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CONTROVERSIES IN NEUROLOGY 2017, ATHENS, GREECE

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 Adamantiades-Behçet's disease, The Greek-Italian contursi kindred: From the past to the future, and The Brain and Mind in Greek Philosophy and Mythology.

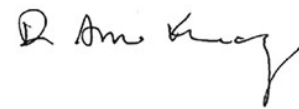
The present special issue of the Journal of THE HELLENIC NEUROLOGICAL SOCIETY – NEUROLOGIA, devoted exclusively to the 11th meeting on Controversies in Neurology includes abstracts of invited lectures and free communication presented at the meeting. It is a tribute to this event allowing it to remain immortalized in an international academic journal.

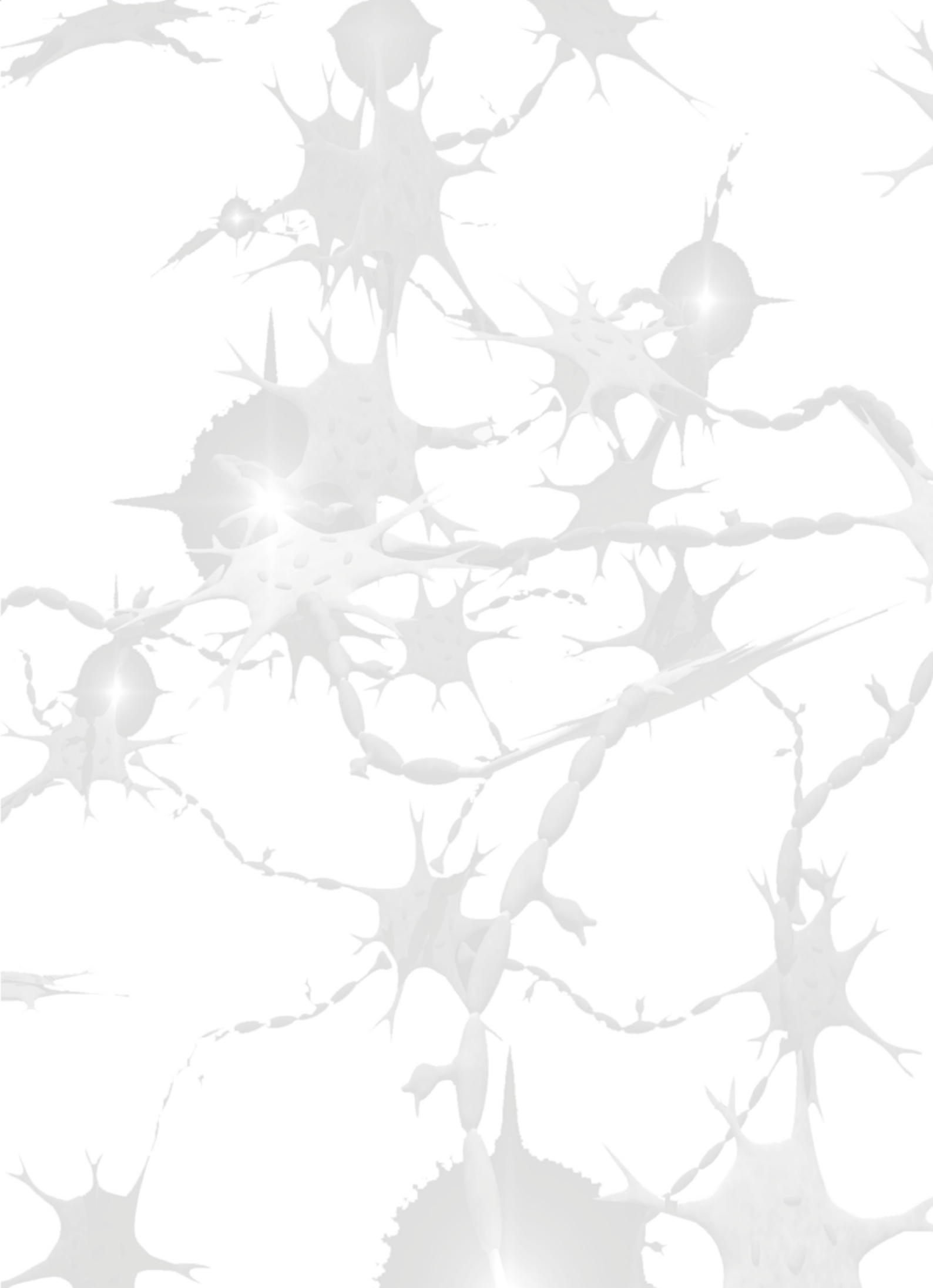
We look forward for more debates and enlightening discussions in CONy 12th, which will take place in Warsaw, Poland (March 22-25, 2018) (<http://www.comtecmec.com/cony/2017/Default.aspx>).

Guest Editor

A.D. Korczyn

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





Invited Speaker Abstracts

*11th World Controversies in Neurology
Athens, Greece
March 23-26, 2017*

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THE DIFFERENTIAL DIAGNOSIS OF NEURO-BEHÇET'S DISEASE

C. Constantinescu

Clinical Neuroscience, University of Nottingham, UK

Adamantiades-Behçet's disease (BD) is a multisystem inflammatory disorder of unclear aetiology. The most common manifestations of the disease are recurrent oral ulcers, recurrent genital ulcers and uveitis. A set of diagnostic criteria for (BD) is established by international consensus. More recently, criteria for the diagnosis of neuro-BD (NBD) are also emerging and being validated. Neurological involvement in BD (NBD) is rare, but recognising it is of paramount importance, as it tends to reflect a more severe form of BD and there is a high risk of complications. Therefore, early and more aggressive treatment is indicated. In diagnosing NBD, it is important to be aware of several differential diagnostic considerations. These are grouped here in several clinical scenarios. Neuroimaging is generally not necessary in patients with known BD presenting with isolated headache without accompanying signs or symptoms. Multiple Sclerosis. The presence of brainstem atrophy, in particular in the absence of atrophy elsewhere in the CNS is a hint to NBD. Oligoclonal bands are rare in NBD but frequent in MS, and the CSF white blood cell count tends to be higher in NBD, with a polymorph predominance. NBD and MS may rarely coexist. NBD versus neurological involvement in other inflammatory diseases with uveo-meningeal syndrome. E.g. neurosarcoidosis, SLE, Sjogren syndrome, and infectious diseases (neuroborreliosis, neurobrucellosis). Some aspects of differential diagnosis from these conditions will be discussed. Atypical presentation: a. meningitic presentation; b. dementia. Relevant cases to illustrate some of the above clinical scenarios will be presented.

CHALLENGES, STRENGTHS AND WEAKNESSES "OF AGGREGATE DATA, INDIVIDUAL PATIENT DATA AND NETWORK META-ANALYSIS

E. Kontopantelis

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NIHR School for Primary Care Research, University of Manchester, UK*

Meta-analysis sits at the top of the evidence pyramid and rightly so. It encompasses a large number of statistical approaches that can aggregate results from numerous studies, to provide conclusive evidence across all research fields. The main meta-analytic approaches include the standard meta-analysis (formally, meta-analysis of aggregate data), meta-regression, individual patient meta-analysis, network meta-analysis of aggregate data and network meta-analysis of individual patient data. First, we will discuss when it is suitable to use each of these broad methodological approaches, in other words, what questions they are designed to answer. Next, in practical terms, we will discuss how a researcher should conduct each of these analyses, i.e. what is the process, what are the appropriate models to use (and software) and, in general, what are the resources required. Finally, we will discuss the strengths and weaknesses of each approach, focusing on common mistakes, misconceptions and oversights.

ADAMANTIADES-BEHÇET DISEASE: A CURRENT OVERVIEW

P. P. Sfikakis

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Adamantiades-Behçet disease (ABD) is a distinct, chronic, relapsing inflammatory disorder classified among the systemic vasculitides. ABD is more prevalent in Mediterranean, Middle and Far Eastern countries across the ancient "Silk Road" trading route. ABD can be viewed as a condition linking autoinflammation and autoimmunity, whereas a genetic contribution is supported by the high sibling recurrence risk ratio and the strong association with HLA-B51. Diagnosis is entirely clinical; a careful past medical history is mandatory due to the relapsing-remitting course of the disease. A patient can be classified/diagnosed with ABD if suffers from recurring oral ulcerations, plus at least any two of the following; a) recurrent genital aphthous ulceration or scarring, b) eye lesions: anterior uveitis, posterior uveitis, cells in the vitreous by slit lamp examination or retinal vasculitis, c) skin lesions: erythema nodosum, pseudofolliculitis, papulopustular lesions or acneiform nodules, d) a positive pathergy test. Other clinical manifestations include arthritis, superficial thrombophlebitis, deep vein thrombosis, aneurysms, central nervous system involvement, epididymitis and gastrointestinal involvement. Ocular involvement is the leading cause of morbidity and, if left untreated, may result in blindness in more than 70% of those affected. Management needs to be individualized and adequately powered, randomized, controlled clinical trials are few. Corticosteroids, colchicine, cyclosporin-A, interferon- α and cyclophosphamide, and azathioprine alone or in combinations are used but none results in disease cure. The successful introduction of anti-TNF treatment is considered a significant advancement in the management of patients with severe, refractory manifestations and especially in relapsing sight-threatening involvement of the posterior eye segment.

NEURO-BEHÇET DISEASE: DIAGNOSIS AND CLINICAL ISSUES AND MANAGEMENT

A. Siva

Neurology, Istanbul University Cerrahpasa School of Medicine, Turkey

Behçet's disease (BD), is an idiopathic chronic relapsing multisystem vascular-inflammatory disease of unknown origin with oro-genital ulceration and uveitis. The disease affects many organs and systems, including the nervous system.

Clinical and imaging evidence suggests that primary neurological involvement in BD may be subclassified into two major forms: the first one, which is seen in the majority, is characterized as a vascular-inflammatory central nervous system disease with focal/multifocal parenchymal involvement, mostly presenting with a subacute brainstem syndrome and hemiparesis; the other, which has few symptoms and a better outcome, is caused by isolated cerebral venous sinus thrombosis and intracranial hypertension, occurring in 10- 20%. These two types rarely occur in the same individual, and their pathogenesis is likely to be different. Isolated behavioral syndromes and peripheral nervous system involvement are rare, whereas a vascular-type headache is relatively common and independent from neurological involvement. Neurologic complications secondary to systemic involvement of BD and related to BD treatments are considered as secondary neurological involvement. The core histopathological phenomenon seems to be a vasculitic involvement in some cases, and low grade chronic non-specific inflammation in others. As the neurological involvement in this syndrome is so heterogeneous, it is difficult to predict its course and prognosis, and response to treatment. Currently, treatment options of NBS are limited to attack therapies with high dose intravenous methylprednisolone followed with a prolonged oral taper and mainly the use of azathioprine, cyclophosphamide, interferon α and anti-TNF agents for long term preventive treatment despite no evidence for their efficacy.

ALZHEIMER'S DISEASE AND THE INVERSE WARBURG HYPOTHESIS

L. Demetrius

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Mathematical Biology, Max Plank Institute for Molecular Genetics, Germany

Epidemiological and biochemical studies show that the sporadic form of Alzheimer's disease (AD) is characterized by the following hallmarks: an exponential increase with age, a prolonged prodromal phase, and an inverse comorbidity with cancer. I will show that these hallmarks, which are now known to conflict with the Amyloid Cascade Model, are consistent with the Inverse Warburg Hypothesis. This hypothesis is a bioenergetic model of AD which postulates that the sporadic form of the disease is the result of *mitochondrial dysregulation* –an age-induced energy deficit in the mitochondrial activity of neurons, and the following cascade of events: *Metabolic reprogramming*– the up-regulation of oxidative phosphorylation in order to maintain adequate energy production and thereby ensure neuronal viability (the Inverse Warburg effect) *Natural selection* –competition for oxidative substrates between intact neurons with normal Oxphos activity, and impaired neurons defined by compensatory increases in oxidative phosphorylation. *Disease propagation*– the spread of metabolic abnormalities within the brain due to the selective advantage of reprogrammed neurons/ul. I will describe the empirical support for the Inverse Warburg Hypothesis and propose a new class of therapeutic strategies for AD, based on metabolic interventions.

DISTANCE LEARNING IN NEUROLOGY

M. Freedman

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Department of Medicine (Neurology), Mt. Sinai Hospital, Canada

Department of Medicine (Neurology), University of Toronto, Canada

Rotman Research Institute, Baycrest Health Sciences, Canada

Technology and globalization have transformed the learning environment into a virtual classroom without borders through distance learning and have enabled health care professionals to greatly enhance communication and international linkages. This has been accomplished at the basic science and clinical levels across the globe without barriers related to geography. This presentation will illustrate the successful impact of distance learning in neurology at a global level involving partners from sites that include Africa, Europe, the Middle East, North America, and South America. Distance learning initiatives spearheaded by neurology faculty will be highlighted within the context of international videoconference rounds for continuing professional development. These rounds are under the auspices of the Canada International Scientific Exchange Program (CISEPO), the Peter A. Silverman Global eHealth Program (PASGeP), and the Canadian Neurological Sciences Federation (CNSF). In addition, there is a parallel international videoconference rounds series organized by, and targeting, neurology trainees. The latter is called NIRVE (Neurology International Residents and Exchange). The presentation will also highlight the role of the World Federation of Neurology in distance learning, including its support of the relatively new International Africa-Canada Behavioural Neurology Rounds series, as well as the role of the World Federation of Neurology and Baycrest Health Sciences in posting international videoconference rounds on the internet. Finally, there will be a discussion of interactivity using the medium of videoconferencing for distance learning.

DEBATE: IS MILD COGNITIVE IMPAIRMENT (MCI) A USEFUL CONCEPT? NO

M. Freedman

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Although the concept of mild cognitive impairment (MCI) is widely accepted, critical examination of this concept shows that it has many weaknesses and flaws that challenge its validity as a meaningful entity. These weakness and flaws are inherent in the central construct of mild cognitive impairment and raise key questions about the clinical utility of mild cognitive impairment for diagnosis, prognosis, and management. The “no” side will argue that whereas mild cognitive impairment may have had value in the past, it represents an entity that has outlived its usefulness and should be abandoned.

WHERE MOUSE MODELS OF AD HAVE LED US?

S. Georgopoulos

Basic Research, BRFAA, Academy of Athens, Greece

Mouse models of Alzheimer’s disease recapitulate various aspects of the disease, as amyloid deposits, neurofibrillary tangles, neuronal loss, neuroinflammation and memory deficits. During the last 20 years, mice have helped us to gain insight into the fundamental pathogenetic mechanisms of the disease. Nevertheless, they are limited as they often represent one or few aspects of the disease which makes difficult to comprehend how the different parameters of the disease interact each other. Moreover, successful therapeutic approaches in AD mouse models have failed in the clinic suggesting that the pathogenetic mechanisms that drive the disease may not be the same between humans and mice. Unfortunately, research has focused mainly on the amyloid hypothesis of Alzheimer’s disease and other parameters of the disease, present both in mice and humans, as neuroinflammation and the role of the immune system in disease progression, as well as the role of Apolipoprotein E, the major risk factor in sporadic AD, have been neglected. Also, the recent generation of novel AD mouse models (knock-ins versus transgenics) has brought a new perspective in the use of AD mouse models. These topics will be discussed.

DEBATE: IS SNAP A PRECLINICAL STATE OF ALZHEIMER’S DISEASE (AD)? YES

K. Jellinger

Institute of Clinical Neurobiology, Institute of Clinical Neurobiology, Austria

Suspected non-Alzheimer disease (AD) pathophysiology /SNAP) is a biomarker-based concept denoting AD-like neurodegeneration in clinically normal elderly individuals or those with mild cognitive impairment without brain amyloid- β ($A\beta$ -) but positive neurodegeneration markers (ND+). It does not fall into the stages of preclinical AD as defined by the NIA-AA, but may have tau on PET scan in temporal lobes. Both SNAP and PART (characterized by NFTs - Braak stage ≤ 4 , and Thal $A\beta$ phase ≤ 2 or 0) cases have a low prevalence of ApoE $\epsilon 4$ and a greater conversion rate to dementia than $A\beta$ -/ND-individuals [1]. Autopsy studies revealed

low level AD (neuritic plaque score 0), AGD, PART or white matter lesions, indicating comorbid pathologic features rather than early evolving AD [2]. SNAP may be a heterogenous condition which may overlap with PART considered an A β -independent subgroup of AD or may be related to severe hippocampal atrophy [3]. From the perspective that SNAP is not AD, however, it is consistent with the concept of preclinical AD, although there is a debate as to whether PART is an early stage or a variant of AD. According to a recent autopsy study PART differs considerably from typical AD [4]. Further studies should subclassify the SNAP group and determine the biological correlates of ND markers among A β -negative individuals and their relations to PART and atypical AD. **References:** 1. Jack CR, Jr., et al., *Nat Rev Neurol* 2016;12:117-124 2. Gordon BA, et al., *JAMA Neurol* 2016;73:1192-1200 3. Mormino EC, et al., *JAMA Neurol* 2016;73:1185-1191 4. Josephs KA, et al., *Acta Neuropathol* 2017; submitted

WHY HAVE WE FAILED TO CURE ALZHEIMER'S DISEASE

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There is widespread recognition in the urgency to understand the causes and mechanisms of senile dementia. Attempts to find cures for Alzheimer's disease (AD) have, however, failed so far, in spite of enormous investments, intellectual and financial. We therefore have to reconsider the problem from new angles. AD is regarded as a disease because of its clinical manifestations and underlying pathology. However, this combination does not define a disease but rather a syndrome, just like hepatic cirrhosis in which liver pathology causes metabolic changes, which can result from many different etiologies. It is unlikely that attacking a downstream phenomenon, like apoptosis or b-amyloid accumulation, can cure AD, or prevent the progression of the disease. It is probable that senile dementia is the result of a combination of several processes, working differently in each person. Epidemiological studies have identified many risk factors for "senile dementia of the Alzheimer type", some genetic but most environmental and therefore modifiable. A concerted action to fight the dementia epidemic must be made by aggressive action against its risk factors, and this battle must begin in midlife, not in old age.

LIMITATIONS OF GENOME-WIDE ASSOCIATION STUDIES IN ALZHEIMER'S DISEASE

G. Koutsis

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Alzheimer' disease (AD) is a genetically complex condition with heritability of 60-80%. Less than 1% of cases are caused by highly penetrant autosomal dominant mutations in *APP*, *PSEN1* and *PSEN2*, discovered in the 1990s. A major genetic risk factor for AD with medium-to-large effect size, the epsilon 4 allele of *APOE*, was also discovered in the 1990s. *APOE* epsilon 4 is thought to account for around 25% of disease heritability. In an effort to discover genetic factors responsible for the remaining heritability, genome-wide associations studies (GWAS) were developed in the mid-2000s. Vast amounts of money and resources were channeled into GWAS over the past decade. The end result has been the discovery of around 20 additional genetic loci associated with AD, exhibiting very small effect sizes (relative risks of heterozygotes in the 1.1-1.2 range), and contributing a mere additional 5% to disease heritability. Although this has often been presented as a great success story, it can also be viewed as a relative disappointment. Criticism of GWAS in AD can be focused on challenging the common disease-common variant hypothesis on which they are based; noting their inability to identify truly relevant genes but only loci in linkage disequilibrium with un-

known functional variants; pointing out that metabolic pathways implicated by newly discovered loci had already been identified as significant in AD pathogenesis before the GWAS era; and finally illustrating that in other complex diseases, such as multiple sclerosis, where therapies are widely available, these bare little relationship to loci identified from GWAS.

GREEK NATIONAL ACTION PLAN FOR DEMENTIA AND ALZHEIMER'S DISEASE

P. Sakka

Hygeia Hospital Memory Clinic, Greek Observatory for Dementia and Alzheimer's Disease, Greece

Currently there are 200,000 people living with dementia in Greece and 400,000 caregivers looking after them. These numbers will increase dramatically in the years to come, making dementia one of the most crucial medical, societal and economic challenges in Greece. Responding to lobbying efforts from the Alzheimer Associations, in October 2013, the Greek State assigned a working group which developed a National Dementia Action Plan. Its key priorities are to raise public and professional awareness, promote early diagnosis and intervention and create support services towards ameliorating the quality of life of people with dementia and their caregivers. In December 2014, the Greek Parliament enacted a law authorising the establishment of an independent public institution, the National Observatory for Dementia and Alzheimer's disease. The Observatory will ensure the implementation and subsequent updates of the National Dementia Action Plan and will provide specific guidance for organising and promoting the national policy in research and education. Dementia Action Plan was approved by the Standing Committee of Social Affairs of the Greek Parliament in March 2016. To this moment, the implementation of the plan has begun: 1. A national dementia registry and a rating system to measure the burden of dementia on families are underway. These will be used by the State to accordingly establish financial benefits for persons with dementia and their caregivers. families—funding 2. Day Care Centers for people with dementia are being implemented throughout the country with funding available from the National Strategic Reference Framework 2014-2020.

ANIMAL MODELS FOR AD HAVE LED US NOWHERE

M. Sabbagh

Neurology, Barrow Neurological Institute, USA

Animal models were developed to accelerate the advancement of drugs for AD. Starting with TG2576, multiple animal models have been developed leading investigators to believe that drug effects in TG animals demonstrates potential clinically efficacy that could be seen in human AD. Despite their short life cycle, drug effects seen in animal models have not been borne in clinical trials. Animal models have largely failed because the pathology is fundamentally different and the biology of the species is less complex than human or non-human primates. While they are easier to manipulate and control, almost no study of animals have been reproduced in human studies.

INNOVATIVE TECHNOLOGY FOR COGNITIVELY IMPAIRED PEOPLE

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Background: There is a constant concern for innovative solutions able to meet the special motor and/or cognitive needs of old persons. Since 2006, the AAIF's RandD department is involved in this research area as medical partner and end-user organization in 16 EU funded projects, and as founder member of 6 communities in EU Joint programmes. Methods and Results AAIF has run the local field trials with primary (PEUs) and secondary end-users (SEUs) for testing, evaluating and validating advanced-technology-based platforms. PEUs were persons with Mild-to-Moderate Dementia (Confidence project), Parkinson Disease (LiveWell) or elderly with compensated motor and/or sensory disabilities (Mobile Sage, Senior TV, My Mate, TSBank). Two thirds of the end-users declared their interest to buy such services, but affordability remains an opened question. As regarding the clinical improvement after using the platforms, the temporo-spatial orientation, recent memory, attention and calculation, as well as the indoor/outdoor mobility may show an improvement with 1-2 points after more than 3 weeks of use. Melioration in SEUs proved noticeable on ZARIT burden interview, and on Yesavage scale for a possible depressive disorder. Conclusions and lessons learned Further developments must especially focus on user centred design. Specific guidelines must be proposed as contribution to standardization. The health care system shall be directed on the equal development of its non-human, complementary component of assisting the patient-caregiver-family unit, which could thus become an active participant and decision maker, and strengthen the principle of participatory medicine inside the AAL area.

IS MILD COGNITIVE IMPAIRMENT (MCI) A USEFUL CONCEPT?

M. Tsolaki

3rd Department of Neurology, Aristotle University of Thessaloniki, Greece

Network Aging Research, University of Heidelberg, Germany

Saint John Day Center, Greek Association of Alzheimer's Disease and Related Disorders, Greece

Today, 14.1.2017, there are 35.972 papers about Mild Cognitive Impairment in PubMed since 1999 and of course many others in other databases. So how can I support the idea that MCI is not a useful concept? We can support this idea because first there is not a clear definition. How can we define MCI according clinical criteria, by assessing early disruptions in network connectivity and plasticity that occur before neuropathological damage and progressive memory dysfunction with EEG, by Using Whole Brain Hierarchical Network with MRI, by CSF or blood proteins, by amyloid or tau or FDG PET or by risk genes? Although there are many studies also about different combinations of the above methods of diagnosis we are not yet sure when a patient with MCI will progress to dementia. The second reason is that we cannot discuss yet about the progression of a patient with MCI. We have problems not only when a patient will progress to dementia but also to which kind of dementia will progress. There are many studies which support that patients with MCI will progress from 20% to 53% during the next three years to Alzheimer's Disease (AD). What happens with the others? The third reason is that although 30 years before in 1986 by Crook et al the idea of Age-Associated Memory Impairment started to be discussed no treatment yet is approved for this "disease". There are many suggestions: natural products, non pharmacological interventions, monoclonal antibodies, cholinesterase inhibitors etc without any results yet. We believe that it was a useful idea until now but we have to find a new definition of a new disease for which we are going to know about its' progression and we'll have treatment solutions.

EPIDEMIOLOGY OF DEMENTIA IN GREECE

M. Tsolaki

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Network Aging Research, University of Heidelberg, Germany
Saint John Day Center, Greek Association of Alzheimer's Disease and Related Disorders, Greece*

The studies on the prevalence of Dementia, Depression and Mild Cognitive Impairment (MCI) in Greece are sparse and show major variations of prevalence depending on geographical areas, nutritional habits and way of living. The aim of this presentation is to talk about three door-to-door studies in three different places of Greece in order to find the prevalence of Dementia, Depression and MCI in rural and urban Greek populations. First study: We investigated the prevalence and incidence of dementing disorders in the city of Pylea, Greece, using a door-to-door three-phase approach, and explored the relationship between age and gender. We were able to visit and examine 380/704 subjects more than 70 years old (54 percent); The prevalence of dementia was 9.2% and the incidence two years later was 57/1,000. Second study: The aim of this study was to determine the prevalence of MCI in individuals aged over 65 in a rural area in the north part of Greece (7 villages). From 1428 residents, 678 were finally examined, with a mean age of 73.35 years. 26.3% were classified as Mild Cognitive Impaired (MCI) without depression, 8.8% as MCI due to depression, 5.9% had solely depression, the 2.4% were diagnosed with dementia and 56.6% had normal mental status. Third study: Four hundred and forty-three individuals over the age of 60 following the application of specific criteria, were diagnosed with: Normal Cognition, Depression, MCI with and without Depression, Dementia with and without Depression in 7 villages of mountain region of Crete. Four diagnostic methods were used, two of which included Mungas correction for age and education. After Mungas adjustment, the results were as follows: Depression: 33.9%; MCI: 15.3%; MCI with depression: 8.6%; Dementia: 2.0%; Dementia with depression: 7.2%. We followed the same methods in three different regions and we found different prevalence numbers. We believe that education is very important in these three studies. Only in Crete the prevalence of dementia was more than in other developed countries.

GENETIC VARIANTS DETERMINE THE ONSET OF ALZHEIMER'S DISEASE AND DEMENTIA

C. Van Duijn

Genetic Epidemiology, Erasmus Medical Center, The Netherlands

Alzheimer's disease (AD) is one of the most heritable (60-80%) diseases in the elderly. In addition to the apolipoprotein E (APOE) gene, 23 mostly common genetic variants have been associated with AD. My group studied the joint effects of these variants and APOE on the lifetime risk and onset of AD and dementia. We studied incident dementia (N=1,262) in 12,255 cognitively healthy participants of the Rotterdam Study (mean follow-up: 10.9 years). Lifetime risks by age 100 years were stratified by APOE genotypes and tertiles of a weighted genetic risk score (GRS) combining the effects of the other 23 AD-associated genetic variants. There was significant evidence for interaction between APOE and the GRS ($p=0.02$). In APOE*44 carriers, by age 85 years there is a risk difference of 24.6% between those in the lowest and highest GRS, translating in a 7 year difference in age at onset. Comparing APOE*22 carriers in the lowest and highest GRS tertile, we find a 29 year difference in age at onset. These findings highlight the importance of common variants in AD and underscore the utility of genotyping in preventive and therapeutic trials.

