR = 3,38) and PLR (HR = 6) are the only predictive markers of a recurrence. The cutoff NLR = 4,6 and the cutoff PLR = 170.

**Conclusions:** NLR and PLR are biomarkers little expensive and easily available. They allow the stratification and the optimal monitoring of the patients risk to make a recurrence.

# WILSON'S DISEASE

## Gastrosocopy findings in Wilson's disease patients before and during D-penicillamine or zinc sulphate treatment

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Gastric symptoms in Wilson's disease (WD) may result from *Helicobacter pylori* infection or disease-related factors, like liver cirrhosis or adverse drug reactions. The aim of this study was to examine the frequency of gastropathy and gastric ulcers in WD patients, and to analyse the effects of therapy on these conditions. All enrolled patients underwent oesophagogastroduodenoscopy and urease test for *H. pylori* infection. Patients were divided into three study groups, treatment naive (n = 37), on D-penicillamine (n = 34), or zinc sulphate (n = 24) therapy. The results of the research show that there was no statistically significant difference in the prevalence of gastropathy and peptic ulcers between untreated patients (64,9% and 10,8%), treated with D-penicillamine (52,9% and 11,8%) or zinc salts (79,2% and 8,3%). The prevalence of *H. pylori* infection in all WD groups (60–70%) was similar to those reported in general Polish population. *H. pylori* infection was related with higher rate of gastropathy (73,3% vs 48,6%), but there was no significant difference in peptic ulcers rate (11,7 % vs 8,6%). In conclusion, our results show that gastropathy and peptic ulcers are frequent in WD, but therapy (d-penicillamine or zinc) does not increase the rates of gastropathy and gastric ulcers in WD.

## Different brain pathology in neurological and hepatic forms of Wilson's disease depicted by quantitative MRI

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**Introduction:** Quantitative MRI is a sensitive tool to study microstructural changes in tissues. This study aims at comparison of differences in quantitative MRI metrics in the deep gray matter nuclei in Wilson's disease (WD) patients with neurological and hepatic form.

**Material and methods:** 40 patients with genetically confirmed WD (30 neurological WD, 10 mild hepatic WD) on a stable anti-copper treatment and 26 healthy controls were investigated. 3T MR system was used to study quantitative susceptibility and T2/T1 relaxation times in globus pallidus, putamen, caudate nucleus and thalamus. Serum ceruloplasmin oxidase activity was measured using the o-dianysine assay.

**Results:** T2 relaxation times were significantly lower in neuro-WD group in globus pallidus, putamen, and caudate nucleus compared to controls and hep-WD, whereas T2 relaxation times in hep-WD did not differ from controls. T1 relaxometry revealed higher T1 values in the thalamus in neuro-WD group compared to both controls and hep-WD patients (p0.02). Significantly higher susceptibility values were found in all studied regions in neuro-WD patients compared to controls and hep-WD patients (p0.02). No difference was found between hep-WD patients and controls. No correlation with the ceruloplasmin oxidase activity was found.

**Conclusions:** Our results show that hep-WD is not associated with significant brain pathology. Decreased T2 relaxation time/ increased susceptibility in the basal ganglia indicate iron deposits, whereas increased T1 relaxation time/increased susceptibility in the thalamus correspond rather to demyelination in neuro-WD group. Iron accumulation is not causally related to decreased ferroxidase activity. Supported by MH CR 15-25602A and 00023001IKEM Institutional support.

## Clinical and laboratory characteristics of different stages of Wilson's disease

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**Introduction:** Wilson's disease (WD) is a rare hereditary disorder of copper metabolism with excellent prognosis, if diagnosed on time. Search of the new simple diagnostic criteria is of great importance.

**Objectives:** To study the most frequent combinations of clinical and laboratory findings in patients with different stages of WD.

**Material and methods:** Clinical, neurological, biochemical and haemostatic status was assessed in 22 patients with hepatic and in 53 patients with neurologic stage of WD.

**Results:** Initial clinical manifestations were distributed as following: signs of liver affection — 43%, haemorrhagic syndrome (nasal, gingival or cutaneous) — 30%, primary neurologic symptoms — 16% and the other variants — 11%. Hyperkinesia, mixed dysarthria, haemorrhagic and menstrual disorders was the most typical combination in 73% of cases in the neurologic stage of WD. Haemorrhagic and menstrual disorders coupled with asthenic autonomic syndrome and mild action tremor in hands were identified in 65% of patients in the hepatic stage. Disturbances of copper metabolism (91%), cytolysis (59%) and cholestasis (52%), thrombocytopenia (57%), changes in platelet function (96%) and coagulopathy (60%) were the leading biochemical findings. Cytolysis and cholestasis were more common ( $p = 0.04$  and  $p = 0.03$ , respectively) and more evident in patients with the hepatic stage, while coagulopathy and thrombocytopenia — in the neurologic stage of WD ( $p = 0.03$  and  $p = 0.02$ , respectively).