DEMENTIA GENETICS IN GREECE: INSIGHTS FROM A LARGE COMMUNITY-BASED COHORT IN THE ISLAND OF CRETE, GREECE

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Introduction: Apart from the gene mutations associated with familial early-onset Alzheimer's disease (AD) and the *APOE* ϵ 4 allele that predisposes to late-onset AD, there have been no other strong genetic determinants of AD identified. **Aim:** Aim of this study was to characterize the genetic background of dementia in a cohort of aged adults on the island of Crete, Greece. **Methods:** Whole exome sequencing (WES) was performed in 201 participants (100 suffering from dementia, of whom 95 with AD, 20 with mild cognitive impairment-MCI and 81 cognitively normal controls) of our cohort. Using WES data, we assessed the genotype of these individuals concerning the early-onset AD associated genes (*PSEN1*, *PSEN2*, *APP*), the *APOE* gene and two genes (*GLUD1*, *GLUD2*) involved in glutamate metabolism. **Results:** As expected, the *APOE* ϵ 4 allele was more common in dementia (25.0%) patients than in cognitively normal controls (8.6%; $p=0.006$). In addition, we identified several variants of potential interest in the *APP*, *PSEN1*, *PSEN2*, *GLUD1* and *GLUD2* genes. In a combined sample of 612 individuals (that included an additional local cohort), we found the *GLUD2* Ser498Ala variant in 7 (3.2%) of 220 dementia X chromosomes, 22 (6.0%) of 370 MCI X chromosomes and 27 (6.5%) of 413 control X chromosomes. None (0%) of 50 male dementia patients had the Ser498Ala *GLUD2* genotype, compared to 7 (8.4%) of 83 male controls ($p=0.05$). **Conclusions:** In this culturally and genetically homogeneous cohort of aged adults, we identified, using a WES approach, a number of genetic variants of potential clinical significance.

NEW TECHNOLOGIES FOR SUPPORTING PATIENTS AND CAREGIVERS

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Recently information and communication technology (ICT) has played a crucial role in supporting patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI) and caregivers in Greece. A large number of research projects have validated novel ICT solutions. Computerized cognitive exercises have been used to enhance cognitive functioning. A wide range of exercises from language and multi-domain exercises to exercises in virtual environments have been implemented. At the same time physical exercises have been administered through ICT in an effort to improve strength and balance. Various smart home systems and wearables have been tested in an effort to support autonomous living of patients and provide useful data to specialists and caregivers. Robotics applications, ranging from tangible robotic interfaces for cognitive training to robotic assistants and software solutions, have also been trialed. ICT has also been used in diagnosis. Apart from traditional computerized tests, novel augmented reality neuromotor markers have been assessed and virtual reality (VR) applications have been used, for the first time, to reliably detect MCI. Caregiver support has been implemented through online portals and videoconferencing. In an effort to integrate and better use available ICT solutions, various platforms have been used for collecting, analyzing and presenting relevant data. Despite the abundance of relevant research projects and their results, wider implementation of ICT solutions is still lacking. Organizations such as the Panhellenic Federation of Alzheimer's Disease and Related Disorders are taking steps to ensure wider ICT implementation and dissemination of research results.

DEBATE: AQUAPORIN 4 ANTIBODY NEGATIVE NMOSD IS A NEW DISEASE

J. Tzartos

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In 2007, the term neuromyelitis optica spectrum disorders (NMOsd) was defined to include NMO and limited forms of the disease in the presence of anti-AQP4 antibodies, as these antibodies predict a relapsing course, AQP4 loss and astrocytic injury in CNS lesions. In 2015, new NMOsd criteria required at least one core clinical characteristic (optic neuritis, myelitis, area postrema syndrome, brain stem syndrome, diencephalic clinical syndrome with typical diencephalic lesions and symptomatic cerebral syndrome with typical brain lesions) and AQP4-antibodies, or two core clinical characteristics (one of which should be optic neuritis, transverse myelitis or an area postrema clinical syndrome) with specific MRI findings, without AQP4-antibodies. Seronegative and seropositive NMOsd groups have similar phenotypes, and there is not yet neuropathological proof or therapeutic basis distinguishing them. Moreover, some "seronegative" patients may have undetectable AQP4-antibodies as the sensitivity of antibody assays is never 100%. These findings support that AQP4-seronegative NMOsd is a subset of NMOsd. However, clinical differences between seropositive and seronegative NMOsd have been observed, including M/F ratio and likelihood of simultaneous optic neuritis and transverse myelitis. Moreover, other autoantibodies have been identified in some anti-AQP4 seronegative patients, such as anti-MOG and anti-AQP1. Indeed, in an AQP4-seronegative NMOsd patient with MOG-antibodies, increased levels of MBP (marker of myelin injury) but not of GFAP (marker of astrocytic injury, increased in AQP4-seropositive NMOsd) were detected in CSF. These findings support AQP4-seronegative NMOsd as a new disease. Such questions, whether anti-AQP4 seronegative NMOSD is a new disease or not, will be raised and discussed.

AQUAPORIN 4 ANTIBODY NEGATIVE NMOSD IS A NEW DISEASE: YES

B. Weinshenker

Neurology, Mayo Clinic, USA

Since the discovery of AQP4-IgG, an important minority of NMO spectrum disorder patients were seronegative. Thus AQP4-IgG seronegative cases were "born" as soon as the antibody was discovered. Whenever cases are diagnosed by exclusion (absence of AQP4-IgG), there is potential for misdiagnosis. Seronegative NMOSD is almost certainly heterogeneous and includes seropositive cases with false negative AQP4-IgG results as well as NMO mimics, including MS, sarcoidosis and certain paraneoplastic and metabolic diseases. However, myelin oligodendrocyte glycoprotein IgG (MOG-IgG) has been recently associated with a subset of NMOSD; 25% of AQP4-IgG seronegative cases have this variant; its existence justifies my argument that this is a "new disease". MOG-IgG induces pathology when passively transferred, as does AQP4-IgG. However, attacks of MOG-IgG-associated NMOSD are not accompanied by prominent elevation of astrocyte injury markers (i.e. CSF glial fibrillary astrocytic protein) that is associated with AQP4-IgG-associated NMOSD. Other pathogenic NMOSD-associated autoantibodies may be defined in the future. To deny the existence of AQP4-IgG seronegative NMOSD is to say that we fully understand NMOSD with the discovery of AQP4. Doing so would force seronegative patients to where they were 20 years ago when they were diagnosed with "multiple sclerosis," a much less specific diagnostic entity and would put them at risk of being treated with multiple sclerosis-directed immunomodulatory treatments, which may harm them, as happened to AQP4-IgG seropositive patients in the past. We need to retain AQP4-IgG seronegative patients in the NMOSD category until we can more accurately understand and classify them.

THE FUTURE TREATMENT OF NMO IS IMMUNE TOLERANCE, NOT IMMUNE SUPPRESSION: YES

B. Weinshenker

Neurology, Mayo Clinic, USA

The time is ripe to explore immune tolerance treatments for NMOSD. First, the autoantigen, AQP4, has been definitively identified as has an immunodominant peptide to which T cells respond, an essential step to facilitating immune tolerance therapeutics. Second, as a consequence of improved understanding of T cell activation and T-B cell interactions, potential therapeutic strategies have been identified. Thirdly, technical advances in immunology and genomics render success achievable. Potential approaches to immune tolerance include: Vaccination to the inciting antigen to induce anergy; Vaccination to autoreactive idiotype-restricted T cells; Vaccination with dendritic cells, possibly modified by immunosuppressive agents, cytokines or antisense oligonucleotides targeting key costimulatory molecules, such as CD40, CD80 or CD86. Transfer of T regulatory cells engineered to be AQP4 antigen specific by transducing AQP4 antibody with an appropriated signaling domain; Transfer or enhancement of B regulatory cells, by a variety of methods. There can be no doubt that this approach is in its infancy, and no dramatic examples of clinical success can be claimed that would leave no doubt of the ultimate success of this "brave new world" of immune tolerance. But there is little doubt that this approach is the future and immune suppression with the need for indefinite treatment, partial efficacy and toxicity (infection, cancer and other autoimmune diseases) is less than desirable. The future is clearly restoring immune tolerance, repairing what is wrong, and working with the immune system as a partner and not fighting the immune system as an enemy.

CAN MEDICAL MARIJUANA OR CANNABIDIOL BE RECOMMENDED FOR TREATMENT OF EPILEPSY-CON...NOT YET

E. Ben-Menachem

Institute of Clinical Neuroscience, Sahlgrenska University Hospital, Sweden

Medical Marijuana (MM) or cannabidiol (CBD) are two different concepts. MM includes the psychoactive component THC as well as CBD, while the CBD products being developed for epilepsy are often restricted to 2 or 3 specific CBDs which have only very minimal amounts of THC. To what extent the CB receptors 1 and 2 are affected is also very important for each preparation. Probably THC is more active on the CB receptors than CBD. Recently one synthetic compound that modulates CBD under development as a medical product was so toxic that the volunteers in the Phase 1 study developed serious neurological deficits and one even died. There is successful ongoing development in clinical trials of a CBD drug for Dravets syndrome, infantile spasms and Lennox Gastaut, and more than 1000 people have used these specific CBD preparations. Still until clinical trials are completed and the side effect profiles of each separate compound is determined as well as interactions, CBD and MM drugs should not be encouraged.. MM is not recommended for people under 15 years of age due to the binding capacity of MM to CB receptors. It is thought that in adolescent years the brain is not adequately developed and potential permanent damage can occur. There is evidence that starting young and using frequently may disrupt brain development. So NO-MM and CBD should not be recommended as yet. We need to be careful and watchful. First do no harm.

SHOULD ANTIEPILEPTIC DRUGS USUALLY BE WITHDRAWN AFTER 2 YEARS OF SEIZURE FREEDOM?

E. Ben-Menachem

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There are many reasons why people with epilepsy who are seizure free for at least 2 years wish to withdraw their antiepileptic drugs (AEDs). Patients have an interest in living without medications if possible. AEDs have significant side effects both short term and long term so the goal of many is to be free of AEDs. Women who are just starting out in life and expect to be married and/or have children understand the teratogenicity of many AEDs and wish to stop as well. Accurately predicting the likelihood of seizure recurrence or the likelihood of being seizure free when the AEDs are withdrawn is an important task of the epileptologist when confronted with this question. Thus in this debate we will learn who can quit safely and who not. The decision to withdraw AED should not be taken lightly but only be taken after careful consideration of the risks and benefits, and informed discussion on individual basis. It is the opinion of this epileptologist that withdrawal should be attempted in children when risk factors are favorable. This can improve school achievement, social development, behavior, maturation and sexual development. Withdrawal can be attempted in adults when risk factors are favorable especially when the adult expresses a wish to try. Chances are good when risk factors are favorable but may be devastating when they are not.

THE IMPORTANCE OF CARDIOVASCULAR FITNESS IN THE PREVENTION AND TREATMENT OF EPILEPSY AND CO-MORBIDITIES

E. Ben-Menachem

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The benefits and risks of physical exercise are seldom discussed in people with epilepsy, and when discussed physical exercise is usually mentioned as a general recommendation without specific instructions. This is understandable because there is a lack of well conducted studies, especially randomized controlled trials, about the benefits of exercise in patients with epilepsy, especially refractory epilepsy. Because there are no adequate studies on the benefits of physical training in epilepsy, overprotection, social isolation, low self esteem, anxiety and depression become barriers to spontaneous exercise. That exercise can have a protective impact against the development of epilepsy was recently shown in a publication by Nyberg et al (2013). All Swedish military recruits born between 1957-1987 (n=1,000,178) who at the age of 18 had different stages of cardiovascular fitness (assessed by work rates at standardized exercise, and expressed as stanine scores) when starting their military training were further followed for up to 40 years afterwards. The results showed that the level cardiovascular fitness at age 18 can influence the development of epilepsy over subsequent years. Specifically, men with high cardiovascular fitness at 18 were significantly less prone to develop epilepsy given all other conditions remained the same such as incidence of traumatic brain injury, diabetes, hereditary factors and stroke. Animal studies have confirmed that exercise can have antiepileptogenic as well as anti-seizure activity, through a variety of putative mechanisms. Uncontrolled clinical observations also suggest a beneficial effect on seizure control. **Conclusion:** Cardiovascular fitness can be an important factor in the development and control of epilepsy.

CAN MEDICAL MARIJUANA OR CANNIBIDIOL BE RECOMMENDED FOR TREATMENT OF EPILEPSY? – ANSWER YES

M. Brodie

Professor of Medicine and Clinical Pharmacology, West Glasgow ACH-Yorkhill, UK

Despite the introduction of a range of new antiepileptic drugs possessing a variety of novel mechanisms of action, outcomes in the common epilepsies of adolescents and adults have not appreciatively improved over the last 20 years. Cannabis has been used to treat seizures since as early as 1800 BC in Sumeria. Indeed, William Gowers lauded its anticonvulsant properties in his 1881 textbook. Anecdotal reports of cannabidiol's substantial efficacy in a handful of children with Dravet syndrome has triggered a global explosion of interest in cannabis products for the treatment epilepsy. These lipid soluble molecules possess a specific pharmacology by binding to a unique range of receptors in the brain. Synthetic compounds such as cannabidiol and cannabidivarin are largely devoid of psychiatric properties. Preliminary open studies with the former in children and adults with pharmaco-resistant epilepsies are providing promising results with overt benefit and acceptable tolerability. A double-blind placebo controlled randomized trial with cannabidivarin in adults with focal epilepsy is well underway. There is increasing support for the effective and safe use of cannabis derivatives for the treatment of a range of epilepsies in children and adults. In conclusion, medical marijuana or cannabidiol can, indeed, be recommended for the treatment of epilepsy. These compounds represent a major area of drug development. They are, however, at an early stage and much work still requires to be done.

SHOULD VALPROATE EVER BE PRESCRIBED TO WOMEN OF CHILDBEARING AGE? ANSWER-SOMETIMES!

M. Brodie

Professor of Medicine and Clinical Pharmacology, West Glasgow ACH-Yorkhill, UK

Sodium valproate has long been prescribed for the treatment of epilepsy, bipolar disorder and the prophylaxis of migraine. In January 2015, the Medicines and Healthcare Products Regulatory Agency stated that "Valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated" because of concerns regarding its teratogenicity. This presentation will highlight some of the circumstances in which valproate could be considered for use in young women. Valproate is an effective treatment for all types of seizures, being particularly useful for the genetic epilepsies. Sodium valproate together with lamotrigine is the only proven synergistic combination of antiepileptic drugs. Valproate also inhibits the metabolism of lamotrigine, allowing lower doses of the former to be effectively employed combined with higher amounts of lamotrigine. In addition to valproate, phenobarbital, topiramate, phenytoin, carbamazepine, oxcarbazepine and lamotrigine all demonstrate dose-dependent teratogenicity. Thus, the lower the dose of valproate prescribed the lesser the risk of teratogenesis. In addition, daily doses of 1000 mg valproate or less are not associated with reduced IQ in exposed infants. Low dose valproate with or without lamotrigine in newly diagnosed or pharmaco-resistant epilepsy can be a uniquely effective therapeutic option, particularly for young women with generalised onset seizures. In addition, not every woman is sexually active or planning to start a family and these issues should be discussed with appropriate patients. Some of these scenarios will be highlighted by illustrative cases. Sodium valproate still has an important role in the treatment of epilepsy in a minority of young women.

DEBATE: DOES GENERIC DRUG SUBSTITUTION POSE RISK IN EPILEPSY? POSITION: YES

M. Holtkamp

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

Substitution of brands by generic drugs helped to save US consumers 160 billion US\$ in 2010. The crucial question is, if change between brands and generic drugs and between generics and generics is safe in regard of seizure control. Seizure recurrence after a previous period of seizure freedom may have paramount impact on driving and working restrictions. The two pharmacokinetic parameters assessed in bioequivalence studies are maximum serum concentration (C_{max}) and area under the concentration–time curve (AUC). The regulatory authorities allow that in generics both parameters may be up to 25% higher and up to 20% lower compared those in brands. In the extreme, this would mean that switching from one generic to another may expose patients to massive fluctuations in serum concentration of up to 45%. Even if recent findings on two different generic preparations of lamotrigine showed bioequivalence with no detectable differences in seizure frequency and tolerability, therapeutic equivalence may be challenged by patients' attitudes towards switching between differently appearing antiepileptic drugs. A case-control-study on antiepileptic drug generics with different color or shape indicated that changes in pill color significantly increase non-adherence. In conclusion, switching from brands to generic antiepileptic drugs significantly saves costs but patients need to be followed closely by therapeutic drug monitoring. After switching to a generic drug, the patients should stick to this particular generic. If generics are available when an antiepileptic drug is initiated, put patients on a generic drug to reduce costs but they need to stick to that particular generic.

CAN PSYCHOGENIC NON-EPILEPTIC SEIZURES BE DIAGNOSED BY ASSESSING BEHAVIOR WITHOUT CONCOMITANT EEG RECORDING?

J. Jędrzejczak

Neurology and Epileptology, Centre of Postgraduate Medical Education, Poland

Outside of epilepsy monitoring units the diagnosis of psychogenic nonepileptic seizures (PNES) constitutes a major challenge. 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 allows experienced epileptologists to predict the diagnosis of psychogenic nonepileptic seizures without the aid of EEG. The ILAE Commission on Neuropsychobiology Nonepileptic Seizures Task Force published a consensus on minimal requirements for diagnosis of nonepileptic events. The authors report that different levels of diagnostic certainty may be required for different scenarios (such as, diagnostic certainty levels may be different for research and for clinical purposes). "Using a consensus review of the literature, this group evaluated key diagnostic approaches. These included: history, EEG, ambulatory EEG, VEM/monitoring, neurophysiologic, neurohumoral, neuroimaging, neuropsychological testing, hypnosis, and conversation analysis. Levels of diagnostic certainty were developed including possible, probable, clinically established, and documented diagnosis, based on the availability of history, witnessed event, and investigations, including VEM" (W. Curt LaFrance Jr., Gus A. Baker, et al, 2013).

EPILEPSY AND PREGNANCY - WHICH ANTIPILEPTIC DRUG SHOULD WE CHOOSE?

Z. Petelin Gadze

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

Women with epilepsy have a slightly higher risk for some pregnancy and birth complications and require increased surveillance during pregnancy. Although two of three women with epilepsy remain seizure free throughout pregnancy, antiepileptic drugs (AEDs) dosages may need to be adjusted and therapeutic drug monitoring should be performed, at least every 4 weeks. Due to pharmacokinetic changes during pregnancy, the most pronounced decline in serum concentrations is seen for AEDs eliminated by glucuronidation, in particular lamotrigine (LTG). Consequently, the risks for uncontrolled seizures during pregnancy need to be balanced against potential teratogenic effects of AEDs. AED pregnancy registries continue to confirm that valproate (VPA) poses a significantly increased dose-dependent risk of structural and cognitive teratogenesis, ranging from 5.6% (750mg/day) to 24.2% (1500mg/day). Phenytoin (PHT), phenobarbital (PB) and topiramate (TPM) likely confer an intermediate risk of congenital malformations. Data thus far suggest that LTG, oxcarbazepine (OXC) and levetiracetam (LEV) are associated with a relatively low risk for both anatomic and developmental adverse effects. Accordingly, women with epilepsy should be treated with a low-dose monotherapy during pregnancy and VPA should be avoided. Supplementary folic acid (5 mg daily dose) is recommended, because this lowers the risk of cognitive teratogenicity. Third-trimester vitamin K supplementation has been suggested for women taking enzyme-inducing AEDs (eg. CBZ, PHT, PB), based on a concern for increased risk of intracranial neonatal haemorrhage. Experiences of the Referral Centre for Epilepsy of the Ministry of Health of the Republic of Croatia in treating pregnant women with epilepsy will also be presented.

SHOULD WE TREAT ELECTROGRAPHIC SUBCLINICAL SEIZURES? NOT ALWAYS

K. Rejdak

*Neurology, Medical University of Lublin, Poland
Medical Research Center, Polish Academy of Sciences, Poland*

Subclinical electrographic seizures represent the phenomenon associated with various clinical scenarios ranging from incidental finding in healthy subjects to non-convulsive status epilepticus in critically ill patients. Decisions upon treatment should be carefully balanced considering the benefit and safety of the patient. The principal idea of "primum non nocere" will always be valid and will have to be fulfilled in this context. The current presentation will focus on the clinical situations when treatment should be avoided in order to limit the possible risk associated with active treatment.

SUBDURAL GRID VS. SEEG: IS ONE BETTER THAN THE OTHER?

E. So

Epilepsy, Mayo Clinic, USA

Background: Stereoencephalography (SEEG) gained resurgence in use for localizing the focus for epilepsy

surgery. Being technically distinct from subdural EEG and requiring separate equipment and skills, questions have been raised regarding the comparative usefulness and roles between the two techniques. **Objectives:** 1) to identify the advantages and limitations of each technique for seizure localization; 2) to know the need for hypothesis-driven strategy when considering each technique; 3) To recognize the importance of concordance among non-invasive test results in guiding the site of electrode implantation with either technique. **Description:** In the absence of published studies that had compared the two techniques in a controlled manner, the format of case analysis will be used to assess the option of SEEG vs. subdural EEG. The audience will be engaged to provide the reasoning that guide each step in selecting and implanting either SEEG or subdural electrodes, or both. Postsurgical outcome in each case will be discussed to demonstrate, if not to validate, the decisions made.

SHOULD WE GIVE A DIAGNOSIS OF EPILEPSY TO SOMEONE WHO HAS HAD ONLY ONE SEIZURE (AS RECOMMENDED BY THE ILAE)?

W. Theodore

Clinical Epilepsy Section, National Institute of Neurological Disorders and Stroke, USA

NO In 2014, ILAE published a position paper recommending a change in the “practical clinical definition of epilepsy adding an additional criteria: “one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%)”. Several studies have shown that even a lesion like mesial temporal sclerosis, often thought a harbinger of seizure recurrence, may be unreliable. Two randomized studies found differing effects of EEG and other variables on recurrence. A study of 798 patients found 59% overall recurrence risk over 10 years. remote symptomatic etiology, simple partial seizures, Epileptiform EEG abnormality, and first seizure from sleep were independent predictors. Imaging lesions were correlated with remote symptomatic etiology, and only predictive of recurrence with etiology removed from analysis. Ten year recurrence risk fell below 60% after 6-12 months of seizure freedom. No patient group had 60% or greater four-year recurrence risk. Adverse consequences of epilepsy diagnosis include cost and potential side effects of AEDs. Children may experience adverse AED cognitive consequences; the elderly are more likely to experience AED toxicity, drug interactions; women the risk of teratogenicity. Even if treatment is withheld after a single seizure, driving restrictions, serious adverse emotional, health insurance, employment, social consequences and stigma may occur. Given the difficulty of predicting seizure recurrence, suggesting that even if one of the predictive factors is present, a diagnosis of epilepsy should not be made immediately after a first seizure.

DOES GENERIC SUBSTITUTION POSE RISK IN EPILEPSY?

W. Theodore

Clinical Epilepsy Section, National Institute of Neurological Disorders and Stroke, USA

NO Regulatory bodies require proof of “bioequivalence” between innovator and generic drugs. Does bioequivalence ensure therapeutic equivalence? Do patients experience more seizures or side effects on generics? US FDA criteria for bioequivalence is 90% confidence that ratios of test to reference mean AUC and Cmax lie within 80% to 125%. EMA and Canada use 0.90 to 1.11. Actual differences between FDA-approved innovators and generics were only 4.35% for Cmax and 3.56% in AUC. Several studies showed measured differences between innovators and generics are similar to differences between different lots of the SAME innovator. Insurance data and physician surveys suggest switching from one generic to an-

other might be detrimental. These reports suffer from several bias sources. Seizures occur randomly, and may be fallaciously associated with medication changes. Patients may be influenced by pill color and cost. Publication bias, commercial, media, and patient advocacy interests may play a role. A meta-analysis of randomized controlled trials through 2009 found no difference in seizure control attributable to generic versus innovator drugs; initiating either a generic or innovator compound led to similar clinical outcomes. EQUIGEN, a randomized double-blind cross-over study in patients switched between two lamotrigine generics found AUC 90% confidence intervals 98–103, and Cmax 90% 99–105, with no significant effects on seizure frequency or toxicity.

Data suggest little risk from generics per se. All AEDs may not have 'narrow therapeutic range;' we tend to obtain AED levels much less frequently with newer than older drugs. The higher cost of innovators than generics places large burdens on patients and society.

DEBATE: CAN PSYCHOGENIC NON-EPILEPTIC SEIZURES BE DIAGNOSED BY ASSESSING BEHAVIOR WITHOUT CONCOMITANT EEG RECORDING?

M. Tripathi

Neurology, NEUROLOGY, AIIMS, NEW DELHI, India

Psychogenic non epileptic 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 non epileptic 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 cues 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 pseudo seizures with true seizures. These can be documented only with simultaneous video EEG. Just depending on manifest behavior could have dangerous consequences for the person with these events. The entity of pseudo pseudo seizures is not rare and there are many focal seizures which could mimic a pseudoseizure. An overconfident approach might risk persons with epilepsy getting wrongly labeled as psychogenic events and ending up with consequences like injuries and SUDEP. The best management practices call for the need of documenting the event with EEG anything short of this would not meet the gold standard of diagnosis leaving a margin for errors.

ELECTRICAL STIMULATION WILL REPLACE MEDICATIONS FOR THE TREATMENT OF CLUSTER HEADACHE

H. Bolay

Neurology and Algology, Gazi University, Turkey

Neurostimulation is a rapidly growing field in the headache disorders and provides an alternative therapeutic option particularly for intractable and chronic primary headaches such as chronic migraine, chronic cluster headache, SUNCT, or hemicrania continua. By employing invasive or non-invasive methods, central or peripheral neural structures can be targeted for stimulation in headache syndromes. Among others stimulation of greater occipital nerve (ONS) and stimulation of sphenopalatine ganglion (SPGS) are promi-

ment for the management of intractable cluster headache patients. The exact mechanism of action for both procedures are still unclear. Review of the patients and follow-up data reveals following serious limitations: 1) ONS and SPGS are invasive techniques with device-related serious complications such as infection, pain, sensorial loss, paresis; 2) they are expensive and not cost effective, 3) battery and cable problems needs further surgeries, 4) Bilateral implantation is needed for ONS as a potential side shift (40%) occurs with unilateral implantation 5) pain and autonomic features are dissociated with ONS, 6) pain recurs upon cessation of stimulation 7) stimulation frequency yields opposite effects 8) lack of randomized studies with the use of a proper sham stimulation 9) Patients having neurostimulation still need concomitant use of prophylactic medications in long-term. Therefore, electrical stimulation of neither ONS nor SPGS will never replace medications for cluster headache.

THE THALAMUS AND CORTEX ARE MORE CRITICAL TO MIGRAINE PATHOPHYSIOLOGY THAN THE TRIGEMINAL NERVE

H. Bolay

Neurology and Algology, Gazi University, Turkey

Migraine is central nervous system disorder and characterized by a severe lateralized pain in the ophthalmic branch of trigeminal nerve, occipital nerve and upper cervical root distribution. Headache attacks are preceded and or accompanied by alterations in sensory perception such as photophobia, phonophobia, osmophobia, and allodynia. A cerebral cortical phenomenon known as cortical spreading depression (CSD) was linked to lateralized headache and shown to be able to activate peripheral trigeminal fibers and second order trigeminal neurons in the brainstem nucleus (TNC) (Bolay et al, 2002). By activating trigeminovascular system, CSD is implicated in releasing CGRP and nitric oxide from trigeminal nerve endings and leading to neurogenic inflammation in the dura mater. CSD is a key to understand familial hemiplegic migraine phenotype, critical involvement of glutamatergic synapse, female hormonal influence and the efficacy of preventive anti-migraine drugs (Eikermann-Haerter et al, 2009; Ayata et al, 2006). CSD is able activate thalamic reticular nucleus (TRN) (Tepe et al, 2015). TRN consists of GABAergic neurons that surround the thalamus and mainly functions as a gatekeeper of sensory outflow to the cortex, which is involved in selective attention, lateral inhibition, and discrimination of sensory stimuli. Sensorial perception is altered and prolonged during migraine headache attacks (Boran et al, 2016). Disruption of temporal discrimination of two consecutive sensorial stimuli seems specific to migraine headache attacks and proposed to be a neurophysiological marker for migraine (Vuralli et al, 2016, Vuralli et al, 2017). Research indicate a cortical alterations and dysfunctional thalamocortical oscillations take a role in activating ipsilateral brainstem pain structures and trigeminal pain nuclei. Migraine syndrome is not a trigeminal nerve mediated peripheral headache and the cerebral cortex and the thalamus have prime importance for migraine pathophysiology.

NEW DAILY HEADACHE IS A SECONDARY HEADACHE

R. Cowan

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According to the International Classification of Headache Disorders (ICHD), New Daily Persistent Headache (NDPH) is classified as a primary headache with sudden onset followed by unremitting headache, not better explained by another headache type. Like all primary headaches described in the ICHD, the diagnostic criteria offered are based entirely on consensus. However, in the case of NDPH (and one might argue other

headaches as well), it is far more likely that NDPH is not a discrete entity but rather a vague description of the phenomenology resulting from a potentially large number of etiologies. The body of evidence suggesting various circumstances which appear to lead to a headache meeting the ICHD criteria for NDPH is growing. Moreover, no compelling pathophysiologic argument have been suggest for the spontaneous transformation from headache-free to constant, unremitting headache, nor have unique characteristics of this headache beyond onset been suggested. Rather, it has been suggested that NDPH has sub-types that resemble Chronic Migraine (CM) and/or Chronic Tension-type Headache (CTTH). Similarly, it has been suggested that treatment can be based on these similarities to “recognized” chronic headaches other than NDPH. Most clinicians will agree that this strategy is neither effective nor logical if one posits NDPH is a unique primary headache. By contrast, multiple sources have described both case studies and series in which the sudden onset of a persistent headache follows a precipitating event, ranging from infection to emotional trauma. It is far more likely that NDPH represents a final common pathway of pain perception following significant trauma from a variety of sources.

CORRECTING THE DERANGEMENT IN SLEEP ARCHITECTURE IS SUFFICIENT TO TREAT CLUSTER AND MIGRAINE HEADACHE WITHOUT MEDICATION- NO

O. Daniel

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The relationship between sleep and headaches has been known for over a century. Migraine and Cluster Headache (CH) may cause sleep fragmentation, insomnia, and hypersomnia. Conversely, sleep disorders may trigger headache attacks. There is some evidence pointing to the anatomical and physiological overlap between sleep and headaches. However, the mechanism linking these two entities is yet unknown. Indeed, relatively small and mostly uncontrolled sleep studies of CH and Migraine have been conducted, and the results are inconclusive and contradictory. Factors known to trigger both Migraine and CH include not only sleep but many additional various factors like: feeding, stress histamine, nitroglycerine, alcohol, as well as environmental conditions. Additionally, the mechanism of action of many current medical therapies is not related to sleep. Thus, correcting the derangement of sleep architecture is insufficient to treat Cluster and Migraine Headache, and medication is required.

RELATION OF CGRP AND THE CGRP RECEPTOR TO MIGRAINE RELATED STRUCTURES IN THE CNS

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The peptide calcitonin gene-related peptide (CGRP) has a key role in migraine, supported by studies showing that CGRP is released in migraine attacks, infusion of CGRP can trigger migraine-like headache in patients and that studies with CGRP receptor antagonists show clinical efficacy. Experimental and clinical studies have shown that these molecules do not pass the blood-brain barrier to a significant degree and that the BBB does not open and close during migraine attacks. Tracing studies from the trigeminal nucleus caudalis (TNC) have demonstrated a clear connection with many of the different nuclei in the thalamus, various regions in the pons and brainstem, with the TNC. The studies show connections, not directions. Can we find CGRP in cytoplasm of cell bodies and CGRP receptor elements CLR/RAMP1 in these regions?

It is very notable with vesicular CGRP around the nuclei. The RAMP1 immunoreactivity is particularly rich in fibers while the CLR is less noticeable in these regions. In cerebral cortex there are numerous cell bodies that store CGRP but very few if any CGRP positive fibers. However, a rich plexus of fibers contain CLR and RAMP1. The role of this distribution remains to be determined. However, using CSD there may be upregulation of CGRP mRNA, and CSD effects in mice can be reduced with administration of a gepants (olcegepant). Caveat; there exist in brain lots of CGRP in cell bodies and fibers that store CGRP receptor elements. The physiology needs to be determined.

MEDICATION OVERUSE NEEDS TO BE TREATED WITH DETOXIFICATION SO THAT PREVENTATIVE THERAPY CAN BE EFFECTIVE IN CHRONIC MIGRAINE. NO

M. JA. Lainez

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It was traditionally thought preventive therapies were largely ineffective in the presence of analgesic abuse. Some studies have changed this vision. The first study demonstrating the efficacy of preventive treatments in patients with analgesic abuse was a European study using topiramate. Most patients (78%) met the definition for medication overuse at baseline. Even with this condition, topiramate reduced the number of monthly migraine days against placebo. Other trial conducted in the USA also compared topiramate with placebo for the prevention of chronic migraine. The subgroup analysis of the patients with MOH at baseline showed a reduction in mean monthly migraine. On the other hand, in the two pivotal trials comparing onabotulinumtoxin A with placebo injections in patients with chronic migraine, about 65% of patients fulfilled the criteria for MOH. At week 24, a larger reduction in the headache days per month –the primary endpoint of the trial– was seen in the onabotulinumtoxinA-treated group than in the placebo-treated group. These studies confirmed that the suppression of analgesics is not essential for preventive treatments to be effective. Other possible approach to MOH treatment is informing the patient about the mechanism of MOH, with the aim of reducing their intake of acute medication. There are some studies that demonstrated compared the effectiveness of advice on MOH with that of either outpatient or inpatient withdrawal of medication showing that advice alone was as effective as the other two interventions. All these studies demonstrate that detoxification is not essential for the treatment of patients with MOH.

ELECTRICAL STIMULATION WILL REPLACE THE MEDICATION FOR THE TREATMENT OF CLUSTER HEADACHE (CH). YES

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Patients with cluster headaches have few therapeutic options and some of them are not effective or are contraindicated. In fact 10–20% develop drug-resistant attacks.

Central (Deep Brain Stimulation-DBS) and peripheral neuromodulation (Occipital Nerve Stimulation-ONS, Stimulation of the Sphenopalatine Ganglion-SPGS, Vagus Nerve Stimulation-nVNS) techniques have been used widely in refractory and regular CH patients.

DBS placement for CH have been reported in very refractory chronic patients, with about 60% of pa-

tients responding positively with a decrease in the attack frequency of more than 50% ONS, in open label data, has been used in medically intractable CCH patients, showing a favorable outcome with a reduction of more than 50% of attacks in around 70% of patients.

SPGS, in a multicenter, randomized study has demonstrated a good efficacy for the acute treatment of chronic CH. Pain relief was achieved in 67.1% of full stimulation treated attacks compared to 7.4% of sham-treated attacks ($P < 0.0001$). A preventive response was observed also in some patients. A total of 68% patients experienced a clinically significant improvement. These data were confirmed in the long-term studies and clinical practice. A novel portable and non-invasive device to self-administer transcutaneous stimulus in the VN has been developed. This device was tried in a randomized study that compared the adjunctive use of nVNS with subject's standard of care (SoC) versus SoC with significant attacks reduction in subjects treated with nVNS. In summary, neuromodulation treatment could be very useful in patients with contraindication, lack of tolerability or refractoriness to the medical treatment.

BLOCKING CGRP WILL BE SAFE, EFFECTIVE AND CLINICALLY MEANINGFUL FOR PATIENTS WITH MIGRAINE AND CHRONIC MIGRAINE

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The various investigational drugs that target CGRP or its receptor would represent the first “designer” drugs for migraine and chronic migraine prevention. The reported reduction in headache hours was statistically significant, further testing will be necessary to determine whether “that is meaningful” in terms of improved function and quality of life. Given that the frequency of migraines can wax and wane, at least some people in these initial trials may simply be getting better on their own. Safety is also a concern. Theoretically, if CGRP is completely blocked you could translate a minor stroke or cardiac ischemia into a full blown stroke or heart attack. So far, the companies say they haven't seen that or other significant side effects in the several thousand people who have completed phase I and II trials, but the drugs have only been administered for up to 6 months – not long enough to judge long-term effects. Furthermore, the site and mechanism of action of CGRP monoclonal antibodies is unclear.

MEDICATION OVERUSE HEADACHE NEEDS TO BE TREATED WITH DETOXIFICATION SO THAT PREVENTIVE THERAPY CAN BE EFFECTIVE IN CHRONIC MIGRAINE

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Medication Overuse Headache (MOH) is common, highly disabling, refractory and most challenging to treat. Treatment of MOH is still controversial. Broadly, the debate is always between treating MOH by “WITHDRAWAL or WEAN of the offending drug Alone” OR “using BRIDGE therapy and starting PROPHYLACTICS at the same time as WITHDRAWAL of the offending drug”. Based on scientific rationale, I will be advocating the simultaneous use of prophylactics along with WEAN for the treatment of MOH. When dealing with MOH, definitions and terminologies need to be uniform. The 3 essentials for MOH are the presence of a background primary headache, overuse beyond specified limits of a drug that can predispose to MOH, and

loss of efficacy of prophylactics. Chronic Migraine (CM) in ICHD3 beta does NOT include Medication Overuse and 'Medical Overuse and Medication Overuse Headache' are not synonymous. We need to go beyond just 'WD alone' and add prophylactics and use a multi disciplinary approach because MOH is a bio-behavioral disorder that does not occur in isolation and MOH patients usually have psychiatric comorbidity and other risk factors. MOH needs to be addressed as a chronic illness that can relapse and since most MOH happens in migraine patients, we need to treat the background Migraine. There are also other genetic, neuroplastic and neurobehavioral factors because of which MOH needs multidisciplinary management. Since preventives will not work without WEAN and since there is a withdrawal syndrome it is necessary to employ all 3 modalities in MOH treatment – WEAN, Bridge therapy and Preventives.

THE STIGMA OF MIGRAINE

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Stigma is the severe disapproval or rejection of a person due to a trait or group membership perceived to indicate her or his deviance from social norms. We sought to measure stigma towards persons with migraine (PwMs) relative to persons with other disorders, and to define factors that influence stigmatizing attitudes towards PwMs. We employed a contrastive vignette technique in which participants (recruited via Amazon Mechanical Turk) answered an identical set of survey questions after being assigned to read one (and only one) of several vignettes describing individuals differing only by an independent variable. Independent variables in vignettes included the disorder of the person described (migraine vs. epilepsy vs. asthma vs. panic disorder) and/or that person's workplace reliability (zero vs. two vs. ten lost workdays per year). We found that the magnitude of the stigma towards PwMs approximated that for epilepsy or panic disorder, but exceeded that for asthma. We also found that stigma towards PwMs did not differ based on the sex of the PwM, but that male persons without migraine stigmatized PwMs more than did female persons without migraine. Stigma towards PwMs correlated with PwMs' workplace unreliability. We also found an individual's stigmatizing attitudes towards PwMs increased with the stigmatizing person's minority race, younger age, status of not having migraine, increased fear of pain, reduced expressed empathy, reduced fear of migraine, and lower income status. These findings further our understanding of the basis for stigma towards PwMs and may help to focus future efforts towards mitigating this stigma.

NEW DAILY PERSISTENT HEADACHE IS A SECONDARY DISORDER. NO

R. Weeks

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New Daily Persistent Headache (NDPH) is an uncommon and under-recognized Primary Headache disorder. Its clinical presentation may resemble migraine or tension-type headaches but a distinguishing feature of NDPH is a majority of patients can pinpoint the exact date of onset of symptoms. Head pain is daily from onset. As its phenotypic presentation is quite heterogeneous, some clinicians and researchers to refer to NDPH as a syndrome versus a distinct disorder. Though a great deal of research has targeted the discovery of an underlying etiology, a review of the literature suggests that over half of these patients cannot identify any underlying biological or behavioral antecedent. Most patients go through an extensive neurological/medical work-up looking for a causal link. The usually negative work-up can be quite frustrating to the

patient and the clinician. The ICHD-3 Beta lists NDPH in the Primary Headache disorder classification section. It is listed as NDPH 4.10 along with "Other Primary Headache Disorders". There is a chapter on Secondary Headaches, and the coding rules state that "when a new headache occurs for the first time in close temporal relation to another disorder that is known to cause headache, or fulfills other criteria for causation of that disorder, the new headache is coded as a Secondary Headache attributed to the causative disorder." This presentation will briefly describe NDPH, review the relevant literature regarding antecedent factors, and underscore how the application of the current classification rules makes NDPH a Primary Headache disorder. Hence, NDPH is NOT a Secondary Headache disorder.

YES - THE USE OF PLACEBO IS ESSENTIAL IN HEADACHE TRIALS

R. Weeks

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In 1962, the Congress of the United States passed the Kefauver-Harris Amendment that mandated that manufacturers provide evidence of drug effectiveness in addition to safety in order for the Food and Drug Administration (FDA) to approve the agent for a specific clinical indication. The FDA in 1970 published guidelines describing what acceptable controls in a clinical trial were. The double-blind randomized clinical trial was established as the "gold standard" for the emerging pharmaceutical industry. In 2012, the International Headache Society (IHS) Clinical Trials Committee published guidelines for controlled trials of drugs in migraine: Third Edition. In 2002, the World Medical Association Declaration of Helsinki stated that when an effective treatment for a disease existed, it was unethical to assign patients in a research study to a treatment known to be less effective. Standards for the acceptable use of a placebo in clinical trials have changed over time, and (with informed consent), it is now considered acceptable to use placebos in clinical trials where withholding the best current treatment will result in only temporary discomfort and no serious adverse effects. The IHS guidelines state that research protocols should allow the use of rescue medication any time after the first primary efficacy time point. This is necessary for the evaluation of "new treatments". In sum, demonstration of treatment efficacy demands that the target (active) agent must be shown to be statistically significantly superior to an inert substance (placebo) not believed to be a specific therapy for the target condition.

CLUSTER STORY; EXCEPTIONS THAT CONFIRM THE RULE. SIGNUM TEMPORIS, CIVILISATION TRENDS...

M. Wysocka-Bąkowska, M. Wysocka-Bąkowska

Specialist Policlinic, ENEL-MED Centrum Medyczne, Poland

Cluster headaches are the hardest challenge for general practitioner, even for a neurologist and for headacher! Cluster attacks are the most excruciating painful episodes, accompanied by autonomic symptoms. By definition we expect cluster periods with nocturnal attacks, occurring almost exclusively in male patients. As a neurologist and headache expert treating over 100 patients with cluster headache for the last 20 years, based on clinical observations, and teleconsultations, I do observe a trend towards rising occurrence of cluster headache in female patients, and the unusual prevalence of cluster attacks during day time. Cluster in women is increasing with years, as already suggested by other authors. Life style changes and masculinisation of women with cluster headache: social and hormonal aspects should be further analysed. Women that are more independent, more involved in professional career and single women seem to suffer

more often from clusters. Hormonal changes as lack of ovulation, PCOS, higher testosterone levels were observed. Careful interview and follow-up are essential for proper diagnosis and treatment. Sleep pattern and work pattern are essential to introduce a more adequate abortive and prophylactic treatment. Case presentation of patients with cluster attacks occurring during day time, after careful analysis of their work schedule, professional specific and surrounding conditions, seem to play a great role in establishing a different treatment recommendations. Different sleep-awake pattern requires a different scheme of medication use, that should be worked-out with patient. This can be achieved only in close contact between patient and doctor. Cluster patients are best contacted directly or via emails and telephones. The role of telemedicine should be strongly supported in those specific patients, suffering from the most painful, known so far, headache attacks with autonomic symptoms.

Female sex is less “protective” against cluster headaches. Not only evidence based medicine, but also medicine based on practical experts experience should be considered in teaching, based on individual “patient stories”, as life is our best teacher.

EARLY RELAPSE FREQUENCY DOES MATTER IN RELATION TO LONG TERM DISABILITY IN MULTIPLE SCLEROSIS

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Relapsing remitting phenotype is the commonest form of multiple sclerosis. A significant proportion of patients presenting with relapsing remitting disease would develop secondary progressive multiple sclerosis over a period of time. The relationship of relapses to long-term disability in multiple sclerosis has not been conclusive. Part of the difficulty in ascertaining the relationship between relapse and disability is the dissociation that exists between a clinical relapse, MRI changes and evolving cognitive, behavioural, sensory or visceral symptoms of multiple sclerosis. However, recent epidemiological data support the notion that frequent relapses in the first two years of the disease and shorter first inter-attack intervals are predictive of shorter times to reach hard disability endpoints (EDSS score of 6, 8 or 10). Shorter latency to secondary progressive disease is likely to be associated with shorter times to severe disability; in one study, time to EDSS score of 8 was significantly shorter among those with high early relapse frequency (≥ 3 attacks), and among those presenting with cerebellar and brainstem symptoms. High early relapse frequencies and shorter first inter-attack intervals are likely to predict disability from neurodegeneration characterising secondary disease progression in multiple sclerosis. The prevention or delay of the progressive phase of the disease is a key therapeutic target in relapsing-remitting patients, and is best achieved with early intervention with dual targets of relapse prevention and neuroprotection.

GENETIC RISKS CONTRIBUTE TO MULTIPLE SCLEROSIS

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Like most human diseases, multiple sclerosis (MS) is caused by complex gene-environmental interactions. The geographical distribution of MS and the migration effect have been attributed to potentially modifiable environmental risks. Recent reviews have indicated plausible associations of Epstein-Barr virus (EBV) infection and smoking with MS risk acquisition. However, there is no epidemiological association of Burkitt's lymphoma, nasopharyngeal cancer or primary CNS lymphoma (all linked to EBV infection) with MS prevalence. Similarly, few patients with ischaemic heart disease, stroke, chronic obstructive lung disease or lung cancer, all strongly

linked with smoking habit, ever present with MS earlier in life or later. Neither the population exposure to EBV infection nor the smoking habit may explain the higher incidence of relapsing remitting MS in younger women, the later onset of primary progressive disease and the geographic variation in MS prevalence. In contrast, population based studies indicate that familial aggregation of MS is genetic with no detectable effect of shared environment. A genetic contribution to MS pathogenesis is also supported by the discovery of *HLA-DR2* locus over 40 years ago. There is also an association of multiple sclerosis with genetic disorders of neural crest development (neurocristopathies). New tools of DNA microarray and genome wide association studies have led to the identification of a number of new MS risk alleles conferring a minor risk; these "at risk" genes are linked to both adaptive and innate immune functions. The study of epigenetic factors such as methylation, copy number variations, and post-transcriptional modifications, may identify the link between the individual genetic background and environment or lifestyle, and remain as future challenges to the researchers. Learning from other complex neurological disorders, such as Parkinson's, it would seem likely that there are MS subgroups with a dominant genetic component that explains the disease course, and in whom the discovery of new candidate genes might lead to targeted drug development and better therapeutic outcome.

RELAPSES DO NOT MATTER IN RELATION TO LONG TERM DISABILITY

J. Kruja

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Multiple Sclerosis (MS) is a chronic disease, commonly causing different levels of neurological disability. There are two main phases of classical MS: relapsing-remitting (RRMS) and secondary progressive (SPMS). During the first phase, the incomplete recovery from each relapse and the following cumulative disability are the main factors influencing the long term disability of the disease. The immunomodulatory therapy approved for the treatment of MS, intend mostly to reduce the frequency of relapses. During dozens of years there are a lot of studies trying to confirm the influence of these therapies on relapses on one hand and indirectly on the long term disability of the disease. We will try to introduce the pros and cons on the matter and to conclude for the most actual agreeably opinion.

IS NEURODEGENERATION IN MS ALWAYS THE CONSEQUENCE OF INFLAMMATION OR IT IS A SEPARATE PATHOGENETIC MECHANISM?

J. Losy

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Multiple sclerosis is a chronic autoimmune, inflammatory disease of the central nervous system, which leads to focal inflammatory demyelinated lesions with secondary neurodegeneration. Inflammation in multiple sclerosis appears as a crucial multi-step process beginning with peripheral immune reactions creating autoreactive T cells, transmigration of immune cells through blood-brain barrier, followed by demyelination, degeneration and axonal damage in the white and gray matter. Multiple molecular and cellular components mediate neuroinflammation in MS. They include CD4+ T cells, CD8+ T cells, B cells, microglia and macrophages. Infiltrating Th1 CD4+ T cells secrete proinflammatory cytokines, which stimulate the release of chemokines, expression of adhesion molecules and can be factors that can damage myelin sheath and axons. CD8+ T cells can directly damage axons. The mechanism of axonal damage is multifactorial and include

also actions of proteases, microglia activation with free radicals released during CNS inflammation and oxidative injury, mitochondrial damage as well as lack of neurotrophic factors provided to axons. A highly significant association between inflammation consisting of T cells, B cells, plasma cells and macrophages and axonal injury exists in MS patients including progressive forms of MS. The above association does not exclude the possibility that neurodegeneration may develop independently from inflammation. Active demyelination in the cortex is associated with microglia activation and related to meningeal inflammation. Some anti-inflammatory, immunomodulating drugs influence the course of MS, have influence on disability and decrease progression of brain atrophy.

OPTICAL COHERENCE TOMOGRAPHY (OCT) IS AN ESSENTIAL TOOL IN FOLLOWING UP MS PATIENTS

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MS patients are monitored during the disease mainly by clinical evaluation (number of relapses, progression of disability) and MRI activity. Optical coherence tomography (OCT) is non invasive technique, which could be used to evaluate neurodegeneration in MS by measurement of RNFL (retinal nerve fibre layer). RNFL and GCIP ((combined ganglion cell and inner plexiform layers (GCIP) thickness correlate with whole-brain volume in MS.. There is a steady decrease in the RNFL thickness over time in MS patients. Progressive RNFL thinning is evident even in the absence of a history of optic neuritis and RNFL thickness shows clinical correlations with disability measures like EDSS. Unfortunately there are several limits, which must be consider in using this technique to follow up MS patients. First RNFL thinning exists only in part of MS population and can not be used in all MS patients Another problem is specificity. OCT measurements are also affected by non-MS ocular conditions like glaucoma, cataracts,high myopia and others. Consensus criteria for retinal OCT underline complexity of the method, which could influence scan to scan reliability. Nevertheless OCT in my opinion has the future as one of tools, not necessary essential, in monitoring complex pathology in some MS patients.

IS MS PRIMARILY DUE TO GENETIC OR MODIFIABLE RISK FACTORS? ENVIRONMENTAL RISK FACTORS

R. Milo

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Genetic predisposition to multiple sclerosis (MS) only explains a fraction of the disease risk. Environmental factors and lifestyle are key contributors to the risk of MS. Environmental rather than genetic factors can account for most epidemiological characteristics as well as the changing natural history of MS observed in recent years, Among environmental risk factors identified, infection with Epstein-Barr Virus (EBV), hypovitaminosis D, smoking, the gut microbiota, high salt intake and obesity in childhood and adolescence seem to contribute significantly to the risk of developing MS. These factors may also interact with each other or with risk genes such as HLA and modulate adaptive and/or innate immunity, pointing at their role in affecting the immune-pathogenesis of MS. Similar to the genetic predisposing elements, the vast majority of environmental factors defined so far exert effects on the immune system, supporting their major contribution to the pathogenesis and etiology of MS. Beyond association, consistent data from epidemiological and experimental studies indicate that EBV, vitamin D and smoking fulfill most Hill criteria for causality and therefore can be considered as causal factors for MS. Additional research into the emerging and exciting field of the microbiome in MS may place it as another central player in the etiology of MS. Unlike genetic

factors, many environmental and lifestyle factors can be modified. Protective and preventive measures may contribute to the prevention and treatment of MS and should be incorporated into practical healthcare, in particular for individuals with a family history of this complex and challenging disease.

OPTICAL COHERENCE TOMOGRAPHY (OCT) IS AN ESSENTIAL TOOL IN FOLLOWING UP MS PATIENTS: YES

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Optical coherence tomography is a rapid and easily applicable technique to investigate the retina, also in diseases of the central nervous system that affect the visual system such as multiple sclerosis (MS). A plethora of OCT studies in the MS field has shown associations of retinal nerve fiber layer and ganglion cell layer thinning with visual function and visual quality of life, disease severity, brain atrophy and inflammatory lesions on brain MRI. Recent research has focused on the clinical use of OCT with regards to disease monitoring and prediction of disease course. Here, newer studies have shown that OCT may help predict disability progression measured by the EDSS in a large cohort of MS patients with various disease courses and stages, and that thinning of the ganglion cell layer in patients with clinically isolated syndrome is predictive of subsequent conversion to MS and retaining a NEDA (no evidence of disease activity) status. Also in case of acute optic neuritis, OCT may help stratify patients according to their risk of poor visual recovery. In sum, topical research supports the use of OCT as tool to follow up MS patients in clinical routine.

BIOMARKERS IN THE CSF ARE HELPFUL IN MEASUREMENT OF THE EFFECTIVENESS OF MULTIPLE SCLEROSIS THERAPY. YES

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A substantial progress in the field of CSF in multiple sclerosis (MS) can be observed in recent years. For example, quantitative and simple nephelometric determination of free kappa light chains has a good chance to replace demanding oligoclonal band (OB) test in the diagnosis of the disease. In addition, determination of neurofilament light chains (Nfl), a biomarker of axonal integrity can predict disability progression in a patient with early MS.