**Conclusions:** Different combination and severity of clinical and laboratory findings in patients with hepatic or neurologic stage of WD should be considered in diagnosing.

## Pseudodominant inheritance of Wilson's disease — case report

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**Introduction:** Wilson's disease (WD) is an inherited autosomal recessive disorder of a copper metabolism. The diagnosis of WD is usually made before the age of 40, so pseudo-dominant inheritance is observed mostly in offspring of WD patients, the risk is 4%. We describe a family, in which WD was firstly diagnosed in a daughter of a father who was asymptomatic up to 60 years old.

**Material and methods:** Proband was diagnosed with WD upon copper at the age of 31 years, when she had an acute hepatic failure. Her brother, age 37, was also diagnosed with WD. He was clinically asymptomatic, but had abnormalities in laboratory liver tests. One year later WD was diagnosed in her father at the age of 62 years. During hospitalisation for an acute bronchitis, he was diagnosed with a liver cirrhosis and an oesophageal varices. He has never suffered from any liver symptoms before. He has also decreased ceruloplasmin level, Kayser-Fleischer rings, neurological symptoms and brain MRI abnormalities characteristic for WD. Genetic showed the same mutation as his daughter has, but present only on one chromosome.

**Conclusions:** This case report shows how important it is to obtain detailed family interviews after diagnosing WD in the proband. Information should be gained not only proband's siblings, but also for other relatives, although recognition of disease in the parents of WD is very rarely described.

## Transcranial sonography in Wilson's disease patients

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**Introduction:** Wilson's disease (WD) is an autosomal recessive inherited disorder of copper metabolism with hepatic and neurological symptoms. Transcranial sonography (TCS) may be useful as a simple and safe technique in many neurodegenerative diseases. The aim of this study was to assess basal ganglia changes in WD patients with TCS in two years observation period.

**Material and methods:** Patients with new diagnosis of WD without previous treatment entered the study. TCS was performed through the preauricular acoustic bone window with a 2.5-MHz phased-array transducer. SN echogenic sizes  $\geq 0.25 \text{ cm}^2$  were classified as hyperechogenic for the used ultrasound system. The area of hyperechogenicity in the lenticular nucleus (LN) was measured by encircling the outer circumference of the hyperechogenic area.

**Results:** 21 neurological and 20 hepatic patients entered the study. Baseline SN hyperechogenicity was found in nine neurological and four hepatic patients. 24 months SN hyperechogenicity was found in one neurological and three hepatic patients. There was no correlation between baseline and 24 months SN echogenicity neurological examination. Baseline LN did not reveal hyperechogenic changes in two neurological and five hepatic cases. One patient in neurological group and three patients in hepatic group did not have LN changes on 24 months TCS.

**Conclusions:** SN hyperechogenicity was not observed in all WD patients and is more often seen in neurological group. LN echogenicity is observed in most WD patients and number of patients with LN changes had risen over the time. Basal ganglia changes observed in WD patients are time dependent probably due to drugs therapeutic effect.

## Limbic encephalitis — diagnostic difficulties

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Limbic encephalitis (LE) was the first described by Brierley in 1960 as a clinic-pathologic syndrome. LE is characteristic with various clinical signs and symptoms. Patients with LE can have memory impairment, confusion, disorientation, agitation, hallucination, sleep disturbance, depression and seizures. In 2016 Graus et al. published the diagnostic criteria for possible autoimmune limbic encephalitis. The clinical diagnosis can be confirmed by investigation of cerebrospinal fluid, EEG, brain MRI. LE is often suspected or diagnosed, but unfortunately, not always confirmed neuropathologically.

Three clinically suspicions of LE were presented. This group consists of 2 men aged 31 and 80 years and 73 years old woman. Diagnosis of LE were done according to the clinical symptoms, brain MRI findings and in two cases with presenting paraneoplastic antibodies. In two cases in neuropathological examination the presence of LE was excluded. Only in 80-year-old man neuropathological changes confirmed the clinical suspicion of LE.

**Conclusions:** Only in one case neuropathological diagnosis confirmed clinically suspected limbic encephalitis. LE is a disease, which can cause controversy between clinical suspicion and neuropathological findings.