CSF Nfl are also helpful in measurement of the effectiveness of MS therapy. As shown in a seminal study from Gothenburg Nfl levels in the CSF normalized to the levels seen in healthy controls in patients treated with a potent agent natalizumab. Furthermore, in a subgroup of 36 patients in the FREEDOMS trial marked reduction of CSF Nfl was found when patients were treated with fingolimod compared to the placebo treated patients. In addition CSF Nfl decreased for more than 50% in 35 patients with primary progressive MS treated with rituximab and mitoxantrone suggesting that CSF Nfl determination could be a potential surrogate marker in progressive MS trials. A simple biomarker test obtained at the diagnosis can sometimes be helpful as a prognostic marker of effectiveness of therapy. In the BENEFIT trial, for example where clinically isolated syndrome patients were treated with interferon beta-1b OB-positive status predicted better response to the therapy. CSF biomarkers could also serve as predictors of possible, severe side effects. In natalizumab treated patients CSF OB sometimes disappear suggesting that the drug modulates B cell activity. This could result in an impairment of humoral immunity-mediated defenses against infectious agents with consequent reactivation of pathogens in the CNS, such as JC virus. A very important problem

of using CSF biomarkers for monitoring the disease activity are repetitive lumbar punctures which need to be as "patient friendly" as possible. Therefore usage of atraumatic needles which reduce the development of post-lumbar puncture headache should be recommended.

IS NEURODEGENERATION IN MS ALWAYS THE CONSEQUENCE OF INFLAMMATION OR IS IT A SEPARATE PATHOGENETIC MECHANISM?

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The pathogenesis of multiple sclerosis (MS) remains incompletely understood. This disorder is associated with susceptibility genes, most of which are implicated in the regulation of immune responses. The strongest association exists for HLA-DRB1*03:01, a major histocompatibility complex class II gene that mediates the activation of CD4⁺ T helper cells. The pathological hallmarks of all MS subtypes are focal areas or of demyelinating plaques in the central nervous system (CNS), with surrounding inflammation and neurodegeneration. Some studies show an abundance of myeloid cells and T cells in all MS lesion subtypes. Patients with early MS respond well to immunoregulatory agents. Some studies indicate that patients with acute disease have no peripheral immune cells in acute lesions, indicating that there may be a subset of patients in whom a primary aberrant adaptive immune response to CNS autoantigens is not required. Presumably, these patients will also not respond to immunotherapy.

DEBATE: BIOMARKERS IN THE CSF ARE HELPFUL IN MEASUREMENT OF THE EFFECTIVENESS OF MS THERAPY: NO

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The rather unpredictable nature of the course of Multiple Sclerosis has led to the search for biomarkers that are able to predict the disease course, diagnosis and therapeutic response. Biomarkers that can predict the response on treatment would be valuable, since it has been shown that changing the disease course is most effective early on in the disease and that delay in effectiveness of treatment leads to possible loss of brain reserve. The cerebrospinal fluid (CSF) is possibly the best site to look for biomarkers that measure therapeutic response, since prevention of damage to neurons and glia cells is what has to be shown. However, within this statement, a major limitation of possible use in daily practice lies, since this means that patients need to undergo repetitive lumbar punctures. For now, the most promising biomarker in the CSF seems to be neurofilament measurement (NFL), which correlates with axonal loss. However, NFL is secondary to axonal loss and, apart from therapeutic effect, timing of the CSF sample in relation to a relapse already poses some problems in interpretation of the data, limiting its specificity and sensitivity towards a therapeutic response. During the debate we will also look at other possible biomarkers and show that, at least for now, not only is a reliable therapeutic biomarker in the CSF not available yet, the practical limitation of repetitive lumbar punctures will also limit its use in daily practice.

DEBATE: MS TREATMENT ALGORITHMS: INDUCTION APPROACHES VERSUS ESCALATING PROCEDURES VERSUS DE-ESCALATING STRATEGIES INDUCTION

B. Wolfgang

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Multiple sclerosis (MS) is an inflammatory demyelinating disorders of the central nervous system with a supposed autoimmune pathogenesis. Pathology of MS is characterized by inflammatory demyelinating lesions in the grey and white matter with secondary neuroaxonal damage and astrocytic gliosis. The extent of inflammation and blood brain barrier damage is greatest in the initial stages of the disease and decreases with age and disease duration. The extent of inflammation within the lesions correlates with the extent of acute axonal damage in the lesions. This acute axonal damage finally leads to extensive axonal loss in the lesions and the normal appearing brain tissue. From the pathophysiological point of view, it makes sense to stop the inflammation in early disease stages as effectively as possible to prevent neurodegeneration associated with it. Therefore, the most effective therapies available should be used and therapy might be de-escalated when inflammation within the lesions is decreased.

BRAIN ATROPHY MEASUREMENTS SHOULD BE USED TO GUIDE THERAPY IN MS - YES

R. Zivadinov

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The assessment of brain atrophy in patients with multiple sclerosis (MS) has become one of the most important correlates and predictors for development of physical and cognitive disability in short-, mid- and long-term. Brain atrophy development is accelerated compared with the general population, continues throughout the course of the disease and is clinically meaningful from the earliest disease stages. There has been an increasing interest in understanding the effects of disease-modifying drugs (DMD) on slowing brain volume loss as an indicator of effectiveness of treatment. As clinical trials in MS are usually powered to assess effects on relapse rate, disability progression and lesion development, assessment of brain atrophy was used only as a secondary or tertiary endpoint in their study design. However, a recent meta-analysis study showed that the treatment effect on brain atrophy is associated with the effect on disability progression, and is partially independent of the effect of active MRI lesions. The majority of first-generation DMDs have shown only modest evidence of slowing brain atrophy, compared to placebo. There is mounting evidence that second-generation DMDs have a more robust effect in reducing atrophy when compared to placebo or active first-generation DMD comparators. Because of increasing evidence that DMDs can significantly slow down rate of neurodegeneration in MS patients, there is an important need to integrate brain atrophy, as metric of disease progression monitoring and treatment response at the group and individual level.

LEPTOMENINGEAL ENHANCEMENT ON MRI IS A PROMISING BIOMARKER TO MONITOR DISEASE WORSENING, ESPECIALLY IN PROGRESSIVE MS - YES

R. Zivadinov

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Gray matter (GM) pathology in multiple sclerosis (MS) is characterized by presence of cortical subpial lesions and leptomeningeal (LM) inflammation in the form of ectopic lymphoid follicle-like structures. It has been proposed that inflammatory cells in the leptomeninges may act to sustain the immune response contributing to development of subpial cortical lesions. Gadolinium (Gd)-based three-dimensional fluid-attenuated-inversion recovery (3D-FLAIR) MRI, shows that leptomeningeal (LM) contrast enhancement (CE) occurs frequently in secondary-progressive (SP) and relapsing-remitting (RR) MS patients, and is associated with subpial cortical demyelination on post-mortem examination. Because cortical subpial lesion pathology is challenging to visualize in-vivo using 3T MRI, LM CE has the potential to become an indirect in-vivo marker of cortical pathology. Therefore, there is an increasing interest for the application of this imaging modality in patients with MS. Given the uncertainty in the literature as to how common LM CE is in MS, with frequency estimates ranging from 1% to 61%, there is an urgent need to determine LM CE prevalence using state of the art MRI methods and a longitudinal prospective, serial study design. MS patients with LM CE showed significantly greater percentage decreases in cortical volume, compared to those without. In a recent retrospective study, while MS patients with presence of LM CE developed more cortical atrophy over 5 years compared to those without, no differences in deep GM volume changes were found between MS patients with and without LM CE, suggesting compartmentalization of inflammatory processes in the cortex.

RISK OF OBSTRUCTIVE SLEEP APNEA: THERE IS NO LINK TO SUB-TYPES OF IRRITABLE BOWEL SYNDROME

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Aims: Non-GI symptoms are common reported in Irritable bowel syndrome (IBS). Previous studies showed that there are changes in the patterns of IBS symptoms when self-reported sleep difficulties of uncertain etiology. This study investigated interactions of IBS-subtypes with risk of sleep obstructive apnea (OSA). **Methodology:** 100 IBS patients based on criteria Rome III and 111 control participants who completed the Berlin questionnaire, BQ scored as high or low-risk for OSA. Sleep quality patients evaluated by PSQI questionnaire. Depression and anxiety rates evaluated using Hamilton tests. Spearman's correlation, logistic regression and Bonferroni correction for the sub-test of batteries. Data were analyzed by the SPSS software, version 20, independent t-test, Chi-square test and regression test. **Results:** One hundred IBS patients included [74 women; age 38.06±11.09 Years]. 15% of patients had a high-risk BQ score compared with 1.8% of the control participants ($P=0.02$). Even after adjustment for age, gender and neck circumference (CI: 95%, OR=6.68, $P=0.02$). In the patients group, 18.9% of women and in the control group 2.3% of women were high risk for OSA ($P=0.001$), women with IBS were higher risk for OSA comparing to men ($P=0.03$). BQ score were not significantly associated with subgroups of IBS ($P=0.34$). Used by ROC curve, the best cut-off point for differentiating high risk from low risk of OSA in IBS was age, BMI and sleep latency equal or greater than

as 41 years, 27 Kg/m², 12.5 min. At these cut-off points, the sensitivity and specificity were 80 %, 73%-80%, 76%-93%, 88%. **Conclusions:** IBS patients were susceptible to OSA and there is a significant association between IBS and OSA. IBS-Mix group had high risk for OSA than the other subgroups, however, there is no significant association. Future studies must investigate relationship between of OSA among subtypes of IBS in regard to gender in greater sample size.

WHAT CAN GENETICS TEACH US ABOUT HUMAN MEMORY?

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Memory is a polygenic behavioral trait with substantial heritability estimates. Despite its complexity, recent empirical evidence supports the notion that behavioral genetic studies of specific memory subtypes might successfully identify trait-associated molecules and pathways. The development of high-throughput genotyping methods, of elaborated statistical analyses and of phenotypic assessment methods at the neural systems level has already facilitated the reliable identification of novel memory-related genes. Importantly, a necessary crosstalk between behavioral genetic studies and investigation of causality by molecular genetic studies will ultimately pave the way towards the identification of biologically important, and hopefully druggable, genes and molecular pathways related to human memory.

DEEP BRAIN STIMULATION EFFECTS ON NOUN AND VERB NAMING IN PARKINSON'S DISEASE

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Introduction: Embodied semantics theory suggests that action language requires the involvement of sensorimotor brain regions. Accordingly, Parkinson's disease (PD) patients have action language deficits. Noun production is preserved, whereas patients perform worse in action verbs compared to healthy controls. We aimed to investigate the effects of subthalamic nucleus deep brain stimulation (STN DBS) on noun and verb naming in PD and whether the effects are similar to the alterations in motor symptoms. **Methods:** Nine PD patients with bilateral STN DBS were included. Patients were tested while "on" medication. Patients performed picture naming tasks consisting of object nouns and action verbs during bilateral on, bilateral off, only left side and only right side stimulation. Motor symptoms were assessed with Unified Parkinson's Disease Rating Scale (UPDRS)- Part III during all stimulation conditions. Accuracy and reaction times (RTs) were analyzed for naming performance. **Results:** Naming performance was overall better in nouns compared to verbs. Stimulation conditions, however, did not have significant effects on naming. Word group and stimulation conditions also did not have interaction effects. Motor symptoms, on the other hand, were significantly improved by stimulation; UPDRS-Part III scores differed in between all conditions. Both noun and verb naming performance did not correlate with UPDRS- Part III scores during any of the stimulation conditions. **Conclusion:** Parkinson's disease patients seem to perform better in nouns than verbs while picture naming. Nevertheless, STN DBS does not seem to affect noun and verb naming as it affects motor symptoms.

ESSENTIAL TREMOR IS A SINGLE ENTITY

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Clinical, genetic, electrophysiological, pathologic, and pharmacological evidence show that essential tremor (ET) is quite uniform non-heterogeneous disease. According widely accepted diagnostic criteria of the Tremor Investigation Group, the diagnosis of definite ET is possible only when there is bilateral postural or kinetic tremor in the hands, without other neurologic signs, for at least five years. Ataxia and parkinsonism may accompany in some patients, both mild, but they are seen uniformly at older patients and are likely to be an expression of disease state.

Recent research revealed that action tremor emerging later in life may completely be a different disease entity than ET with its own clinical characteristics (mostly in contrast with ET) like short life span, cognitive deterioration, and other neurodegenerative properties. According to defenders of this assumption age-related tremor (so called ART) is a discrete entity leaving ET a disease with quite uniform age of onset. Nearly all of the treatments that have shown to be effective for ET, to date, involve the enhancement of a single and specific brain neurotransmitter system [i.e. GABA-ergic system]. Recently, a large GWAS of ET cases from Europe and North America detected association with SNPs in three markers (rs12764057, rs10822974, rs7903491) all in the cell-adhesion molecule CTNNA3 Cell adhesion molecules significant in pace making may also give a signal about a uniform nature of ET.

HOW DEMENTIA IN THE PARKINSON'S DISEASE BEGINS: VASCULAR PROCESS OR INFLAMMATORY PROCESS?

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Background and purpose: To answer the question of the inflammatory biomarkers have a suitable power in comparing to vascular biomarkers for diagnosis of dementia in the Parkinson disease, we investigate the effects of serum concentration of hs-CRP and IL-6 as representative of systemic inflammation on serum levels of ICAM-1 and VCAM-1 reflecting of endothelial relaxation which can consider as a possible factor for increasing of deimination process leads to the presence of anti-cyclic citrullinated antibody in serum of Parkinson patients with dementia. **Methods:** 75 consecutive definite diagnosed PD patients included which divided into idiopathic PD (n=55) and Parkinson's disease with dementia (PDD; n=20) based on DSM-IV criteria for diagnosis of dementia. Serum levels of vascular and inflammatory biomarkers investigated by ELISA assay and compared between PD and PDD. **Result:** An increase of serum levels of VCAM-1 found in PDD compared to PD (56.06±58.16 ng/ml vs 30/43±38/30, P=0/03), even after adjustment age, gender and hypertension (OR=1/01, P=0/05). Used by ROC curve, the best cut-off point for differentiating PDD from PD without dementia was VCAM-1 levels equal to or greater than 40/14 ng/ml. At this cut-off point, the sensitivity and specificity were 73%, 64%. **Conclusion:** PDD patients had higher mean levels of VCAM-1 than idiopathic PD after adjusting for risk factors such as hypertension, gender and age, suggesting the serum levels of VCAM-1 may be a useful marker for PDD diagnosis. Future studies are needed to investigate possible association between VCAM-1 levels with progression from mild cognitive impairment to dementia in larger sample size.

PROPOSITION: THE GASTROINTESTINAL SYSTEM IS IMPORTANT IN THE PATHOGENESIS OF PD PRO

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According to Heiko Braak pathological findings and staging, Parkinson's disease (PD) seems to involve a neurodegeneration which starts in the gastrointestinal tract (GIT) and progressively ascend and spread through the brain stem and basal ganglia up to the cortex. There are proofs that alpha-synuclein aggregates can propagate transsynaptically, which support Braak's scenario. Hypotheses of toxic or infectious PD etiology were taken into account in the last decades but no clear proof was obtained for either of them. However different studies suggested that only a part of PD cases respect this pathology expansion and today it is well accepted that PD has different clinical phenotypes. Recent work in different fields stresses out that microbiota is important for triggering pathological changes and/or modulates evolution of diseases and this theory might have an impact in PD as well. Last but not least, constipation is frequently an early sign in PD, fact that suggests that at least in a part of cases involvement of GIT is an early event and might have an importance in PD pathogenesis.

DEBATE: IS ALPHA-SYNUCLEIN A USEFUL BIOMARKER IN PD? NO

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Parkinson's disease (PD) is the second most frequent neurodegenerative disease, after Alzheimer's. As all neurodegenerative disorders, PD is characterized by aggregation of abnormal proteins, such as alpha-synuclein, in the form of Lewy bodies and Lewy neurites, which are also the pathological hallmarks of PD. Due to the long time course of pathological PD evolution before clinical symptoms onset, identification of biomarkers with high sensibility and specificity might allow earlier diagnosis and rethinking of neuroprotection clinical trials. Since according to Braak neuropathological staging alpha-synuclein aggregation is the first abnormality in CNS of PD patients, it makes sense to develop a method sensitive enough to detect alpha-synuclein early in disease progression. However, so far, in different studies exploring alpha-synuclein levels in blood, CSF, saliva and urine yielded interesting results, especially for the hyperphosphorylated form and extracellular vesicles species, but without clear specificity for PD. Alpha-synuclein was also found in skin and sympathetic nerve terminals in PD patients, but only a small number of patients were tested. An alpha-synuclein ligand for brain PET is not available yet and different research projects targeted such a development. In brief, alpha-synuclein cannot be used as a biomarker for early PD yet, but there is reasonable hope that further research will develop a method to help an earlier PD diagnosis.

IS IT POSSIBILITY OF MODIFYING ON PROGRESSION PARKINSONS DISEASE USED TRAINING OF GAIT?

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Aim: Now, symptomatic effectiveness of methods of gait correction with external cues (for Parkinsons Disease (PD) patients) is confirmed in randomized trials and in meta-analyses. Authors of abstract used self-development method of tempo-rhythmic correction (TRC) of gait (Russian Patent #2281695). Essence of TRC is special testing to select the individual frequency of auditory cues. During the gait synchronized with the tempo of the auditory stimulation. Gait trainee with step synchronization to an optimal frequency were held weekly, 3-6 times per day. We confirmed symptomatic effectiveness TRC (increased of gait parameters). The purpose of investigate was study potential modifying PD progression training of gait (due increased BDNF or other neurotrophic factors). Materials and Methods. We have retrospective evaluation data of PD stage in control group (n=30) vs. experimental group with TRC (n=30) at baseline, 6 months and 1 year. At Baseline both groups have 3 stage of PD, stable pharmacological treatment, step parameters, and have not statistic significant differences. **Results and Discursion:**

			Control group
Baseline	3,0	3,0	
6 months	2,73±0,52*	2,97±0,32	
1 year	2,90±0,48*	3,17±0,53	

*-p=0.05 (vs. control)

Conclusion: In 1 year timepoint experimental group had stage less, than control (2,90±0,48 vs. 3,17±0,53, p0.05). We see differences between baseline, 6 months, 1 year (p=0.05) in experimental group. In control group have not differences between baseline and 6 months, but have differences between baseline and 1 year (p0.05). The Gait training can have modifying effect on progression Parkinson's disease from our opinion. We need continue the research (prospective, with other endpoints, other scale measurements and more strict conditions).

DEMENTIA WITH LEWY BODIES AND DEMENTIA OF PD ARE THE SAME DISORDER

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Dementia with Lewy bodies (DLB) is the second most common degenerative dementia subtype following Alzheimer's disease. It is characterized by progressive dementia accompanied by one or more core feature, i.e. fluctuations in cognition, visual hallucinations, and spontaneous features of parkinsonism, and supportive features such as rapid eye movement sleep behavioural disorder, reduced uptake on dopamine transporter imaging and neuroleptic hypersensitivity. The underlying mechanisms of cognitive decline and progression in DLB are poorly understood, but it is likely that both the cortical Lewy body and the Alzheimer-type pathology, which occurs in most DLB patients, contribute. Parkinson's disease (PD) is characterized by motor symptoms of parkinsonism but cognitive impairment and dementia occurs in most patients during the disease course. Like in DLB, wide-spread cortical Lewy bodies and the variable presence of Alzheimer-

type pathology contribute to cognitive decline in PDD. Despite the fact that different clinical diagnostic criteria have been utilized for DLB and PDD, the clinical symptoms, cognitive and behavioural manifestations and results of paraclinical examinations remain very similar (although they may vary in individual subjects). Recently, specific non-motor subtypes of PD have been described based on possible routes of spread of pathology. In fact, the amnesic (cholinergic) mild cognitive impairment PD subtype seems to be indistinguishable from DLB. Thus the same disease can be named differently depending on whether the patient is handled by the movement disorder specialist or dementia specialist. Further research is warranted to bring evidence for this assumption.

IS THERE ENOUGH EVIDENCE FOR THE USE OF ANTIPSYCHOTICS IN PD PSYCHOSIS? NO

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Many PD patients develop in the advanced stages of their disease psychosis. Mostly, this is related to treatment with dopamine agonists, anticholinergics, amantadine or comedication. For this reason, it is mandatory to make a careful analysis of all drugs used by PD patients. Common treatment is started by tapering-off or cessation of such drugs, starting with anticholinergics, amantadine and then dopamine agonists. If this is not helpful or sufficient the use of antipsychotics is normally initiated. In general, most developed country can use clozapine and in some countries off-label use of quetiapine may be an option and finally in some countries pimavanserin is licensed. Pimavanserin has a unique mechanism of action relative to other antipsychotics, behaving as a selective inverse agonist of the serotonin 5-HT_{2A} receptor, with 40-fold selectivity for this site over the 5-HT_{2C} receptor and no significant affinity or activity at the 5-HT_{2B} receptor or dopamine receptors. The drug has met expectations for a Phase III clinical trial for the treatment of Parkinson's disease psychosis. Side effects were leg oedema and there is some concern with respect to QTc time prolongation. Clozapine has also major constraints due to its problems with possible agranulocytosis which make frequent blood test mandatory. In addition, clozapine may cause a delirium. Thus, many neurologists have a tendency to use quetiapine which is believed to have a sufficient efficacy in modest PD psychosis. And here comes the problem: we don't have any convincing study which would show a real high potency of quetiapine in treatment of PD psychosis. Thus, all existing anti-psychotic drugs show major limitations and thus it may be best to avoid psychosis by careful selection of PD drugs.

THE ETIOLOGY OF PD IS PREDOMINANTLY GENETIC? NO

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While we know, that more and more gene defects are related to PD it is also generally accepted that most patients do not suffer from a monogenetic form. This may be different in countries such as Israel and Northern Africa where many patients with PD present with a LRRK2 point mutation. In addition, there are reports that genetic abnormalities in the glucocerebrosidase (*GBA*) gene are important and common risk factors for Parkinson's disease and related disorders. Hypotheses proposed to explain this association include a gain-of-function due to mutations in glucocerebrosidase that promotes α -synuclein aggregation; substrate accumulation due to enzymatic loss-of-function, which affects α -synuclein processing and clearance; and a bidirectional feedback loop. But even if this is true, it is obvious that the majority of patients do not present with such genetic abnormalities. We and others could demonstrate in animal models that the exposure

to toxins such as rotenone induce PD pathology and phenomenology. The most often used PD model, the MPTP-model also uses a toxin to destroy dopaminergic cells and from environmental medicine we know that farmers in Iowa and California who use herbicides and pesticides and drink their own dwelled water have a considerably higher incidence of PD. Finally patients who were exposed to manganese and carbon monoxide also develop PD. Since the pathology, i.e. accumulation of abnormal alpha-synuclein starts in the olfactory bulb and the enteric nervous system in the gut, it is intriguing to speculate that some substances from the environment may cause the initiation of this alpha-synuclein pathology. If this is true, it has to be discussed why not everybody develops PD. For this it is important to consider that there seem to be genetic patterns, but not monogenetic abnormalities, that may make patients prone to develop PD when they are exposed to toxins or other substances from the environment. Taken together, there seems to be a link between genetic and environmental factors that may explain the so-called idiopathic Parkinson syndrome.

THE NEW ANTIPARKINSON DRUGS: ARE THEY REALLY BETTER?

L. Vecsei

Psychosis (PDP) develops in over 40% of Parkinson's disease (PD) patients. The most frequently used medications have been clozapine and quetiapine. Recently a selective 5-HT_{2A} inverse agonist, pimavanserin has gained approval for the treatment of hallucinations and delusions in PD. Clinical trials have confirmed its efficacy to improve PDP with excellent tolerability, safety and a benign effect on motor function. Levodopa (LD) treatment remains the gold standard for controlling motor and nonmotor symptoms of the disease. LD is extensively and rapidly metabolized by peripheral enzymes, namely, aromatic amino acid decarboxylase and catechol-O-methyltransferase (COMT). Opicapone (OPC) is a novel COMT inhibitor that has been recently approved as an adjunctive therapy to combinations of LD and aromatic acid decarboxylase inhibitor in PD patients with end-of-dose motor fluctuations. Safinamide is an alpha-aminoamide derivative with a combined, dopaminergic and non-dopaminergic mode of action. Phase III clinical trials with safinamide, as add-on therapy to dopamine agonist and to LD in early and advanced stage of PD, respectively, demonstrated an improvement of the motor symptoms. Alpha-Synuclein (Alpha-Syn) represents an important therapeutic target for synucleinopathies, including PD. Passive and active immunization targeting Alpha-Syn have both been tested in preclinical studies with promising results. Initial-phase clinical trials are already underway. Furthermore, alterations in glutamatergic neurotransmission contribute to the neurodegenerative processes and the development of motor symptoms in PD. Elevation of the level of the NMDA antagonist kynurenic acid (KYNA) might be a novel disease-modifying therapeutic tool and also for the management of LD-induced dyskinesia (Supported by GINOP-2.3.2-15-2016-00034).

THE ETIOLOGY OF PD IS PREDOMINANTLY GENETIC

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Parkinson's disease is a neurodegenerative disorder that is traditionally believed to be caused by an interplay between genetic and environmental factors. Highly penetrant mutations producing rare monogenetic forms of Parkinson's disease have been discovered in genes such as SNCA, Parkin, PINK1, DJ1, LRRK2, VPS35. Several other unique variants with incomplete penetrance have been discovered in LRRK2 and GBA. A simple estimation of an overall heritability of Parkinson's disease, taking into account the aforementioned genes, explains only 30% of familial and 3-5% of sporadic cases. The missing heritability of familial Parkinson's disease is estimated that will be discovered soon with the new whole genome approaches as

with the case of VPS35 gene. In terms of sporadic disease, numerous risk loci have been associated with PD through genome wide association studies. The following use of meta analysis of several data sets identified or confirmed 28 independent disease associated risk loci. The effect sizes of each of these loci are individually modest however the risk conferred by these in a certain individual can be large. Forthcoming GWAs with more comprehensive approaches will help resolving the genetic architecture of this disorder in the near future. On the other side, large epidemiological studies have revealed numerous environmental factors that are implicated in the etiology of Parkinson's disease. Interestingly, recent studies have shown that the association between many of these factors and Parkinson's disease may be affected by genetic factors. Therefore, the genetic component seems to be the strongest in the etiology of Parkinson's disease.

BIOLOGICAL NANOPARTICLES-EXOSOMES: NOVEL RESTORATIVE THERAPY FOR NEUROLOGIC INJURY AND DISEASE

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We have demonstrated that the biological mechanisms underlying the efficacy of cell-based neurorestorative therapy for stroke and neurological injury are attributed to the cellular release of exosomes. Exosomes are nano-size bilipid layer particles released by nearly all cells. They contain proteins, mRNA, lipids and microRNAs (miRs). Thus, we have employed exosomes harvested from stem-like cells, e.g. multipotent mesenchymal stem cells (MSCs), umbilical cord blood cells, as well as other cells, for the subacute (-1 day) treatment of stroke, traumatic brain injury (TBI), peripheral neuropathy, and other neurodegenerative diseases. Here, I will focus on the use of exosomes harvested from MSCs for the treatment of stroke and TBI. I will demonstrate that the exosomes are highly efficacious in promoting neurovascular remodeling and subsequently enhancing functional recovery post stroke and TBI. Data will also be presented that miRs play a primary role in mediating the therapeutic benefit of exosome therapy. I will also show that exosomes may be engineered to contain specific miRs, which can amplify their therapeutic benefit. Likewise, externally administered exosomes, will be shown to evoke a chain reaction-like effect, by stimulating endogenous parenchymal cells to further release their own exosomes, which contribute to functional recovery and neurological outcome. Thus, exosome therapy represents a novel and potentially highly efficacious means to treat stroke and neural injury. Exosomes are superior to stem cells; they do not evoke any adverse effects, such as malignancy, or induce microvascular occlusion, and, importantly, they can be designed to amplify targeted therapeutic benefit.

CPAP IS THE ONE AND ONLY RELIABLE TREATMENT FOR OSAS?

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CPAP treatment is unanimously accepted as the gold-standard treatment for all OSA patients with a Respiratory Distress Index (RDI) 30 events per hour, regardless of symptoms, based on the increased risk of hypertension and other cardiovascular issues. CPAP treatment is indicated for patients with an RDI of 15 to 30 events per hour (moderate type of sleep apnea) or even with an RDI of 5-15 events per hour (mild type of sleep apnea) accompanied by symptoms of reduced daytime functionality (i.e., excessive daytime sleepiness and fatigue), impaired cognition, mood disorders, insomnia, or documented cardiovascular

diseases to include hypertension, ischemic heart disease, or stroke. Evidence on the treatment of all the above-mentioned symptoms and/or Sleep Apnea comorbidities has been mostly produced with CPAP trials, which could provide more comfort to the sleep physician.

STROKE REHABILITATION SHOULD BE OFFERED ONLY IN A REHABILITATION FACILITY (FOR IN- OR OUT-PATIENTS)

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The stroke survivors may present many types of impairment: motor, sensory, cognitive, behavioral, communication and also activity limitations and participation restrictions. Rehabilitation is a medical process that assists stroke patients to achieve and maintain optimal functioning in interaction with their environment. Rehabilitation identify a patient's problems and needs, relating them to relevant personal or environmental factors, defining goals, planning and implementing treatments and assessing the effects. Rehabilitation is offered in hospital, institutional and community settings for in- or out-patient and as a home-base process. Advantages following rehabilitation offered in a facility: In a rehabilitation facility the doctors, therapists, nurses and other staff think and work as a team communicating a common understanding of what rehabilitation is. Team meetings for assessment and reposition to new goals are regular as the process goes on and the patient needs change. There is familiarization with protocols. Team members feel certainty from the presence of the specialized physiatrist-coordinator. There are limited interventions of the home helpers.-The stroke patient obtains motivation and gets familiarized to the new conditions through the contact with other patients with disabilities. His participation is better, as the staff can deal with the fact that his wishes and goals may differ from the assessment of the health professionals. Financial compensation usually is offered by the patient's insurance.

BOTULINUM TOXIN IN POST STROKE SPASTICITY. TREATMENT IN CHRONIC PHASE

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Spasticity in the chronic stage has characteristics witch specialists have to consider before perform botulinum toxin therapy. In this stage patients have adopt a consolidate motor and postural pattern due to maladaptive neuroplasticity. Owing to this fact the dosage will be much higher than in acute or subacute stage especially to the key muscles, responsible for the abnormal pattern. The dose performed to this muscle is estimated, not only by the Ashworth grade, but as well as its participation to the motor pattern. Is well known already that the grade of spasticity in the chronic stage is much higher as well as much more muscle groups are involved than in the acute and subacute stage. This fact is also one of the main reasons of using higher doses of botulinum toxin type A in this particular stage. Another component we have to consider in this stage is the possible changes in muscle composition established, local biomechanical changes, contractures, and fibrosis. Even in this case botulinum toxin therapy before as well as after the intervention optimizes the result. Especially in this stage we have to carefully set the goals of this particular treatment. The goals in this particular stage may be the motor facilitation, melioration of the motor and postural pattern, improvement in activities of daily living, facilitation of the patient or the care givers in hygiene, relief from the pain, prevention from complications due to spasticity, fitting of splints.

WELLNESS, COACHING AND MEDICINE – WHAT DO THEY HAVE IN COMMON?

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The fields of wellness, coaching and medicine have their own unique history and goals. Their emergence in the world is owed to humankind's pursuit for health, longevity and quality of life. Along the years and centuries the best of human knowledge has been applied to each of these fields. We will take a look at the objectives, definitions, origins, applications and modalities of wellness, coaching and medicine. We will examine how these fields merge for the benefit of patients and all human beings. We will place them in the light of the theory of evolution of human consciousness. Moreover, we will discuss the importance of mental, emotional and spiritual health, as well as how the doctor-patient relationship can support them. Gold star evidence for the effectiveness of wellness coaching in the medical model will also be presented. Doctors will be called to live a life of health and quality, and therefore become living examples of wellness. Their practice of self-love and self-care while making healthy choices for a more successful existence has the potential to inspire their patients and lead them by example.

BOTULINUM TOXIN IN POST STRIKE SPASTICITY-TREATMENT IN EARLY STAGE

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Spasticity can contribute to poor recovery of upper and lower limb function after stroke and therefore become a major cause of morbidity and disability. Spasticity management is essential for many patients during the subacute (early stage) and chronic phase of stroke. Conservative measures (physiotherapy, stretching, positioning, use of orthoses) are often inadequate to control spasticity, whereas oral antispastic drugs may provide poor results as well as side effects (dizziness, sleepiness, etc) leading to their discontinuation. Key role to post stroke spasticity treatment has the use of intramuscular botulinum toxin, which is licenced for both upper and lower limb spasticity. The following presentation debates on the time and setting of the onset of therapy with neurotoxin after stroke. Although there are sufficient guidelines about the selection and dosage of the administered toxin, the criteria of patient selection and especially the suggested onset of therapy remain unclear. Moreover, the indications and dosages for post-stroke spasticity management differ in relation to the different botulinum toxin types. A systematic review of bibliography reveals the heterogeneity of medical practice concerning the beginning of botulinum injection as well as the frequency, dosage, and muscle selection for the treatment.

NEUROPROTECTION DURING CORONARY ARTERY BYPASS FOR PREVENTING ISCHEMIC STROKE

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Background: Cerebral infarction due to coronary artery bypass considered to be an important factor for morbidity and mortality after cardiac surgery. This study has done to Evaluate the effect of Two drugs Citicoline and Piracetam on the protection of the ischemic stroke in people who undergo CABG. **Method:** We have considered 305 Patients who undergo CABG, they have given neuroprotective therapy including Piracetam and citicoline for four days. The incidence of ischemic stroke has examination during hospitalization. The data collection was analyzed by independent t-student, spearman correlation, logistic regression. **Result:** The post operate ischemic stroke was 3.2% (n=248) in case group and 11.5% (n=52) in control group ($p = 0.02$). After adjusting the sex, age, HTN, HLP, diabetes, smoking, ejection fraction (EF), bypass time, clamp time, these factors including bypass time, clamp time and EF ($P=0.01$, $P=0.04$, $P=0.04$) had an increasing effect on incidence of ischemic stroke. **Conclusion:** The results suggest that the relation between reduction of ischemic stroke and administration of Piracetam and citicoline during hospitalization. These findings may be to assist clinicians in reducing stroke mortality rates and improving the quality of life of survivors.

ANTICOAGULATION THERAPY SHOULD NOT BE RESTARTED IN NON-VALVULAR ATRIAL FIBRILLATION PATIENTS WITH ANTICOAGULANT-RELATED LOBAR INTRACEREBRAL HEMORRHAGE

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Anticoagulation-related lobar intracerebral hemorrhage (ICH) is typically caused by cerebral amyloid angiopathy, a condition that predisposes elderly patients to high recurrent ICH risk. Based on a Markov state transition decision model stratified by location of hemorrhage, restarting anticoagulation in such patients with non valvular atrial fibrillation can cause an unacceptably high risk of recurrent ICH, a risk that outweighs any potential gain from embolic risk reduction. For such patients with prior lobar ICH, withholding anticoagulation therapy was strongly preferred, providing the patient almost 2 quality-adjusted life years. For this reason, it is preferable to consider non-anticoagulant based embolic prevention therapies in such patients who had anticoagulation-related lobar intracerebral hemorrhage attributable to cerebral amyloid angiopathy.

DEBATE: STROKE REHABILITATION SHOULD BE OFFERED ONLY IN A REHAB FACILITY (FOR IN OR OUTPATIENTS) NO, HOME IS THE BEST PLACE FOR STROKE REHABILITATION

A. Galata

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Limited evidence based information is available on the best way to organize stroke rehabilitation after hospital discharge. Since stroke is a medical condition with significant long-term impact there is a need for further discussion on the most effective rehabilitation options for these patients. Moreover, there is a growing interest in cost-effective care, as health systems suffer increased economic pressures and prioritize a short in-hospital care, even when the patients are not fully independent to live at home. Many recent studies have suggested that home rehabilitation is more effective and cheaper than the usual in- or out-patient rehabilitation care. However, stroke is a multidimensional disease and several factors should be taken into account in order to reach safe conclusions. These factors include the age, the type and location of stroke, the degree of disability and functional dependence, socioeconomic status, the availability of an accessible and safe house, the support of family caregivers, and access to community and health services. Considering these factors, I will build a case for the value of the early home-based rehabilitation on functional independence and quality of life. It appears that home rehabilitation accelerates recovery and improved cost-effectiveness by reducing the use of hospital rehabilitation beds without compromising clinical outcomes. Furthermore, interventions that performed in a real-life scenario, to which therapists and patients can adapt according to the limitations, offer patients the added psychological benefit of being at home. Certainly a sustained communication and coordination among mobile rehabilitation team members and patients' family, friends, and other caregivers are paramount in maximizing the effectiveness and efficiency of rehabilitation potential.

TRANSCRANIAL STIMULATION MAY BE EFFECTIVE IN POST-STROKE APHASIA. YES

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Non-invasive brain stimulation (NIBS) can modulate the excitability and activity of targeted cortical regions and thereby alter the interaction within pathologically affected functional networks; this kind of intervention might promote the adaptive cortical reorganization of functional networks after stroke. In poststroke aphasia several studies attempted to restore perilesional neuronal activity in the injured left inferior frontal gyrus by applying excitatory high frequency repetitive transcranial magnetic stimulation (rTMS) or intermittent theta burst stimulation (iTBS) or anodal transcranial direct current stimulation (tDCS), but most NIBS studies in post-stroke aphasia employed inhibitory low frequency rTMS for stimulation of the contralesional pars triangularis of the right inferior frontal gyrus (BA 45) in order to reduce right hemisphere hyperactivity and transcallosal inhibition on the left Broca's area. While most studies reported single cases or small case series with chronic poststroke aphasia without any control condition, only a few controlled studies including sham stimulation were performed in chronic stage after stroke. In one controlled randomized study changes in PET activation pattern in the subacute course were related to the clinical improvement. In this "proof-of-principle" study the shift of the activation pattern to the dominant hemisphere induced by inhibitory rTMS over the right inferior frontal gyrus could be demonstrated in the PET activation studies and correlated to improved performance in aphasia tests. NIBS might be a treatment strategy which could improve the effect of other rehabilitative efforts.

MECHANICAL THROMBECTOMY IS EFFECTIVE IN M2 OCCLUSIONS: YES

O. Kargiotis

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Current guidelines for acute ischemic stroke treatment adopt a powerful recommendation for mechanical thrombectomy (MT) in carefully selected patients with emergent large-vessel occlusions (ELVO). The recommendation derives from the 5 recently published randomized trials that primarily investigated patients with proximal large-artery occlusions. However, these trials recruited also 94 patients with M2-segment middle cerebral artery occlusions, including 51 that received MT. A recent meta-analysis of the individual patient data from the 5 trials showed a trend for a better outcome with MT in M2 occlusions [OR 1.28 (95% CI:0.51-3.21)]. Another retrospective cohort study of 522 patients, including 288 treated with MT, disclosed a 3 times greater probability for good outcome in the interventional group, despite the control group having received more often intravenous thrombolysis (iv-tPA). A review of 83 patients with M2 occlusions from the IMS-III trial showed that outcome did not differ between M2-trunk and M1 segment, provided that both are successfully reperfused. The latest AHA/ASA guidelines outline that although there is limited data, patients with M2 or M3 occlusions could also be treated with MT (Class IIb; Level of Evidence C). Moreover, it is true that the differentiation between M1 and M2 segments is not always straightforward and some patients treated for M1 actually harbored M2 occlusions. Finally, cases with M2 occlusions and clear contraindications for iv-tPA, constitute a patient group with considerable neurological deficit that could potentially be reversed with successful recanalization. Thus, stroke physicians should not restrain from performing MT in carefully selected patients with M2 occlusions.

PATIENTS WITH EMBOLIC STROKE OF UNDETERMINED SOURCE SHOULD BE ANTICOAGULATED – YES

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The optimal treatment regimen for patients with cryptogenic stroke has been a matter of debate for decades. Several early large trials compared antiplatelet options with oral anticoagulation. However, in many of these trials dosing of medications in both arms were suboptimal according to present standards. In addition, patient populations were heterogenous. Therefore, results were inconclusive and even though some of the trials did suggest a small advantage of anticoagulation this was nullified by an excess of bleeding complications. Ever since two important aspects have changed. First, Embolic Stroke of Undetermined Source (ESUS) now defines a subgroup of cryptogenic stroke patients with much higher pathophysiological probability to benefit from anticoagulation. Indeed, as studies show at least a good proportion of these patients suffers from undetected paroxysmal atrial fibrillation. Second, the implementation of Direct oral Anticoagulants (DOACs) offer a safety profile almost comparable to antiplatelet therapy. Large clinical trials are underway to proof that DOACs are superior to antiplatelets in ESUS patients.

STROKE SECTION: THROMBOLYSIS AND THROMBECTOMY: TO WHOM AND WHEN? PROPOSITION: MECHANICAL THROMBECTOMY IS EFFECTIVE IN M2 OCCLUSIONS. POSITION: NO

V. A. Lioutas

Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, USA

Recent large, randomized clinical trials have proven the safety and efficacy of endovascular treatment (thrombectomy) in anterior circulation acute ischemic stroke. These well-executed trials included patients with occlusion of the internal carotid artery (ICA), M1 and M2 segments of the middle cerebral artery (MCA) and, in certain studies, the anterior cerebral artery. The results of these studies drastically changed the landscape of acute stroke management, making endovascular thrombectomy the standard of care in patients with angiographically proven vessel occlusions. Despite the unequivocal benefit for patients with distal ICA and proximal (M1 segment) MCA occlusions, the role of thrombectomy remains uncertain in patients with distal (M2 segment) MCA occlusions. The reasons for this uncertainty are several: First, the natural history of isolated untreated M2 occlusions is different and more favourable compared with M1 occlusions; therefore patients with isolated M2 occlusions might not derive a comparably robust benefit from thrombectomy. Second, the aforementioned trials were not powered to examine the effect of thrombectomy stratified by location. In fact, the number of isolated M2 occlusions was very small, comprising less than 10% of the treated population and making even post-hoc analyses problematic; therefore even the recent, large-scale clinical trials have not provided enough data to answer this question. Third, there are technical and anatomical considerations that need to be taken into account: the more distal location, smaller diameter, variable anatomy of the M2 branches make it more challenging for interventionalists.

PROPOSITION: NEUROSONOLOGY IS USEFUL IN ACUTE ISCHEMIC STROKE (AIS) MANAGEMENT. POSITION: NO

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Neuroimaging is an integral part of acute ischemic stroke management, guiding triage of patients and treatment decisions. Advances in technology have made several different options available, each with its advantages and disadvantages. Ideal properties of an imaging modality would include diagnostic accuracy, high sensitivity and specificity, safety, ease of access and reasonable cost, among others. Transcranial Doppler (TCD) can provide useful information regarding the vessel patency in patients with acute stroke. Its major advantages include safety and the ability to monitor patients in a continuous, dynamic manner. However, there are certain features that significantly limit the practicality and feasibility of its use in the acute setting: It requires the presence of a trained operator which is not feasible on a 24-hour basis and the study interpretation is highly operator-dependent. Moreover, vessel insonation is not possible in 5-10% of patients due to poor bone windows. TCD lags behind CT Angiography in specificity and sensitivity, especially for posterior circulation vessels and for distal branches of the anterior circulation vasculature. It does not provide information on structural aspects of the vasculature such as atherosclerotic plaque burden or vessel tortuosity. An additional potential advantageous property of TCD is the proposed enhancement of fibrinolysis with continuous insonation of the thrombus in conjunction with other lytic therapies. However, relevant clinical trials, including a recent Phase-III study have failed to demonstrate a clinical benefit.

HIGH-DOSE STATINS SHOULD BE ADMINISTERED IN ALL PATIENTS WITH ACUTE LARGE ARTERY ATHEROSCLEROTIC STROKE: YES

G. Tsivgoulis

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Taking statins before stroke may improve early outcomes including early neurologic deterioration, mortality, and disability in patients with acute ischemic stroke (AIS). In a recent meta-analysis, statin pretreatment was found to reduce mortality risk, while increasing good functional outcome at 3 months after stroke onset. In another systematic review, the beneficial effect of statin pretreatment in AIS was more profound in patients with high vascular risk and in patients with ideal low-density lipoprotein levels. Large artery atherosclerotic (LAA) stroke carries the highest risk of early recurrent stroke in comparison to other AIS subtypes. Our group and other investigators have shown that the potential beneficial effect of statin pretreatment and treatment during the first days of ictus is accentuated in patients with AIS due to LAA. The potential underlying mechanisms are related to improvement in cerebral blood flow due to the vasodilatory and pleiotropic effects of statins and to reduction of micro-embolism and artery-to-artery embolism due to statin-induced atherosclerotic plaque stabilization.

STATINS SHOULD BE DISCONTINUED IN PATIENTS WITH ACUTE INTRACEREBRAL HEMORRHAGE

D. Werring

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Although statins are of clear benefit in reducing the risk of ischaemic stroke, post hoc analyses suggest that statins are associated with increased risk of developing intracerebral haemorrhage (ICH). The underlying mechanisms remain unknown but could include decreased serum total cholesterol and low-density lipoproteins as well as pleiotropic effects (e.g. including anti-inflammatory, antithrombotic actions). By contrast, other data suggest that statins might improve outcomes when continued or initiated following ICH. Different underlying ICH types might be affected differently by statins. Increasing observational data suggesting that statins may be specifically associated with intracerebral haemorrhage caused by cerebral amyloid angiopathy (CAA). Associations between statin use and lobar intracerebral haemorrhage for those with the *ApoE* $\epsilon 4/\epsilon 4$ or *ApoE* $\epsilon 2/\epsilon 4$ genotypes has been described, while other studies report higher clinical impact of statins in those with lobar haemorrhages. Statins are also associated with lobar microbleeds, a presumed marker of CAA. Based on available evidence, recent decision analyses support the use of caution when prescribing statins in those with CAA. Data from large prospective observational and randomised studies are needed to improve understanding of the possible risks of statin use in ICH, and whether this risk is greatest for CAA. In this talk I will make the case for discontinuing statins in some patients with acute ICH.

THE DISCOVERY OF THE P.A53T MUTATION IN ALPHA-SYNUCLEIN GENE

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The mutation p.A53T (n. G209A) in alpha-synuclein gene, the first of its kind identified in families with Parkinson Disease (PD), was reported in *Science*, 27 June 1997. This was a publication of historical significance, as it represented the first evidence of a genetic cause for PD, a common neurodegenerative disease. The study was based on linkage analysis of the large Italian Kontursi kindred, but would have been incomplete without the identification of the same mutation in seemingly unrelated families from Greece, all with autosomal dominant inheritance of the disease. The publication was immediately followed by a wide number of comments in prestigious scientific press. The discovery of the mutation appeared in leading world newspapers, it was included in the New Year 1998 President's speech in USA and it created an interest by various bodies on the genetics of PD and patient recruitment. The publication had a great impact on PD research worldwide. It was soon shown that it is a rare PD mutation, nevertheless, it has appeared more than once in humans. Other point mutations, gene duplications and triplications were identified in diverse ethnic groups. However, from the beginning, the question of paramount importance was whether this mutation was the cause of PD, or instead, represented a linked polymorphism. Several pieces of experimental evidence supported a causal relationship. This opened a huge field of investigation of possible mechanism(s) of alpha-synuclein action, linked to alpha-synuclein expression, which, more recently, are central in the attempts for development of therapy for the disease.

THE NUANCES OF NEUROPATHOLOGY IN CARRIERS OF SNCA MUTATIONS

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The discovery that a missense mutation in the α -synuclein gene (*SNCA*), resulting in a p.A53T substitution, underlies autosomal dominantly inherited Parkinson's disease (PD) in members of the Contursi kindred provided a key step forward in understanding the disease. The importance of α -synuclein in idiopathic PD was emphasised by the observation that Lewy bodies, the pathological hallmark of PD, contain aggregated α -synuclein. The presence of α -synuclein in intracellular inclusions is now recognised as the defining feature of the group of neurodegenerative diseases known as α -synucleinopathies which includes PD, dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). Since the discovery of the first disease associated mutation in *SNCA* other mutations leading to amino acid substitutions and *SNCA* multiplications have been described. These mutations are associated with neurodegeneration and α -synuclein aggregation forming inclusions in neurons and, to a lesser extent, also in glial cells. This presentation will summarise the neuropathological findings associated with different *SNCA* mutations and multiplications in the context of the neuropathology of sporadic PD, DLB and MSA. Distinctive features associated with some mutations may alert the neuropathologist to an underlying mutation. Despite the rarity of *SNCA* mutations study of the neuropathological features in these cases will inform our understanding of the α -synucleinopathies and may provide insight into disease mechanisms.

USING NEURONALLY DIFFERENTIATED IPSCS DERIVED FROM PATIENTS WITH THE P. A53T MUTATION IN THE ALPHA-SYNUCLEIN GENE TO DISENTANGLE PARKINSON'S DISEASE PATHOGENESIS

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α -Synuclein (α Syn) is the major gene linked to sporadic Parkinson's disease (PD) while the G209A (p.A53T) α Syn mutation causes a familial form of PD characterized by early onset and a generally severe phenotype, including non-motor manifestations. Here we generated *de novo* induced pluripotent stem cells (iPSCs) from patients harboring the p. A53T mutation and developed a robust model that captures PD pathogenic processes at basal conditions. iPSC-derived mutant neurons displayed novel disease-relevant phenotypes, including protein aggregation, compromised neuritic outgrowth and contorted or fragmented axons with swollen varicosities containing α Syn and Tau. The identified neuropathological features closely resembled those in brains of p. A53T-patients. Small molecules targeting α Syn, reverted the degenerative phenotype both at basal and induced-stress conditions, indicating a treatment strategy for PD and other synucleinopathies. Further, mutant neurons showed disrupted synaptic connectivity and widespread transcriptional alterations in genes involved in synaptic signaling, a number of which have been previously linked to mental disorders, raising intriguing implications for potentially converging disease mechanisms.

THE OTHER MUTATIONS IN THE ALPHA-SYNUCLEIN GENE: IS THERE A COMMON DENOMINATOR?

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The alpha-synuclein protein, which has a central role in the pathogenesis of Parkinson's disease, is encoded by the SNCA gene. In the twenty years since the discovery of the first mutation in the Contursi kindred (A53T), a handful of further SNCA point mutations leading to missense amino acid changes have been discovered (A30P, E46K, H50Q, G51D, A53E). All but one are in the same exon, and appear to have arisen independently at most two or three times. The phenotype and age of onset can vary, with G51D the most severe, and therefore any unifying pathogenetic model would have to correlate molecular with clinical and pathological effects. Intriguingly, all affect the N-terminal domain of the protein, which can adopt an alpha-helical conformation when membrane-bound, with two helices and a hairpin. Disruption of membrane binding is therefore a plausible pathogenic mechanism. As the oligomerisation and aggregation of alpha-synuclein is seen as a key step in pathogenesis, a lot of work has investigated the aggregation propensity of mutants, and most lead to a clear increase in aggregation and fibrillisation *in vitro*. Furthermore, all but A30P cluster in a protein loop, situated between the two helices, indicating the importance of this region. The controversial tetramer model for α -synuclein has this loop at its core, so tetramer disruption is another possible mechanism. It should be noted that, in addition to these mutations, copy number variants (duplications and triplications) have been reported, and are indeed more common. Increased alpha-synuclein protein can therefore also lead to disease.

CARRIERS OF THE P.A53T MUTATION IN THE A-SYNUCLEIN GENE IN GREECE TODAY: AN OPPORTUNITY FOR BIOMARKER DISCOVERY AND CLINICAL TRIALS

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Introduction: There has been a paucity of recent studies with more detailed assessments of p.A53T SNCA mutation carriers with or without Parkinson's Disease (PD). Furthermore, biomarker studies or an assessment of the potential for clinical trials have not been reported. **Methods:** Within the MEFOPA FP7 Consortium, we have screened for the p.A53T SNCA mutation in select PD patients. We recruited 30 subjects, and characterized basic clinical features over a 2-year period. In addition, we have examined blood mRNA, and serum/plasma/erythrocyte alpha-synuclein levels. In more recent studies, we have enrolled such subjects in the Genetic PPMI study, and performed more detailed assessments, especially of non-motor features, in comparison to sporadic PD patients (sPD) also recruited through PPMI. **Results:** There was evidence of significant progression, especially of non-motor features, but also marked clinical heterogeneity, ranging from incomplete penetrance to very severe forms presenting with a fronto-temporal dementia-like picture. Blood mRNA levels of SNCA, or monomeric/dimeric alpha-synuclein in erythrocyte membranes were not different, whereas serum and plasma alpha-synuclein levels were lower than in controls. Detailed testing in the PPMI cohort revealed significantly lower scores in the mutation carriers in tests of olfaction and specific domains of cognitive functioning affecting frontal and parietal circuits. **Conclusion:** p.A53T SNCA mutation carriers appear to have certain clinical and biological differences with sPD. Accelerated disease progression, especially of non-motor features, may prove an asset in a clinical trial with disease-modifying agents targeting alpha-synuclein, if a sufficient number of patients can be recruited.

CEREBRAL LOCALIZATION IN ANTIQUITY

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Cerebral localization theories ascribe human functions to specific areas of the brain. These functions concern not only data of the senses but also of the intellect and emotion. Cerebral localization has become a topic of research for various disciplines, such as cognitive sciences, psychology, especially the experimental, neuropsychology, neurophysiology, psychiatry, neurology, psychosomatic medicine, philosophy (especially philosophy of the mind) and even theology. Although research on this field has made significant progress since the 19th century, the idea of cerebral localization of human faculties is not new but goes back in time as far as at least 3700 years. In this paper will be presented the most important theories on cerebral localization in antiquity as well as their evolution throughout the centuries.

NEUROLOGY IN THE EYES OF ANCIENT GREEK PHILOSOPHERS AND THE BIBLE: CONCEPTS ABOUT THE BRAIN/SOUL, NEUROLOGICAL SYNDROMES, AND SPIRITUAL THERAPEUTIC EFFECTS

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The roots of modern Neurology hold back thousands of years in ancient Greece and even earlier. Following a long debate about the location of the "soul" and the source of thoughts and emotions, the Hippocratic theory prevailed. Hippocrates taught that the brain is the source of all these and he established the principles of modern clinical Neurology. He gave fights to persuade that epilepsy is not a "holy" disease. The philosophers of this era also contributed to the discussion about the spiritual part of our body and nervous system. In parallel, numerous neurological conditions are mentioned in the Bible and the New Testament and the spiritual and "carnal" parts of each of these are often mixed and overlapping. Along with these descriptions, spiritual ways to affect the soul, and the "psychic" part of neurological diseases appeared, utilising principles of "faith/belief" in contrast to the purely orthologistic way of the scientists and philosophers in Greece. The intermarriage of these two ways, i.e. the logical approach and the -irrational- spiritual/psychic one, seems to represent the "golden path" for dealing with neurological diseases in general, even nowadays.

THE POINT OF UNITY IN MESOPOTAMIA

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All of us as a human need to one reference in own mind which can coordinate the conflicting ideas and effectively response to the conflicting events, then, Human can drain mental and physical stress and reached into relative balance. If this reference can't accountable, mental and physical stress will go to the internal feedback which source of incidence of various diseases. This point have many names such as God, Universe, Manna, Nirvana, Yahweh, Allah and etc. One of the Origins of modern civilization is the land of mesopotemia. People was lived in these areas who had believes on the multicenter power which the greatest was called El. During the time, Mesopotamia has undergone numerous social pressures such as war, Famine, natural disaster, etc. Polytheism beliefs were declined and the common belief was monotheism. People could converge heir thinking from multi-centered power at one point of unity that cause of creation adhami religions. Given this history, the theory arises whether social pressures can be converge our conception of interpretation facts to one point which called integrity or the specific idea can affect on our structure of mind and brain. Polytheism religions often covered a certain place with certain range, while, Gods of Abraham and Jacob promise that I'm keeper whenever human go. We are witnessing a breadth of coverage areas. It seems important how one Idea has been created which can be accepted by community and continuously be survive.

THE EVOLVING CONCEPT OF THE MIND-BRAIN RELATION FROM HOMER TO GALEN

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A prerequisite to answering the question of the relation between the mind and the brain (or any other bodily structure) is the existence of the concept of "mind". Yet no such concept was evident before and around the 8th century B.C. Different versions of it did, however, begin to emerge towards the end of the archaic era and have continued to proliferate from that time onward. The purpose of this presentation is to describe the relation of what we now classify as manifestation of mind with co-temporal physiological processes as that relation was understood at several pivotal points in the history of the development of the mind concept starting before its appearance and ending with its formulation by the Stoics and Galen in the 3rd century A.D.

THE ANCIENT HISTORY OF DEMENTIA

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Ancient Greek, Roman and Byzantine medical or medico-philosophical literature treats a vast variety of subjects relating to the early history of medical entities. Only a few are positively identified and matched to modern nosological entities, such as epilepsy or cancer. Nevertheless, bearing in mind that after Hippocrates, medical authors offer detailed descriptions of symptoms, clinical manifestations, prognosis and therapeutic methods, one may be lead to assumptions about possible connotations between ancient and modern diseases. Such is the case with dementia; under the terms "morosis", "moria", "anoia", or simply with the description of "an" illness, the ancient testimonies provide us with etiological factors, clinical manifestations, and prognosis of what we could possibly identify as modern types of dementia. The texts studied (medico-philosophical or literary) date back to the Pythagorean philosophers (~6th c. BC) up to Byzantine medical authors of the 13th century AD, shedding light to the evolution of the relation between the brain and the medical entity studied and to the way the physicians regarded "dementia" initially as a result of ageing and later as an illness per se.

HIPPOCRATIC CORPUS WORK "PRECEPTS": PHILANTHROPY AND UTILITY IN MEDICINE

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Hippocrates of Kos (460-377 BCE) is recognized as the father of scientific medicine, since he was free from superstitious beliefs and based diagnostic hypotheses on clinical signs. The renown Greek physician and his followers wrote many works, which constitute the Hippocratic Corpus. In this collection of medical texts, some were obviously composed several centuries after Hippocrates, since they contain anachronistic philosophical views and language styles. One such work, written in Greek but also containing latinisms, is 'Precepts' (Παραγγελῖαι), a book devoted to medical ethics. This text clearly comprises many concepts

introduced by Asclepiades of Bithynia (124-40 BCE), a Greek physician influenced by Epicurean philosophy who was famous in Rome for his humane and naturalistic opinions. 'Precepts' pronounces that "healing is a matter of time, but sometimes also a matter of opportunity", as a reference to Asclepiades' original notion of acute disease. It emphasizes that medical practice should be based on "empirical observation combined with reason and not on theories" and "evident facts transmitted to the mind through the senses", following the Epicurean approach based on sensual observation and inference by means of signs. It articulates several Epicurean views for the behavior of physicians, including the utility of actions and not pretentious words, the avoidance of arrogant attitude and flamboyant appearance, as well as their concern for the pleasurable state of the patients. Furthermore, it contains the Epicurean motive of goodwill to all humans: "For where there is philanthropy (friendship for humans), there is also friendship of the art (of medicine)".

FROM HIPPOCRATES TO THE 21TH CENTURY; THE ROLE OF PHYSICIANS IN SOCIETY

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Contemporary medicine is influenced by numerous factors that often lead to a collision between doctors' *ethical code* and *material world*. We will explore the evolution of social behavior towards physicians from antiquity until today, their attitude towards patients, and how the doctor-patient relationship has been formed. In order to understand the evolution of this relationship we should go back to the description of its primordial form in the Hippocratic era. In the treatise of the Hippocratic Corpus "*Precepts*" medical practice is marvelously described as an act of humanity: *Where there is love for man, there is love for science. A doctor should act with wisdom, reason and righteousness*. Medicine and high technology are converging as a natural progress but also as a necessity. Appealed by advanced medical equipment, physicians inevitably turn into technocrats. The technological advances have established a feeling of overwhelming confidence often leading to arrogance. This is the time that *A doctor should not be allured by the technological glamour and neglect or undervalue clinical practice*. Now more than ever doctors should reveal their philosophical thinking and grasp the essence of human nature. Let's remember how Galen criticized the physicians of his time: *We have reached a point where we praise Hippocrates and consider him the most important physician of all times; nevertheless we would do everything else but resemble him*. Concluding, the question is could young doctors become true leaders, examples for our society, better than their teachers?

THE HARD PROBLEM

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The conscious mind is our life as we experience it: we see the world, feel our emotions and think our thoughts, thanks to consciousness. Yet, for 21st century science, one of the greatest challenges is to explain *what consciousness really is*. Consciousness is currently one of the hottest topics in psychological science, neuroscience, and philosophy. How does consciousness, our subjective self or soul, arise from the activities of the brain? Why is consciousness such a difficult phenomenon to explain scientifically? Firstly, the legacy of Descartes' "*Cogito*"-argument forces us to accept that consciousness is something very real, something that really exists and whose existence we cannot possibly deny or even coherently doubt. Secondly, despite the certainty and the importance of consciousness, there is so far *no known mechanism* by which neural activities

(or any purely objective physical processes) could be converted to subjective experiences or consciousness. Many current philosophers claim that there cannot even be any *imaginable* mechanism mediating between the brain and consciousness. The lack of any conceivable mechanism between the brain and the conscious mind is labeled *the Hard Problem*, also known as *the Explanatory Gap*. In this lecture, I will first define the problems and then discuss what are the prospects for solving them. Does the Hard Problem force us back into some kind of Cartesian Dualism, or is it possible to explain consciousness neuroscientifically without seriously challenging the standard physicalist scientific worldview?

E-Poster Abstracts

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ADAMANTIADIS-BEHÇET'S DISEASE**POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME AS THE INITIAL CLINICAL MANIFESTATION OF NEURO-BEHÇET'S DISEASE: A CASE REPORT**

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Neuro-Bechet (NBD) is a presentation of Behcet's Disease where the central nervous system (CNS) is affected; this insult is too, heterogeneous in its features. Specifically, NBD largely consists of two clinical entities affecting the CNS: the more common form of meningoencephalitis arising from parenchymal insult, and a phenotype consisting of cerebral sinus thromboses' sequelae (non-parenchymal NBD). Among variations reported in the literature, reversible posterior cerebral venulitis has been previously reported as a potential phenotype of the non-parenchymal NBD variant. In a similar manner, Posterior Reversible Encephalopathy Syndrome (PRES) is a heterogeneous clinicoradiological entity typically comprised of a clinical symptom including headache, seizures and visual disturbances, combined with MRI findings indicative of reversible posterior leukoencephalopathy and vasogenic edema. As PRES became increasingly recognized, atypical radiological phenotypes were also described; the unilateral and reversible diffusion restriction variants. We present here the report of a case of a 72 year old female patient with a personal history of inflammatory bowel disease and Adamantiades-Behcet's Disease (ABD) that presented a clinicoradiological syndrome in the spectrum of atypical PRES, coinciding with the complication of ABD with the non-parenchymal variant of NBD. Though autoimmune disease has been proposed as an etiological factor of PRES, we are the first to our knowledge to specifically report a case of PRES in the setting of a first-onset NBD. Furthermore, we argue that in ABD, PRES may represent an intermediate, benign phenotype of NBD where endothelial dysfunction is transient, and thus the full spectrum of non-parenchymal NBD may not be developed.

ALZHEIMER'S DISEASE AND DEMENTIA**ENHANCEMENT OF COGNITIVE FUNCTIONS BY RICE BRAN EXTRACT VIA REGULATION OF PPAR γ IN NEUROINFLAMMATORY ALZHEIMER'S DISEASE MOUSE MODEL**

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Alzheimer's disease (AD) is a neurodegenerative disease for which currently there exists no effective therapy. Recent clinical trials of PPAR γ receptor agonists in AD patients revealed improvement in memory, representing a promising treatment for AD. Recent studies have demonstrated the protective effect of rice bran extract (RBE) on AD models. Moreover, Rice bran constituents, namely, polyunsaturated fatty acids and γ -oryzanol were recently considered as PPAR γ modulators. Accordingly, the effect of RBE on memory and cognition in a neuroinflammatory AD mouse model was examined. Furthermore, this study tested whether RBE improves cognition through modulating PPAR γ . Neuroinflammatory AD mouse model was developed by injecting LPS i.p (250 μ g/kg) for 7 consecutive days. Mice were administered by oral gavage for 21 days RBE (100mg/kg) or the known PPAR γ agonist pioglitazone (30mg/kg), or the PPAR γ antagonist GW9662 (3mg/kg) followed by RBE or pioglitazone. Mice were subjected to object recognition test, y-maze and

water maze test. Additionally, PPAR γ DNA binding activity was measured in mouse brains. Results indicate a significant improvement of the spatial working and recognition memory by RBE in the LPS mouse model. Interestingly, the effect of RBE on memory was abolished in the group injected with PPAR γ antagonist before RBE treatment, indicating the important role of PPAR γ in the mechanism of action of RBE. Furthermore, PPAR γ DNA binding was increased by RBE and this effect was reversed by PPAR γ antagonist. These findings demonstrate that RBE improves cognition and its effects are correlated with its action on PPAR γ .

SLEEP DISORDERS AND MILD COGNITIVE IMPAIRMENT

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Introduction: Mild cognitive impairment (MCI) is the transient stage between the normal old age and dementia. The transition from the normal aging in the MCI is sensitive. The observation of sleep changes can distinguish the healthy aging from dementia. Taking into consideration that the MCI diagnosis is based on neuropsychological evaluation, we must check to what extent sleep disorders contribute to the cognitive impairment of these people. **Objective:** The current literature review is going to analyze sleep disorders in people who were diagnosed with MCI. **Methods:** A systematic review of the existing literature was conducted in the following databases: PubMed, Embase and Medline. **Key words:** sleep disorders, mild cognitive impairment, elderly, AD. The articles were published from 2006 to 2016. **Results:** It is evident from the literature review, that the sleep disorders as one of the most common neuropsychological symptoms, are more frequent in patients who suffered from MCI compared with healthy elderly. On the top, their treatment may deter the onset of dementia. **Conclusions:** Sleep disorders are prevalent among the elderly diagnosed with MCI and neurodegenerative diseases. The determination of sleep changes could be transitive indicators in cognitive impairment or dementia. The disclosure of the relationship between sleep changes and changes in cognition is a gap in the literature in which future studies should investigate.

DISTINGUISHING BETWEEN WORKING MEMORY AND INHIBITION IMPAIRMENT IN DEMENTIA

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Dementia is often associated with impairments of both working memory and inhibitory control. However, it is unclear whether these are functionally distinct impairments. So far the eye-tracking studies of IC have relied heavily on studies that are based on the average scores from groups that were tested at a given time point. A detailed assessment of individual cases can address questions in relation to the dissociation of cognitive operations, which cannot be resolved by the average scores from a group of diverse patients. A key aim is to determine the value of eye-tracking in detecting early dementia. Are deficits of eye-tracking evident before impairments in traditional cognitive assessment in people with dementia? Do impairments of working memory and inhibitory control emerge at the same time in dementia? The patient group consisted of 18 patients with early dementia (13 males, 5 females). All patients underwent a detailed clinical history, physical/neurological examination and routine investigations. An old control group 18 healthy participants (8 males, 10 females) were volunteers from the local Lytham community. All OC participants underwent a detailed neuropsychological assessment. Tests for the dissociations of neurocognitive inhibitory control (anti-saccade) and working memory span were conducted with reference to the control sample using the revised

standardized difference tests. **Results:** 33% patients from the original sample (N=17) met the Crawford and Garthwaite (2005) statistical criteria for a “strong” dissociation. Some patients revealed a preserved working memory capacity together with poor inhibitory control in the anti-saccade task. A longitudinal follow-up revealed that the defective inhibitory control emerged 12-months before the dementia was evident on the mini-mental state examination assessment. Other cases revealed a poor working memory together with a well-preserved level of inhibitory control. There is increasing evidence that people with early Alzheimer’s disease have subtle impairments in cognitive inhibitory control that are often undetected by traditional cognitive assessments. We suggest that inhibitory impairment should be a focus of treatment, disease monitoring and assessment in pharmacological drug trials.

A UNIQUE PATTERN ON MEMORY TESTING IN DEMENTIA SCREENING PREDICTS OBSTRUCTIVE SLEEP APNEA

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Objective: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is used to screen for dementia. A unique pattern of Immediate Memory lower than Delayed Memory scores (IM<DM) predicted Obstructive Sleep Apnea (OSA), a potentially reversible cause of “dementia” in our Memory Care Clinic (MCC) patients. We reviewed the results for all patients evaluated in our MCC for a total of three years. **Methods:** A retrospective chart review of all patients seen in our MCC from December 2011 to December 2014 was completed. Those with the pattern of interest (IM<DM) were compared to those without the pattern for the presence of OSA. **Results:** A total of 191 patients fit the inclusion criteria of completing the RBANS during the period of the study. Of the total group, 81 (42%) displayed the IM<DM pattern; 54 of these patients had been or were subsequently tested for OSA and 35 were positive (65%). The average age of the positive group was 74 and 60% were women. A previous study showed that Body Mass Index (BMI) was not significantly different between the two groups. **Conclusions:** OSA is a known risk factor for cognitive dysfunction. It is a potentially treatable cause of memory loss and can be clinically silent. This study shows that a unique pattern (IM<DM) on the RBANS commonly used at Memory Clinics can identify a group of patients who can be evaluated for this common and remediable condition.

INVOLVEMENT OF NITRIC OXIDE IN ALUMINIUM NEUROTOXICITY: EFFECTS OF L-NAME ARE PROTECTIVE AND DOSE-DEPENDENT

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Undoubtedly, aluminium is a very harmful substance when it enters the human body, which happens primarily unintentionally from the environment. When accumulated in the brain, it is involved in severe damages found in chronic neurodegenerative diseases, including Alzheimer’s disease. Knowing the pathogenetic

mechanisms of these damages could improve prevention/treatment of aluminium-induced neurotoxicity. Since the important role of nitric oxide (NO) in these processes, in our research, just prior to aluminium chloride, a nonselective nitric oxide synthase inhibitor N ω -nitro-L-arginine methyl ester (L-NAME) was applied in the hippocampus of Wistar rats with three doses. Effects of both substances were examined clinically by the active avoidance test and biochemically by measuring cytochrome c oxidase and glucose-6-phosphate dehydrogenase activity in the forebrain cortex, basal forebrain, striatum and hippocampus. It was demonstrated that inhibition of NO synthesis protects animals against aluminium neurotoxicity. That was registered through improved behaviour, or even its reversion, i.e. the decreased number of active avoidance responses induced by aluminium chloride reached the values of control animals by the pre-treatment with L-NAME. Also, aluminium-induced disrupt of glycolysis and mitochondrial oxidative phosphorylation was statistically significantly improved with the highest dose of L-NAME. Neuroprotective effects of L-NAME against aluminium neurotoxicity was shown to be dose-dependent.

COMPARE THERAPY OF ALZHEIMER'S DISEASE WITH CHOLINESTERASE INHIBITOR (ARICEPT OR NIVALIN) PLUS AKATINOL-MEMANTINE

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Abstract BACKGROUND/OBJECTIVE: To compare the effectiveness of combination therapy with cholinesterase inhibitors (ChEI) plus Akatinol-Memantine in all AD patients and in older AD patients (age 75 years). **METHODS:** The Akatinol-Memantine Study was used to compare the clinical effects of combination therapy of Aricept plus Akatinol-memantine (n = 19) or Nivalin plus Akatinol-memantine (n = 16) in all AD patients, and in older AD patients separately, at 6 months with ChEI only monotherapy, and at 2, 4, and 6 months after addition of Akatinol-memantine to the treatment schedule (8 months total). **RESULTS:** The addition of Akatinol-memantine resulted in stabilization of the Mini-Mental State Examination scores and Hasegawa dementia rating for 6 months, and then significantly declined at 8 months in both subgroups. Frontal assessment battery (FAB) declined significantly at 8 months after Akatinol-memantine addition in the Aricept subgroup, while the Nivalin subgroup significantly improved at 4 months. Affective functions were well preserved after Akatinol-memantine addition until 8 months, except for the apathy scale at 8 months after Akatinol-memantine addition in the Nivalin subgroup. The combination therapy of Aricept plus Akatinol-memantine was better for apathy in older AD patients, and Nivalin plus Akatinol-memantine was better for cognitive functions. **CONCLUSIONS:** The addition of Akatinol-memantine stabilized cognitive scores much more for 4 months and affective scores for 8 months in the Aricept subgroup. Additionally, Akatinol-memantine significantly improved FAB at 4 months in the Nivalin subgroup although apathy scale became significantly worse at 8 months.

ASSOCIATION BETWEEN SERUM HAPTOGLOBIN AND THE PATHOGENESIS OF ALZHEIMER'S DISEASE

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Objective: Haptoglobin (Hpg) is known to have several functional properties, including antioxidant and anti-inflammatory activities. In addition, it has been shown that the pathogenesis of neurodegenerative disorders, such as Alzheimer's disease (AD), involves inflammation as well as oxidative stress. However, evidence suggesting an association between the serum Hpt level and AD is lacking. Therefore, we conducted this study in order to investigate whether serum Hpg is associated with AD. **Methods:** We compared the serum Hpg levels of 121 patients with newly diagnosed AD, 58 patients with Parkinson's disease (PD) and 43 healthy controls. We also evaluated the relationship between the severity of cognitive impairment in patients with AD and the serum Hpg level. **Results:** The mean serum Hpg level of the patients with AD was significantly higher than that of the healthy controls ($p=0.042$), although it was not significant different from that observed in the PD group ($p=0.613$). We also found a significant positive association between the serum Hpg level and the severity of cognitive impairment, as measured using several neuropsychological tests, in the patients with AD. The odds ratio (95% confidence interval) of the patients with AD grouped according to the Hpg level was 2.417 (95% confidence interval=1.134-5.149). **Conclusion:** We observed a significantly higher mean serum Hpg level among the patients with AD compared to the healthy controls. These results support the hypothesis that oxidative stress and neuroinflammatory reactions play a role in the pathogenesis of AD.

THE IMPACT OF MUSIC THERAPY AS A METHOD OF TREATMENT IN PATIENTS WITH ALZHEIMER'S DISEASE

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The notion of a specialized and independent memory system for music in the human brain is supported in several studies. Explicit memory for music differs between healthy people, patients with dementia and patients with Alzheimer's disease. Alzheimer's disease is the most common cause of degenerative dementia including progressive cognitive and behavioural alterations. Musical memory is the last to be impaired in comparison to other memory regions of the brain in the very late stages of the disease. Patients' poor response to medications has led to the development of non-pharmacological methods of treatment, especially music therapy due to the preservation of musical memory. Several studies show that music stimulation leads to the improvement of explicit memory, linguistic skills, and behavioural, emotional and social manifestations, as well as to the enhancement of motor learning and physical activity and an overall improvement of quality of life. Our pilot study in the Neurophysiology Laboratory of the University of Cyprus Medical School including neurophysiological tests in healthy young and elderly people and in patients with dementia and Alzheimer's disease aims to determine the differences in cognitive functions between these groups. Understanding these differences contributes to the development of music therapy as a simple and safe supplementary method of treatment with long-lasting effects. Our results support the further investigation of the cognitive alterations during aging and the potential neural mechanisms associated with music therapy's beneficial effects in patients with Alzheimer's disease. **Keywords:** music therapy, memory, Alzheimer's disease.

COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS: RECENT FINDINGS

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Cognitive impairment is one of the many symptoms in multiple sclerosis, which plays a critical role in the patient's everyday life. The most common cognitive deficits appear in information processing speed, attention, memory, learning, and executive functions. After years of research there aren't clear instructions in the assessment, which creates problems in the therapeutic process. This article is a literature review of the recent findings in deficits in MS patients and in neuropsychological tests' validity and reliability. Fifty seven articles published from 2006 to 2016 were selected. Most studies confirmed declining deficits in the domains that were mentioned in previous literature in various MS subtypes, but also in social cognition and emotion recognition. The examination of various already established cognitive tests in the detection of cognitive impairment and deterioration showed that SDMT (Symbol Digit Modalities Test) is the strongest measuring tool for IPS and working memory alongside with PASAT (Paced Auditory Serial Addition Task). The short version of BRB (Selective Reminding Test, PASAT-3 and SDMT) also had great results and covered many cognitive domains. CVLT-II (California Verbal Learning Test-II) was a sensitive test for verbal memory while BVMT-R (Brief Visual Spatial Memory Test-Revised) was a good screening tool for visual memory. Verbal fluency/executive functions can be assessed with WLG (Word List Generation). MSNQ (Multiple Sclerosis Neuropsychological Questionnaire) is recommended for everyday functioning and TASIT (The Awareness of Social Inference Test) for social cognition screening.

APOLIPOPROTEIN E E4 ALLELE FREQUENCY IN KOREAN PATIENTS WITH PARKINSON'S DISEASE DEMENTIA

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Background: It has been well known that the APOE ε4 allele is a strong risk factor in Alzheimer's disease (AD) and occurs at an increased frequency in dementia with amyloid pathology. However The clinical significance of the apolipoprotein E (Apo E) ε4 allele in Parkinson's disease dementia (PDD) with synucleinopathy has been a subject of debate. PDD is one of the second most common subtypes of dementia in Korean population. The Apo E allele frequencies were evaluated in Korean patients with probable PDD diagnosed by the MDS task force criteria for the diagnosis of PDD in this study. **Method:** Forty patients participated in the study, Twenty patients with PDD and 20 age matched healthy controls. The Apo E genotype was determined by the polymerase chain reaction (PCR) and allele specific hybridization using the Apo E typing test kit. **Results:** The Apo E ε4 allele frequency in the PDD group was 35% and was significantly higher than those of normal controls (15%) ($p < 0.05$). The Apo E ε4 carrier frequency in the PDD group was 60%, and also significantly higher than those of normal controls (30%) ($p < 0.05$). The Apo E ε3 allele was the most frequent genotype in Korean population generally in this study. **Conclusion:** These results that the elevated Apo E ε4 frequency in the PDD with synucleinopathy in which the overall brain neuritic plaque burden was low, indicates that apoE ε4 might contribute to neurodegeneration through mechanisms unrelated to amyloid processing.

DOES PERSONALITY INFLUENCE THE EFFICACY OF ART ON PAIN AND MOOD IN PATIENTS WITH ALZHEIMER'S DISEASE? EVIDENCE FROM A RANDOMIZED CONTROLLED TRIAL

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Art interventions are often proposed to patients with Alzheimer's disease (AD) and patients with chronic pain. Personality was demonstrated to play a role in the clinical evolution of both AD and chronic pain. This study aimed at assessing the role of personality on the efficacy of art intervention on pain and mood in patients with mild AD who also complaint about chronic pain. **Methods:** Fifty mild AD patients were randomized to a 12-week art intervention (painting or choral singing). Personality was assessed with the Big Five Inventory, identifying 5 traits according to the Big Five Model (Neuroticism, Openness, Conscientiousness, Agreeableness and Extraversion). Chronic pain, anxiety and depression were assessed before, just after intervention and 1 month later. The relationship between personality traits and the evolution of these three measures were assessed with mixed linear models. **Results:** The only significant change after art interventions was associated with neuroticism: a high level of neuroticism was associated with a paradoxical increase of chronic pain. In contrast, in patients with lower levels of neuroticism, pain decreased significantly after art interventions (Numeric Scale: $F=9.63$; $p=0.002$; Simplified Visual Scale: $F=5.92$; $p=0.016$; Brief Pain Inventory: $F=6.47$; $p=0.012$). Moreover, the evolution of mood disorders after art sessions was not influenced by personality. **Conclusion:** The present findings suggest some efficacy of art interventions in patients with lower neuroticism, but not for patients with a high level of neuroticism. They reveal the importance to identify these patients and to propose them alternative care.

DEMENTIA IN THE PRESENCE OF RBD IS SUFFICIENT FOR DIAGNOSIS OF PROBABLE DLB

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REM sleep behavior disorder (RBD) is characterized by dream-enacting behaviors with excessive motor activity. It has long been known that RBD precedes the development of neurodegenerative syndromes, especially synucleinopathies such as Parkinson disease (PD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB). RBD occurs in up to 70% of DLB patients and detection of RBD in patients with neurodegenerative dementia may suggest a Lewy body pathology¹. Third report of DLB consortium added REM sleep behavior disorder to the suggestive features of DLB diagnosis in 2005. RBD has been found to represent a red flag for progressing cognitive impairment^{2,3} and can precede other aspects of synucleinopathies by up to half a century⁴. In a study of patients with autopsy-confirmed DLB with low to high likelihood, the presence of RBD in the clinical history was associated with a higher likelihood of DLB pathology and less severe Alzheimer-related pathology in the medial temporal lobes, whereas absence of RBD was characterized by greater hippocampal and lateral Temporoparietal atrophy on MRI and increased phospho-

tau burden⁵. large cohort study of 174 patients with idiopathic RBD showed that the risk of developing a neurodegenerative syndrome from the time of idiopathic RBD diagnosis was 90.9% at 14 years⁶. In only a 4 year follow up, about third of patients (n=51) converted to DLB or PD⁶. There is a strong belief that RBD, when diagnosed by Polysomnogram, might be the strongest risk factor for DLB when compared with other signs^{7,8}. This body of evidence calls upon the experts to revisit the DLB diagnostic criteria and to consider RBD as one of the core features of DLB. Basically, RBD in the presence of dementia represents Probable Dementia with Lewy bodies.

THE VARIATION IN THE RELATIONSHIP BETWEEN MEMORY, COGNITIVE CONTROL AND THEORY OF MIND IN TWO GROUPS OF ELDERLY; PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND PATIENTS WITH VASCULAR RISK FACTORS

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Several studies have linked non-diagnosed vascular pathology with cognitive impairment. It is reasonable to maintain that since vascular disease affects the brain, it also affects cognitive functioning especially functions supported by the frontal lobes. The theoretical approach of the "vascular hypothesis of cognitive aging" posits hypertension, hyperlipidemia, and diabetes mellitus as basic risk factors for vascular disease. A step further in regards to cognitive decline, the term "Mild Cognitive Impairment (MCI)" was introduced to describe a subtle decline in cognition identified as a first "indicator" of the dementia trajectory. Besides the well established memory deficits, many patients with MCI deal with problems in executive functions or cognitive control processes while in the more recent literature, we come across studies on Theory of Mind (ToM) in MCI. The present study aims to investigate the differences of older adults having vascular risk factors and MCI patients in regards to the pattern of the relations between cognitive control, memory and Theory of Mind. The sample consisted of two groups (VRF and MCI) of older adults (n = 50), matched for gender, age and educational level. The findings indicated that complex ToM as indirect speech understanding was at a significantly lower level in MCI patients, as compared to community dweller VRF group. Moreover, MCI patients had a serious deficit in recruitment of combined executive functions in order to support indirect speech understanding.

AUTO-IMMUNE DISEASES

SERONEGATIVE NEUROMYELITIS OPTICA SPECTRUM DISORDERS, CHALLENGES IN DIAGNOSIS AND MANAGEMENT, A CASE REPORT

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24 year old female presented with few days history of pins and needles on her right toes and bilater-

ally on her fingers. She has background of chronic back pain and anxiety depression. A week later she presented to A+E with severe back pain and weakness on her right leg and left arm. A+E performed an assessment and she was reassured that her symptoms did not appear to be organic so she was discharged. Two weeks after the initial complaint she presented with severe weakness of her right leg, left arm and urinary retention. She was admitted and despite the rapid progression of her symptoms she appeared to have a functional element that made the diagnosis challenging. Two days later, after the presentation in the acute neurology ward she had progressed to being tetraplegic, with hard signs suggestive of spasticity. The MRI of her neuroaxis depicted extensive transverse myelitis sparing the brain. She was treated with intravenous methylprednisolone on the presumption that this is neuromyelitis optica but she did not show any signs of improvement. Her AQP4 and MOG antibodies returned negative but we endeavoured to treat her with plasma exchange. After the third plasma exchange she demonstrated signs of recovery on her upper limbs and after completion of the immunotherapy she started showing some improvement on the lower limbs as well. This very didactic case demonstrates the challenges that can be faced when there is a significant functional overlay and no serological confirmation, furthermore it depicts the dilemmas in treating immunoinflammatory conditions of uncertain aetiology.

ACUTE RETINAL NECROSIS (ARN) FOLLOWING RITUXIMAB THERAPY IN A NEUROMYELITIS OPTICA (NMO) PATIENT

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Background: Rituximab is the main disease-modifying treatment for Neuromyelitis Optica (NMO). It can be associated with severe complications. **Methods:** Case report: An NMO patient who developed Acute Retinal Necrosis (ARN) while on rituximab treatment. **Results:** A 36-year-old male was diagnosed with NMO five years prior to presentation. Treatment with rituximab (1g IV every 6 months) for the past 4 years, resulted in clinical remission. In September 2016 the patient presented with sudden loss of vision in the left eye (20/50) with associated mydriasis. Ophthalmologic examination was consistent with ARN. Cranial and orbital MRI revealed thickening and edema of the left optic nerve extending to adjacent chiasm, without contrast-enhancement. CSF PCR for viruses and toxoplasma were negative. He was also seronegative for HIV. PCR for HSV1 was positive in aqueous humor biopsy. IV acyclovir (750 mg three times daily) was given for 14 days; he was then switched to oral valaciclovir (1500 mg daily) for 3 months. Prednisone (60mg/d) was added. The patient had a remarkable recovery of visual acuity in the affected eye (20/25) at four months after symptom onset. **Conclusions:** ARN is a rare viral pan-uveitis that can be induced by rituximab treatment. In NMO patients on chronic treatment with this potent immunosuppressive agent, viral ARN should be considered when unilateral visual complaints occur. Clinicians should maintain a high index of suspicion to properly distinguish ARN from other NMO-related causes of visual loss, such as optic neuritis, so that prompt treatment is initiated.

AUTONOMIC NERVOUS SYSTEM DISORDERS

THE OUTCOME OF GANGLION CLIPPING IN HYPERHIDROSIS AND ACCIDENTAL WRONG CLIPPING

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Objective: The definite treatment for hyperhidrosis and facial blushing remains on surgery. This study is to assess the outcome, side effects and convey the concept of reflex sweating (RS) after sympathetic blockade (ESB) for the disorder. **Methods:** Between Aug 2001 and Dec 2003, data from 106 patients who underwent thoracoscopic ESB with clipping for various sympathetic disorders were retrospectively reviewed. In total, 69 patients had hyperhidrosis palmaris (HP), 30 hyperhidrosis craniofacialis (HCF) and 7 facial blushing (FB) were collected. **Results:** For HP, after T4 blockade, all successful with no reflex sweating. For HCF, after T3 blockade, all successful with mild reflex sweating. For FB, after T2 blockade, all successful with one patient intolerable reflex sweating (clipping reversed). There was no recurrence. Accidental finding of 4.4% of patients were unintentionally unilaterally clipped at wrong ganglion level→different feeling between two sides→confirmed by chest radiography→reclipped. **Conclusions:** The blocked level under the principle of Lin-Telaranta classification is of high successful rate, with very low side effects. Even an experienced surgeon would intervene the wrong ganglion and clipping provides a good marker for postoperative assessment.

THE INFLUENCE OF INTENSIVE UPPER-EXTREMITY TRAINING ON ENDURANCE AND CARDIAC AUTONOMIC REGULATION SYSTEM OF CHILDREN WITH UNILATERAL CEREBRAL PALSY: A SELF-CONTROL CLINICAL TRIAL

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Background: An intensive hybrid program improves upper extremity function as well as walking endurance of children with unilateral cerebral palsy (UCP). Endurance improvement may be associated with the cardiac autonomic regulation system (CARS) adaptation, known to be impaired among these children. **Objective:** To examine the influence of an intensive hybrid program on CARS, walking endurance and the correlation with upper extremity function of children with UCP. **Methods:** 24 children aged 6-10 years with UCP participated in a hybrid program, 10 days, 6 hours per day. Data were collected pre-, post- and 3-months post-intervention. Main outcome measures included the Polar RS800CX for heart rate (HR) and heart rate variability (HRV) data, the 6-Minute Walk Test (6MWT) for endurance, and the Assisting Hand Assessment (AHA) and Jebsen-Taylor Test of Hand Function (JTTHF) for bimanual and unimanual function. **Results:** A significant reduction in HR and an increase in HRV at post- and 3-month post-intervention was noted ($\chi^2_2=8.3$, $p=0.016$) along with a significant increase in 6MWT with a median increase of 81 meters ($\chi^2_2=11.0$, $p=0.004$) at the same interval. A significant improvement was noted in unimanual and bimanual performance following the intervention. **Conclusions:** An intensive hybrid program effectively improved CARS function as well as walking endurance and upper extremity function in children with UCP.

EPILEPSY

ANTIEPILEPTIC DRUG EFFECTS ON SEX-STEROID HORMONES IN WOMEN WITH EPILEPSY

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Introduction: Women with epilepsy are at risk for reproductive health dysfunction. Alterations in hormone levels are a direct effect of epileptic discharges, both in animals and humans. Antiepileptic drugs (AEDs) are known to have endocrine side effects in women with epilepsy. Distinguishing the side effects of antiepileptic drugs (AEDs) from the many other factors that influence the patients can be difficult. **Methods:** Sex-steroid hormones were evaluated in 20 reproductive-aged women with epilepsy receiving an AED in monotherapy. None of the patients had been diagnosed with an endocrine disorder before starting AED treatment or had used drugs that may interact with endocrine function. 10 women were treated with levetiracetam (LEV) and 10 with lamotrigine (LTG) for at least 2 years. Estradiol (E2), testosterone (T), dehydroepiandrosterone (DHEA), sex hormone-binding globulin (SHBG) were evaluated in follicular phase and progesterone (P) in luteal phase of menstrual cycle. **Results:** E2 levels were normal in all women. T levels were abnormal in 5 (25%) patients: elevated in 4 (2 on LEV, 2 on LTG) and lowered in 1. DHEA levels were elevated in 5 (25%) patients (2 on LEV, three on LTG). SHBG levels were elevated in 4 (20%) patients (2 on LEV, 2 on LTG), P levels were lowered in 9 (45%) patients (6 on LEV, 3 on LTG). Any abnormalities were found in 10 (50%) women (6 on LEV, 4 on LTG). **Conclusion:** These preliminary results indicate that new AEDs may alter sex-steroids levels in women with epilepsy.

ACOUSTIC RANGE MAGNETIC STIMULATION IMPROVES LEARNING AND MEMORY FUNCTION IN GENETICALLY PRONE TO AUDIOGENIC SEIZURE RATS

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Deterioration of the cognitive function is associated with epilepsy. Antiepileptic drugs lead to memory damage. Therefore, we decided to study effects of acoustic range magnetic stimulation (MS) on learning and memory functions in genetically prone to audiogenic seizure rats (GEPRs) and inbred white rats (n=14) by the use of a multi-branch maze. For this task a part of GEPRs and a part of inbred rats were radiated with MS. MS – 10000 Hertz frequency, 1,5 m/Tesla, during 5 days, 20 min per day changed behavioral seizure manifestations in GEPRs. MS decreased the number of errors (getting in the deadlock branch) that the rat was making to reach the destination and the time needed for passing the maze in both groups, especially in GEPRs. The time needed to reach the destination was less in GEPRs ($p \leq 0.05$) compared to inbred ones. We assumed that MS decreases anxiety and enhances exploratory activity of the GEPRs. Audiogenic seizure rats have damaged memory. MS on these rats improve their memory and this may lead to a new treatment for memory improvement. In our study we showed the positive effects of MS on learning and memory functions. Therefore, acoustic range MS can apply partial or complete suppression of seizures and improvement of memory function. These results provide further insights for a better understanding of the fundamental neurobiology of memory. Research was supported by FR /257/7-270/14.

HOW THE RATE OF TITRATION OF LAMOTRIGINE INFLUENCE TO ITS TOLERABILITY AND FREQUENCY OF SIDE EFFECT AND IS IT REALLY OPTIMAL?

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The prescription lamotrigine without titration significantly increases the risk of adverse reactions - most often a skin rash, which is the most common reason for early discontinuation of this drug. But in the available literature there is no clear substantiation of the rate of titration of lamotrigine suggested in the instructions. We studied the tolerance and safety of lamotrigine in 186 patients with epilepsy who have used the schemes more rapid titration, depending on additionally using AED. The drug as a first monotherapy was administered to 27 patients, 106 patients were used lamotrigine as an additional AED (without using valproic acid), and 43 - lamotrigine was added to valproic acid. The age of study participants was 18 to 54 years. Patients in history with a skin rash associated with the use of medicines or other allergic reactions associated with the medication, the study was not included. Monitoring of patients was carried out monthly for 12 weeks after lamotrigine prescription and dose beginning. For further analysis, we considered the frequency of such side effects as skin rashes, dizziness, nausea, vomiting and sleep disturbances as the most frequent for lamotrigine using. The frequency of adverse events in the study were compared with data from metaanalyses and multicenter clinical trials. Comparison of survey data with that obtained in the sources of the literature showed that increasing the speed of the titration of lamotrigine twice does not affect the increase in the frequency of more often side effects lamotrigine and the percentage of patients requiring drug discontinuation because of their appearance, as for all patients which used lamotrigine and as for separate clinical groups.

IS OVERDIAGNOSING OF EPILEPSY A COMMON TREND?

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Epilepsy is a neurological disease which affects around 0.5-1.0% of the population. Approximately 10% of the population goes through at least one seizure (febrile, metabolic, toxic, withdrawal etc.), but are not diagnosed with epilepsy. Further obstacle to correct diagnosis is the vastness of different types, including nonconvulsive attacks e.g., absence seizures. Thorough medical history correlated with the type of seizures present, supported by diagnostic research (including electroencephalography), plays a crucial role in proper diagnosis. In this study, we present only selected clinical cases of patients hospitalized in our department, who were earlier diagnosed with epilepsy which we could not confirm. In the majority of these cases, we diagnosed migraine with visual aura. In one case a patient was formerly diagnosed with complex partial seizures secondarily generalized seizures. The second case was previously diagnosed with absence seizures. In our opinion, clinical signs in both patients suggested psychogenic seizures. **Conclusion:** Even though this is not a population study but a presentation of selected cases, we have come to realize that overdiagnosing of epilepsy is an existing trend. There seems to be a necessity for more rigorous use of current guidelines or even a creation of new, more detailed ones, to enable correct diagnosis of epilepsy.

EPILEPSY IN PATIENTS WITH DOWN SYNDROME

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Subjects and Methods: At the period 2000-2016 at the Department of Psychoneurology N2, Russian Children Clinical Hospital and Department of Child Neurology, Neurosurgery and Medical Genetics, Russian National Research Medical University were observed 11 patients with Down syndrome (7 boys and 4 girls). Nine children with classic variant (47,XX,+21) and one boy with mosaicism (46, XX/47,XX,+21). **Results:** Age of epilepsy onset varies from 1,5 month to 4 years (8 month at the average), in 10 from 11 patients (90,9%) before 1 year of life. The most part of patients with DS presented West syndrome (n=7, 63,6%), 3 patients with Markand-Blume-Ohtahara syndrome or severe epilepsy with multifocal independent spike foci – SE-MISF (27,3%) and one girl with focal frontal lobe epilepsy, Lennox-Gastaut-like phenotype (9,1%). West syndrome was characterized by flexor and flexor-extension tonic spasms, serial and single. SE-MISF characterized of combination of tonic spasms, ophthalamo-tonic, myoclonic and versive tonic seizures. Lennox-Gastaut-like phenotype – with pseudo-generalized tonic axorhizomelic and myoclonic seizures. Clinical remission was observed in 6 of 11 patients with DS (54,5%), significant decreasing of seizures (75%) –in 4 (36,4%) of children and moderate decreasing– in 1 (9,1%). **Conclusion:** Epileptic seizures in DS predominantly had manifestation in infancy (90,9%). Epilepsy had predominantly good prognosis (complete remission of seizures in 54,5% and significant decreasing of seizures – in 36,4% of cases). The most effective drugs were valproates in monotherapy and in combination with ethosuximide, lamotrigine, benzodiazepines and barbiturates.

SURGICAL TREATMENT OF NONLESIONAL NEOCORTICAL EPILEPSY

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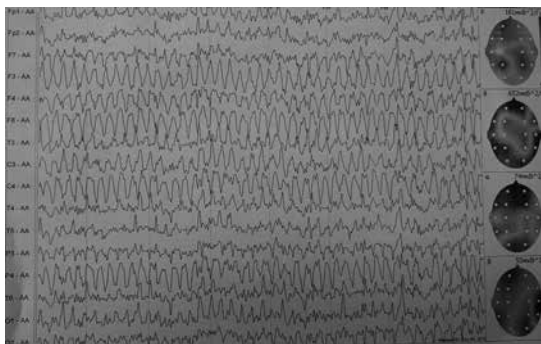
Objective: The proportion of surgery for nonlesional neocortical epilepsy has recently increased, with a decrease in surgery for mesial temporal lobe epilepsy. The objective of this study was to evaluate the long-term surgical outcome and to identify possible prognostic factors in patients with nonlesional neocortical epilepsy. **Methods:** We included 109 consecutive patients without MRI-identifiable lesions who underwent focal surgical resection for drug-resistant neocortical epilepsy. Follow-up information for at least 10 years was available for all but one patient. Univariate and standard multiple logistic regression analyses were performed to identify the predictors of surgical outcomes, and a generalized estimation equation model was used for the longitudinal multiple logistic regression analysis of up to 21 years of follow-up. **Results:** At 1 year after surgery, 59 out of 109 patients (54.1%) achieved seizure freedom, and 64 out of 108 (59.3%) patients achieved seizure freedom at the last follow-up. Only 11 out of 108 patients (10.2%) experienced definite changes in postoperative seizure status. Localizing patterns in functional neuroimaging, concordant results in presurgical diagnostic evaluations, the presence of aura, and complete resection of areas of ictal onset with frequent interictal spikes during the intracranial EEG study were favorable surgical outcome predictors. **Conclusion:** Our study showed that nearly 60% of patients with nonlesional neocortical epilepsy achieved long-term seizure freedom, and that changes in postoperative seizure status were rarely observed. Several predictors of favorable surgical outcomes were identified, which can help select optimal candidates for surgical treatment among patients with nonlesional neocortical epilepsy.

PSYCHOANALYTIC TREATMENT OF IDIOPATHIC EPILEPSY

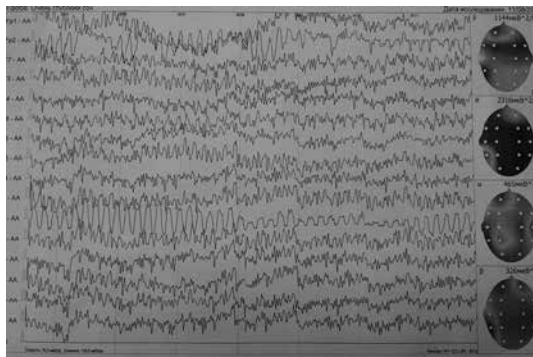
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Idiopathic epilepsy are common at different ages and varied in clinical manifestations. However, they all have common morphological substrate: a violation of the interaction of the hippocampus and the amygdala, as a structure who are responsible for switching of consciousness a variety of clinical manifestations helps the diagnosis of epilepsy, but does not play a fundamental role in the treatment. We affirm that idiopathic epilepsy have mixed ethiopathogenesis: they are caused by primary or acquired weakness amigdalo- hippocampal communication and psychological reasons. When the drug provides 100% control of seizures, - we begin psychoanalytically oriented psychotherapy. This type of therapy is aimed at the realization of unconscious processes, including - aggression, which plays a key role in causing excitotoxicity amygdala. Also, this type of therapy affects the re-evaluation of the meaning of experienced events that defines the operation of the hippocampus in the formation of long-term memory, stability of mind in situations of unbearable levels of sensory processing and experiences while sleeping. The treatment process includes regular testing and assessment of the patient's condition changes affective reactions, which allows you to determine when you can begin to undo AEP. Cancel preparations made gradually, for an average of 1-1.5 years. Changing control affect allows us to cancellation of a reliable product. Clinical example. Changed EEG pattern. EEG at the beginning of treatment.



Last EEG



Stopped seizures

THE EFFECT OF B12 DEFICIENCY IN ADULT SEIZURE OCCURENCE

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Introduction: Patients with known epilepsy, antiepileptic drug treatment, alcohol abuse, metabolic, cognitive or psychiatric disorders were excluded. Both groups were submitted to brain imaging. Correlation between the participants' variables and quantitative electroencephalographic (QEEG) values was estimated. Re-evaluation was repeated three months after B12 treatment. **Results:** Patients, with B12 200 pg/mL, showed statistically significant differences of their QEEG parameters both in relation to the control and second patient group. An increase of paroxysmal EEG activity was observed and 7% of them presented seizures. EEG recordings of the 2nd group were characterized by pronounced theta rhythms in the fronto-temporal regions and alpha3/alpha2 frequency ratio reduction, correlating with detected memory deficits. Restoration of EEG abnormalities was noted 3 months after intramuscular cobalamin supplementation. **Conclusion** B12 insufficiency appears to be associated with EEG rhythm alterations. Evaluation of B12 serum levels should be undertaken in differential diagnosis of late onset seizures 400 pg/ml).

NON CONVULSIVE ELECTRIC STATUS IN A PREGNANT PATIENT

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Introduction: Pregnant women comprise 25% of patients with epilepsy. Most of them require long-term treatment with AED. NCSE accounts for 4-25% of cases with SE. ESE constitutes 35-40% of cases of NCSE. Here we present the case of a pregnant with NCSE presented with psychotic symptoms during hospitalization makes ESE SE followed by the NCSE. **Clinical case:** the case of a 32 years old woman, in 33-34 week of pregnancy known for epilepsy F-T from many years, treated with VPA which was interrupted before 11 months. The patient presented to the emergency with frequent behavior psychotic left front-parietal crises partial, without loss of consciousness, mood swings, ramp head right and difficulties to communicate, lasting several minutes. During the first day the patient enters the SE for about 4 h and was treated with IV Phenytoin. On the second day of hospitalization was significantly improved but the situation electrically ESE EEG results. Phenytoin treatment continues according to the protocol of Lamotrigine start. On the 5th day patient was seizure free and improvement of EEG track is observed. **Conclusion:** In women with epilepsy condition can deteriorate during pregnancy. NCSE can cause psychosis-like behavior. Hormonal changes during pregnancy crisis explain clinical presentation. ESE cases are very rare and more in pregnancy. Management of women with epilepsy in the perinatal period remains a challenge in medicine.

EPILEPSY AND PREGNANCY - WHICH ANTIPILEPTIC DRUG SHOULD WE CHOOSE?

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Women with epilepsy have a slightly higher risk for some pregnancy and birth complications and require increased surveillance during pregnancy. Although two of three women with epilepsy remain seizure free throughout pregnancy, antiepileptic drugs (AEDs) dosages may need to be adjusted and therapeutic drug monitoring should be performed, at least every 4 weeks. Due to pharmacokinetic changes during pregnancy, the most pronounced decline in serum concentrations is seen for AEDs eliminated by glucuronidation, in particular lamotrigine (LTG). Consequently, the risks for uncontrolled seizures during pregnancy need to be balanced against potential teratogenic effects of AEDs. AED pregnancy registries continue to confirm that valproate (VPA) poses a significantly increased dose-dependent risk of structural and cognitive teratogenesis, ranging from 5.6% (750mg/day) to 24.2% (1500mg/day). Phenytoin (PHT), phenobarbital (PB) and topiramate (TPM) likely confer an intermediate risk of congenital malformations. Data thus far suggest that LTG, oxcarbazepine (OXC) and levetiracetam (LEV) are associated with a relatively low risk for both anatomic and developmental adverse effects. Accordingly, women with epilepsy should be treated with a low-dose monotherapy during pregnancy and VPA should be avoided. Supplementary folic acid (5 mg daily dose) is recommended, because this lowers the risk of cognitive teratogenicity. Third-trimester vitamin K supplementation has been suggested for women taking enzyme-inducing AEDs (eg. CBZ, PHT, PB), based on a concern for increased risk of intracranial neonatal haemorrhage. Experiences of the Referral Centre for Epilepsy of the Ministry of Health of the Republic of Croatia in treating pregnant women with epilepsy will also be presented.

PANDAS DISEASE AS A CAUSE OF EPILEPSY? A CASE REPORT

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Background: PANDAS is an acronym for Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection, a rare disease that usually appears in children. It involves a subset of patients that rapidly develop obsessive compulsive disorder and/or tic disorders after an infection with group A beta-hemolytic streptococci (GABHS). The cause for this is an autoimmune reaction against a pathogen (GABHS) that shares a similar epitope with the basal ganglia, therefore affecting them and interfering (permanently) with their function. Despite the growing number of reported cases, a comprehensive review of the literature did not show any papers suggesting a link between PANDAS DISEASE and epilepsy. There is both clinical and electrophysiological evidence supporting the involvement of the *basal ganglia* in epileptic *seizures*. Basal ganglia affect activity in the frontal cortex through a series of neural projections. **Materials and methods:** We present the case of a previously healthy 9 year old boy who 2 weeks after a pharyngitis caused by GABHS developed a tic disorder, and a month after that developed generalized tonic-clonic seizures with an epileptogenic focus on the right frontal leads as evidenced by a video EEG. An MRI as well as a SPECT scan showed no abnormalities, but a PET scan showed increased activity in his basal ganglia. **Results:** the patient was left with epilepsy minimally responsive to antiepileptic drugs. **Conclusion:** We therefore demonstrate a connection between GABHS infection and frontal lobe epilepsy, by affecting basal ganglia functions.

KAR-MEDIATED GLUTAMATE RELEASE FACILITATION AT MOSSY FIBER-CA3 SYNAPSES OF THE HIPPOCAMPUS INVOLVES CALCIUM-CALMODULIN AND A HIGH CALCIUM THRESHOLD

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Kainate-type glutamate receptors (KAR) participate in conventional neuronal transmission and processes like Long-Term Potentiation (LTP) and Long-Term Depression (LTD) that are believed to be responsible of the plastic changes that occur in the CNS during development, learning and memory and recovery after CNS lesions. The inadequate activation of KARs has detrimental effects that have been related to excitotoxicity, epilepsy and other disorders. The hippocampus is a sensitive region for epilepsy and KARs have been suggested as mediators of some of the epileptic effects of the potent neurotoxicine kainate. At mossy-fiber hippocampal synapses presynaptic activation of KARs modulates glutamate release but the mechanisms involved in this modulation are not entirely known. The aim of this work was to establish the mechanisms involved in glutamate release facilitation mediated by KAR-activation at mossy fiber-CA3 synapses in mice. We used whole-cell patch-clamp recordings for this purpose. We found that activation of presynaptic KARs facilitated glutamate release via activation of adenylate cyclase (AC) by the Ca²⁺-calmodulin complex. This effect was highly-dependent on the intracellular Ca²⁺ levels and involves the entry of Ca²⁺ by L-type voltage-gated calcium channels, GluK1 containing KARs, and Ca²⁺-induced Ca²⁺ release from intracellular stores. Next step of our research is to determine whether preventing the activation of this cascade prevents some of the epileptogenic effects of kainate.

THE ROLE OF EPILEPSY SURGERY TREATMENT IN QUALITY OF LIFE OF THE PATIENT WITH REFRACTORY EPILEPSY- EXPERIENCE FROM LOCAL OUTPATIENT CARE

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Purpose: To evaluate quality of life of the patients who underwent epilepsy surgery treatment before and after procedure in 6 months follow up in epileptologist outpatient care. **Methods:** The validated Czech 1.0 version of the questionnaire QOLIE-31 (health-related quality of life for adults with epilepsy) has been used to evaluate the quality of life of the patient with refractory epilepsy before and 6 months after epilepsy surgery. The questionnaire consists of 31 questions focusing on 7 sub-groups of quality of life with reachable maximum of 100 points. Descriptive statistics and a two-tailed *P*-value less than 0.05 was considered statistically significant. **Results:** We have prospectively examined 17 adults (8 men, 9 women) with refractory epilepsy. One man was excluded from the final analysis due to not passing the follow-up visit. Mean age while operation performed in men group was 36,25 ± 8,12 years, and in women group mean age was 36,33 ± 9,24 years. QOLIE-31 mean total score before the operation was 39,59 ± 17,80 points. After the epilepsy surgery mean total score value was 81,25 ± 21,39. Difference mean was 41,69 ± 23,05 (*p*=0.001). 15 patients improved. One patient worsened with -3,4 points difference. We also can see distinct improvement of all subgroups of quality of life except for medication category. **Conclusions:** We conclude epilepsy surgery as highly effective treatment of refractory epilepsy patients with significant improvement of quality of life.

GENERAL

SEXUAL DYSFUNCTION IN PATIENTS WITH MULTIPLE SCLEROSIS

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Background: Sexuality is an important part of health. Patients with multiple sclerosis (pwMS) may experience sexual difficulties (SD) due to multiple factors. The objective of this study was to detect possible contributing factors. **Methods:** This was a study conducted in tertiary care center over 10 months. SD and symptoms that interfere with sexual activity or satisfaction over the last six months were evaluated using 15-item Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ). Data were analysed using descriptive statistics (IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA)). **Results:** Hundred and one consecutive pwMS (75 female, 26 male; mean age 42.09 (range 19-77 years), mean Expanded Disability Status Scale (EDSS) score 3.1 (range 0.0-7.0)) participated in this study. On MSISQ 26.2% (N=16) female pwMS report inadequate lubrication, 41.7% (N=10) male pwMS difficulty with erection. 28.3% (N=23) pwMS report lack of sexual interest or desire, 19.8% (N=17) less feeling or numbness in their genitals, 32.9% (N=27) report it takes too long to orgasm or climax. In 32.6% (N=32) bladder problems, 16.3% (N=14) pain, burning or discomfort, 20.9% (N=18) tremors or shaking, and in 28.1% (N=25) muscle tightness or spasms in their arms, legs or body interfered with their sexual activity. 20.2% (N=17) report

feeling less masculine or feminine due to MS. **Conclusion:** Multiple factors may contribute to sexual difficulties which must be considered when managing pwMS.

REGENERATIVE THERAPY FOR CEREBRAL PALSY: TRANSPLANTATION OF UMBILICAL CORD BLOOD STEM CELLS AND UMBILICAL CORD MESENCHYMAL STROMAL CELLS

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Objective: Regenerative therapy for prevention of cerebral palsy (CP) has been initiated in Japan. Hypoxic-ischemic encephalopathy (HIE) leads to CP. We already started umbilical cord (UC) blood stem cells (UCBSCs) therapy for neonatal HIE in addition to Therapeutic hypothermia (TH). We also have been preparing to start a clinical trial of UC mesenchymal stromal cells (UCMSCs) therapy for patients who did not have a sufficient effect or could not take the UC blood. **Methods:** UCBSCs was collected aseptically and prepared by using SEPAX. UC-MSCs were collected aseptically from UC and cryopreserved after culture. Infants admitted to the NICU of 6 hospitals in our research group will be eligible if they are ≥ 36 weeks' gestational age and birth weight ≥ 1800 g with HIE and meet the cooling criteria. **Results:** UCBSCs therapy for neonatal HIE in addition to TH was performed in 4 newborn patients. All of them have survived from 7 months for 1.9 years. UC-MSCs have been defined and characterized as follows; (1) abundant sources and ease of collection, storage, and transport; (2) little ethical controversy; (3) multipotency to differentiate into various cell types; and (4) low immunogenicity with significant immunosuppressive ability. **Conclusions:** Good results in combination therapy of UCBSCs and TH for newborn HIE were obtained in our 4 patients. UC-MSCs therapy will give the possibility of treatment to patients who could not take UC blood.

TESTAMENTARY CAPACITY ASSESSMENT TOOL: A NEW INSTRUMENT FOR THE EVALUATION OF TESTAMENTARY CAPACITY IN PATIENTS WITH DEMENTIA

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Introduction: The characterization of a person as incapable of will making, due to deficits in recall

memory, is misleading because his/her intention of how and to whom he/she desires to dispose his/her assets may remain intact. **Methods:** We developed a short tool (TCAT –Testamentary Capacity Assessment Tool), consisting of four subtests assessing the patient’s characteristics which are required for TC: memory (orientation, autobiographical memory and realistic perception of beneficiaries), existence or not of psychopathology, financial parameters (value of assets, everyday life products, bills) and intention (vignettes, theory of mind). For its validation, we examined 64 patients visiting the 2nd Department of Behavioral Neurology and Neuropsychology. The decision of the expert served as the gold standard for the evaluation of the TC. Also, the newly scale was compared to the MSSE by applying ROC analysis in both cases. **Results:** For the total scale by using a maximum score of 48, the best combination of sensitivity (82.6%) and specificity (100%) was obtained for a cut-off score of 32/33. Moreover, a cut-off score that can be used in order to increase the levels of sensitivity is the value 38/39: sensitivity (95.7%) and specificity (80%). The Cronbach Alpha analysis showed high levels of internal reliability for the scale ($\alpha=0.86$) and the point-biserial correlation coefficients showed high levels of criterion-related validity ($r_{pb}=0.797$, $p<0.001$). **Conclusion:** We believe that the TCAT is a reliable screening tool for the evaluation of TC and can be used by both the expert and the non-expert.

FABRY DISEASE WITH LENTICULAR DEGENERATION WITHOUT PULVINAR SIGN

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Background: FD is an X-linked lysosomal storage disorder caused by a GLA gene mutation. The most frequent neuroimaging finding is non-specific T2 HSI in the periventricular white matter while the most specific MRI sign of brain involvement in FD is HSI in the bilateral pulvinar on T1WI. **Case Report:** A 38-year-old man visited the neurology department with a tingling sensation in both the upper and lower extremities in 2016. He had been on hemodialysis since 2009 due to end-stage renal disease (ESRD). He was diagnosed with Fabry disease (FD) via GLA gene testing [c.902GA (p.Arg301Gln) hemizygote]. The patient had been stable with regular hemodialysis. Neurologic examination showed no abnormal findings except decreased deep tendon reflexes. Brain MRI revealed high signal intensity (HSI) in the bilateral lentiform nuclei on T1-weighted imaging (T1WI), of which the core lesion was iso-intense. The core of the lesion showed low signal intensity (LSI) on T2-weighted imaging (T2WI) and diffusion-weighted imaging. There were no abnormal signal intensities in either thalamus. No other significant findings, such as cerebral atrophy or periventricular white matter changes suggesting cerebral small vessel disorders, were observed. **Conclusion:** In the present case, lesions were unexpectedly found in the lentiform nuclei with a similar appearance to the pulvinar signs observed in previous studies. The present case described an unusual neuroimaging finding of FD. Further observations are needed to determine whether FD should be included in the differential diagnosis of bilateral T1 hyperintensities in the lentiform nuclei.

HEADACHE & PAIN

INSUFFICIENT SLEEP IS PREVALENT AMONG MIGRAINEURS: A POPULATION-BASED STUDY

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Background: The aim of this study was to evaluate the association between perceived insufficient sleep and migraine using the data of the Korean Headache-Sleep Study (KHSS). **Methods:** The KHSS is a nation-wide cross-sectional population-based survey regarding headache and sleep for all Korean adults aged 19 to 69 years. A difference of one hour or more between sleep need and average sleep duration indicated insufficient sleep. **Results:** Of 2,695 participants, 727 (27.0%) individuals were classified as having insufficient sleep. The prevalence of insufficient sleep among individuals with migraine (45.5%) was significantly higher compared to that among individuals with non-migraine headache (32.9%, $p = 0.004$) or among non-headache (20.4%, $p = 0.001$). Average sleep duration did not differ among migraine, non-migraine headache, and non-headache groups (7.3 ± 1.2 vs. 7.2 ± 1.2 vs. 7.3 ± 1.4 , $p = 0.207$). Multivariable logistic regression analyses demonstrated that migraine had an increased odds ratio (OR) for insufficient sleep after adjusting for sociodemographic variables, short sleep duration, insomnia, poor sleep quality, anxiety, and depression [OR = 2.8, 95% confidence interval (CI) = 1.9 – 4.2, $p = 0.001$]. **Conclusions:** The prevalence of insufficient sleep was significantly higher among migraineurs compared to that in non-migraine headache or non-headache group.

ACUTE INTERHEMISPHERIC HEMORRHAGE MANIFESTING SOLELY AS A HEADACHE

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Background Interhemispheric subdural hemorrhage (ISH) is a rare and distinct type of subdural hemorrhage because of their unusual location. The patient with ISH usually reported a sudden onset of painful headache with other neurological deficit. We report unusual two cases of ISH presenting headache as the sole complaint. **Case 1)** A 66 year old man visited to outpatients' clinic of neurology with a five days history of headache. His headache was continuous, dull-pulsating in quality and located in bilateral occipitotemporal regions. The physical examinations were normal and there was no traumatic lesion. A CT scan revealed a linear high density lesion in the posterior interhemispheric fissure, suggestive of acute ICH. Gradient Echo MRI revealed low signal intensity in the same region. **2)** An 81 year old female visited for a gradually worsening headache for two days. The headache was bilaterally located, pulsating in quality but lasting more than 6 hours in a day. The physical examinations were normal and there was no traumatic lesion. A CT scan showed a hyperdense interhemispheric area on the right with no contrast enhancement and with a moderate mass effect. **Conclusions** The most common cause of ISH is by traumatic laceration of bridging veins between the parietooccipital cortex and the superior sagittal sinus. Even though ISH is a rare event, it should be considered among the diagnostic possibilities in elderly patients who present with headache as the sole symptom without other clinical features such as meningeal irritation signs, focal neurological defect and alteration of consciousness.

PREVENTATIVE TREATMENT OF HEADACHES ACCOMPANIED BY OTHER NEUROLOGICAL SYNDROMES IN CHILDREN AND ADOLESCENTS

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Discirculator headache comprises 43%, neurotic and neurosis headache 36%, liquorodinamic headache 20% of chronic headache in children and adolescents. In 66% of cases discirculator headache is accompanied by NEURO CIRCULATOR DISTONIA, in 25% by IMPAIRMENT OF ASSOCIATIVE LINKS, in 81% by AMBLYOPIA. Neurotic and neurosis headache in 30% of cases is accompanied by ENURESIS, in 20% by ASTENIC-DEPRESSIVE STATE, in 10% by NEUROTIC TICT. Liquorodinamic headache (basically in hypertension-hydrocephalic syndromes) in 30% of cases accompanied by OSES CULO-MOTORIC IMPAIRMENT, in 23% by PYRAMIDAL EMPAIRMENT, in 10% by AFFECTIVE-RESPIRATORY PAROXYSMS. /h5 TREATMENT Neurotic and neurosis headache in 10% of cases runs itself when the patient is engaged in interesting for him activities. At Discirculator headache with IMPAIRMENT OF ASSOCIATIVE LINKS, we have used CITICOLINE and have observed a positive effect in 88% of cases, at Discirculator headache with NEURO CIRCULATOR DISTONIA we have used CITICOLINE+VASCULAR DRUGS and observed a positive effect in 91% cases. At Neurotic and neurosis headache with ASTENIC-DEPRESSIVE STATE we have used only ADAPTOL and observed a positive effect in 92% cases. At Neurotic and neurosis headache with ENURESIS we have used ADAPTOL+MELIPRAMIN+PANTOQAMUM, and observed a positive effect in 87% of cases. At Neurotic and neurosis headache with headache of muscle strain we have used the ADAPTOL+PANTOQAMUM+MAGNE-B6, and observed a positive effect in 55%-60% of cases. At Neurotic and neurosis headache with headache of muscle strain when we used the ADAPTO+PANTOQAMUM+MIDOKALMUM (miorelaxants) positive effects have been observed in 65% cases.

THE PERSISTENCE OF ARTERIOVENOUS MALFORMATION INFLUENCES THE CLINICAL PHENOTYPE OF HEADACHE SECONDARY TO NON TRAUMATIC SUBARACHNOID HEMORRHAGE

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Background: Although the severity and suddenness of onset is the most characteristic features of headache secondary to subarachnoid hemorrhage (SAH), little is known about other headaches attributes in reference to SAH origin and its pathogenesis. **Methods:** The medical records of 431 consecutive non traumatic SAH patients (264 females and 167 males), ages from 19 to 91 years, presenting with headache (70.3%) and without headache (29.7%) during period of 11 years have been reviewed. **Results:** Among all analyzed data in reference to headaches features, although the persistence of arteriovenous malformation (AVM) was not in the association with headache occurrence in non traumatic SAH (OR 0.71 [95% CI: 0.41-1.21], $p=0.213$), its existence was in positive association with previous headache history (OR 1.74 [95% CI: 1.11-3.03], $p=0.046$), headache intensity (OR 2.24 [95% CI: 1.29-3.89], $p=0.004$), persistence of vomiting/nausea (OR 2.08 [95% CI: 1.13-3.83], $p=0.018$) and localized pain (OR 18.76 [95% CI: 9.68-36.37], $p=0.0001$) in these patients. **Conclusions:** The presence of AVM is not recognized as a predictor for headache occurrence in non traumatic SAH but its existence could be associated with previous headache history, its intensity, accompanied symptoms and pain localization. **Keywords:** headache, non traumatic subarachnoid hemorrhage.

PSYCHOLOGICAL MECHANISMS HEADACHE

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Headache is divided into three problems: - migraine - tension headache - headache not migraine or tension. Cenestopathy headache that refers to bodily hallucinations. Mechanisms of disorders: Migraine: a consequence of the impossibility of understanding to avoid some of the situations and experiences of life. This explains the swift ischemia, which extends from the occipital region to the gyrus centralis. Gyrus centralis - it is an area which is the conscious projection of the identification. Occipital area- creates a "vision". Mental inability to connect "Seen", that is unacceptable to interpret the established way of identity with the identity - leads to the attack of disconnection of the possibility of by ischemia distance between them. Tension headache. Two options: The lack of resources in the process of thinking - for example, do not have enough information; Incorrect use of inappropriate information- imputing meaning. Cenestopathy headache: a violation of the psychological treatment of mental pain. Subspecies - phantom headache. Often of other somatization when psychic pain experienced through physical symptoms, and his head felt as something burdensome. Characteristically for hypertension.

CORRELATION OF A HYPOCRETIN-2 RECEPTOR POLYMORPHISM WITH CLUSTER HEADACHE SUSCEPTIBILITY AND A SEROTONERGIC 5-HYDROXYTRYPTAMINE RECEPTOR POLYMORPHISM WITH TRIPTAN TREATMENT RESPONSE

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Cluster headache (CH) is a primary neurovascular headache with an increased hereditary risk. The less common A allele of the CH associated *HCRTR2* gene polymorphism rs2653349, seems to reduce disease susceptibility. The *GNB3* gene polymorphism rs5443 was associated with positive triptan treatment response. Carriers of the mutated T allele are more likely to respond positively to triptans compared to C:C homozygotes. DNA from buccal swabs of 1464 non related individuals was collected and analysed. Gene distribution for the polymorphism rs2653349 was G:G=77.8%,G:A=20.3% and A:A=1.9%. The frequency of wild-type G allele was 92.3%. The frequencies for rs5443 polymorphism were C:C=44,8%,C:T=41.9% and T:T=13.3%.The frequency of wild-type C allele was 70.0%. The odds ratio of male vs. female volunteers for rs2653349 exhibited no statistically significant difference, but for rs5443 polymorphism a statistically significant difference ($p=0,0292$) between the genders could be demonstrated. Comparison of study population polymorphism frequencies vs. other populations showed that rs2653349 A allele appeared only 7.7% while in global and in European population the frequency was 12,1% and 18,4% respectively. Further, we observed that male homozygotes for the protective mutant allele are 2-fold more than female. Results indicate that investigated Greek population has great similarity to the European population regarding rs5443 allele and genotype distribution. Based on our results we could assume that the pathophysiology of CH is affected by multiple factors, however, the genotyping analysis of polymorphisms may play a significant role in susceptibility and treatment of CH suffering patients.

PARINAUD SYNDROME AND MRI FINDINGS

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Introduction: We examined if neuroophthalmological findings in patients with Parinaud syndrome (PS) differ between patients with intrinsic (intraaxial) and extrinsic (caused by pineal gland tumors) brainstem lesions. **Methods:** Medical records of patients with PS were retrospectively reviewed. **Results:** Twenty six patients with PS were identified. Eight patients had extrinsic brainstem lesions with hydrocephalus. Two patients had hydrocephalus due to aqueduct stenosis and ependymoma of the fourth ventricle, respectively. Sixteen patients suffered from intrinsic brainstem damage (ten tumors, five vascular and one traumatic lesion), seven were associated with hydrocephalus. The most frequent finding was convergence – retraction nystagmus (85%), followed by light-near dissociation of pupil reaction (80%), upgaze limitation (46%) and eyelid retraction (27%). The ophthalmological findings did not differ between patients with extrinsic or intrinsic brainstem lesions. Patients with low or moderate brainstem lesions and hydrocephalus had more clinical findings than patients with the same degree of brainstem involvement without hydrocephalus ($p=0.03$ and $p=0.04$). The resolution rate of the ophthalmological findings did not differ between individual subgroups. A complete resolution was achieved in 8% patients, partial in 25% and 67% of patients remained unchanged. **Conclusions:** The routine MRI techniques do not allow conclusions about the ophthalmological findings in patients with PS. The presence of hydrocephalus is an important factor influencing the clinical findings in intrinsic lesions. The prognosis of PS is less favorable than generally reported.

MOTOR NEURON DISEASE

SENSORY NERVE FIBRES ARE INVOLVED IN AMYOTROPHIC LATERAL SCLEROSIS

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Introduction: It is accepted that motor neurons invariably degenerate but sensory nerves are generally considered to be intact in ALS. However, in the last two decades, supportive arguments on sensory involvement in ALS came from both neurophysiological evaluations and pathological studies. In this study we assessed sensory involvement in ALS patients. **Methods:** Nerve conduction studies (NCS), somatosensory evoked potentials (SSEP), laser evoked potentials (LEP), and quantitative sensory testing (QST-at least 2 abnormal tests) were performed in 16 definite and 2 probable ALS patients based on Awaji criteria and 31 controls. In addition, skin biopsies were evaluated in ALS patients using quantification of intraepidermal nerve fiber density (IENFD). **Results:** The percentages of abnormal neurological examinations, NCS, SSEP, LEP, QST, and skin biopsies were 38.8%, 72.2%, 56.6%, 72.2%, 11.1% and 16.6%, respectively. **Conclusions:** Our study confirmed that sensory fibers are involved in ALS. The pattern of sensory involvement in ALS (myelinated sensory fibers are affected more than unmyelinated ones) is opposite to what we usually see in distal symmetric sensory polyneuropathies.

CLINICAL APPLICATION OF AUTOLOGOUS MESENCHYMAL STEM CELLS IN AMYOTROPHIC LATERAL SCLEROSIS: YES OR NO? THE GREEK EXPERIENCE

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Objective: The evaluation of safety and clinical effectiveness of the transplantation of autologous mesenchymal stem cells (MSCs) in greek patients with amyotrophic lateral sclerosis (ALS) and discussion of the results according to the scientific references. **Methods:** Forty patients (Group A) with definite ALS were enrolled in the study. Bone marrow was collected from the posterior iliac crest and MSCs were expanded at the laboratory of the Hellenic Cord Blood Bank (HCBB) of the Biomedical Research Foundation of the Academy of Athens (BRFAA). The cells suspended in 2 ml of autologous CSF were transplanted intrathecally. A second group of patients with ALS (Group B) without transplantation was also enrolled in the study. The clinical progress of the disease was evaluated by the ALSFRS-R scale. An evaluation of the clinical profile of the two groups with the ALSFRS-R before and after the transplantation has been done for a long period with a follow up of 4 years. **Results:** A significant slowing down of the decline of the disease after transplantation has been ascertained during these 4 years. **Conclusion:** Our results demonstrate that the injection of MSCs intrathecally to ALS patients is safe well tolerated and without adverse events.

ASSOCIATION OF *TBC1D1* GENE VARIANTS WITH SPORADIC AMYOTROPHIC LATERAL SCLEROSIS IN GREEK PATIENTS

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Amyotrophic lateral sclerosis (ALS) is one of the most common forms of motor neuron disease. ALS is a neurodegenerative disorder that affects the upper and lower motor neurons in the motor cortex, brain stem, and spinal cord and leads to death within 3-5 years. Approximately 90% of the ALS patients suffer from sporadic ALS, having both an environmental etiology and a strong genetic component. Today, there is no effective treatment or diagnostic means for ALS patients. We have previously identified novel genomic loci to be associated with sporadic ALS in sporadic ALS patients of Greek origin. Here, we have performed whole-genome sequencing of 10 ALS patients and 7 healthy (non-ALS) individuals of Hellenic origin, using the DNA nanoballs proprietary approach of Complete Genomics Inc (110x sequencing depth). Following extensive data analysis, we identified 174 genomic variants that were present in all 10 ALS patients but none of the 7 non-ALS ethnically matched controls. Replication of genotyping in 27 sporadic ALS patients and 50 ethnically matched control individuals showed that *TBC1D1* genomic variants are positively associated with the disease phenotype (p0.017). *TBC1D1* has been identified as a regulator of insulin-dependent glucose transport and variants in the *TBC1D1* gene were linked to obesity. This is the first study that reveals an association between the *TBC1D1* gene and ALS pathobiology. Nevertheless, due to the small sample size, this should only be considered a pilot study and replication in a larger population cohort is needed to confirm this finding.

HYPERMETABOLISM IN ALS: COMPLICATION OR PART OF PATHOGENESIS?

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Hypermetabolism is one of not motor-related signs of ALS. Hypermetabolism in ALS has not been fully elucidated, but its signs could be detected before first motor symptoms of ALS. The aim of our study was to investigate the prevalence and severity of hypermetabolism in early stage ALS patients of the Russian population and try to clarify its correlation with neurodegeneration. The study concerned 40 ALS patients and 20 patients of the control group. Hypermetabolism was valued via questionnaires, anthropometric and biochemical data (blood levels of albumin, lipoproteins and zinc-alpha 2-glycoprotein, ZAG, as an adipokine). The rate of neurodegeneration was estimated by clinical and anamneses' data and levels of marker (phosphorylated heavy chains of neurofilaments, pNfH). Concentrations of markers were measured in CSF and blood of patients by ELISA. According to our investigation hypermetabolism was diagnosed about in half of cases of early stage ALS. Levels of pNfH were significantly different in ALS and control groups: 350,2 pg/ml [150; 500] 65,2 pg/ml [48; 148] correspondingly. Levels of ZAG were not significantly different: 48,9 mcg/ml [40,7; 60] in ALS and 45,6 mcg/ml [42,6; 49,9] mcg/ml in control group. Also a slight positive correlation of pNfH and ZAG in CSF was detected. Prevalence of hypermetabolism in early stage ALS patients of Russian population is high and comparable with previously published data. Results of biochemical study show that hypermetabolism is involved in pathogenesis of ALS already in an early stage of the disease, but further studies are needed to determine its exact role.

MULTIPLE SCLEROSIS

GLIOBLASTOMA FOLLOWING TREATMENT WITH INTERFERON BETA-1A FOR RELAPSING-REMITTING MULTIPLE SCLEROSIS

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Introduction: Glioblastoma is an uncommon and aggressive primary brain tumor with an incidence of 3 per 100,000 annually. Several types of brain tumors have been described in association with multiple sclerosis (MS) such as astrocytoma, oligodendroglioma and glioblastoma. Possible predisposing factors to this co-existence include a subclinical immunosuppressive state and the activation of autoimmune mechanisms in effort to induce remyelination. We report a 45 year-old woman diagnosed with glioblastoma within 10 years of induction of interferon beta-1a therapy for relapsing- remitting MS. To our knowledge this is the first report of a potential association between interferon and glioblastoma development. **Conclusion:** MS patients have an increased risk for brain and genitourinary tumors. Diagnostic procedures relating to the differentiation between pseudotumoral MS lesions and gliomas are imperative. The role of immunosuppressive treatment of MS in carcinogenesis remains a matter of debate.

DAWSON FINGERS POINT TO DIELECTROPHORETIC FORCE IN THE ETIOLOGY OF MULTIPLE SCLEROSIS DISEASE

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Thus far, Dawson fingers (DFs), which are periventricular, ovoid and oriented perpendicularly to the ventricular surface, have been assumed to be the lesions of multiple sclerosis. These lesions have been characterised as mechanical damage resulting from the differences in blood pressure along the Virchow-Robin spaces, or the spaces around the veins. After a Magnetic Resonance Imaging (MRI) scan, formations similar to DFs can be seen in the shape of a wedge in some regions of the brain: in particular, in the ependymal surfaces, the vertex of the blood vessels, and some areas around the posterior and anterior horns. These DF-like formations in the brain cannot be explained by mechanical damage. The purpose of this study is to determine the main formation mechanism of these DF-like formations in the brain. The main cause of DFs is secondary electromagnetic radiation from the collecting veins, which are perpendicular to the ventricular surface. In this context, the antenna model approach to DFs is crucial; in fact, it is the tenth new clue of the Canbay hypotheses on the etiology of multiple sclerosis (MS). Using the Canbay hypotheses, the potential places for the initiation of these plaque formations can be estimated.

PULMONARY TOXICITY DUE TO ALEMTIZUMAB'S INFUSION. DIAGNOSTIC AND TREATING DILEMMAS

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Introduction: Alemtizumab is a novel monoclonal antibody indicative for active relapsing remitting multiple sclerosis. Alemtizumab targets CD52 protein of mature B and T lymphocytes, leading to their depletion. The most notable adverse events are immune mediated conditions like idiopathic thrombocytopenic purpura, thyroid disorders or nephropathies and also infusion-associated reactions. **Case description:** A 21 year old woman showed at the fourth day of alemtizumab infusion acute chest pain, cough and shortness of breath with no fever. The x-ray detected lung consolidation at both sides and the following computer tomography (CT) confirmed the lower lobar consolidations with focal ground-glass opacity and numerous small opacities through lungs. The differential diagnosis included pneumonia, infection of pneumocystis carinii and drug-induced interstitial lung disease (DILD). Alemtizumab was withdrawn and antibiotic treatment was initiated. The next day the patient was improved as did the imaging exams, so antibiotics discontinued and she got only supportive care and corticosteroids. Ten days later the new CT was normal and symptoms had totally been resolved. **Discussion:** Alemtizumab could cause pulmonary toxicity and immune inflammation to the lungs maybe due to drug specific antibodies or T cells. But how easy is to diagnose DILD in a patient under immunosuppression treatment excluding other etiologies considering the lack of consensus for a diagnostic approach in patients with DLID? How should be determined the prognosis? Because alemtizumab is an immunosuppression drug with increased risk to cause infections have the antibiotics a place in the DILD's treatment? Is there a risk for relapse in future rechallenge with alemtizumab.

COEXISTENCE OF MULTIPLE SCLEROSIS AND SYSTEMIC SCLEROSIS. DIAGNOSTIC AND TREATMENT CONSIDERATIONS

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Background: Coexistence of autoimmune diseases and multiple sclerosis (MS) has been reported. Whether if not there is a genetic association between them has to be clarified. MS is rarely reported in association with systemic sclerosis (SSc). Herein we report on a case of with long-lasting SSc which presented with sensory disturbances and finally came out with the diagnosis of MS. **Case report:** A 43-year-old woman was admitted with a 20-days history of sensory disturbances. These started as numbness on the feet and progressively came up to the low thoracic region bilaterally and symmetrical, reflecting transverse myelitis. On brain and spinal cord MRI demonstrated dissemination of lesions in space and time, thus full-filling the revised 2010 Mc Donald criteria for MS. The diagnosis of coexistence of MS was made after excluding alternative diagnosis. Among the FDA approved immunomodulatory first line treatments glatiramer acetate was preferred due to less known link to autoimmune diseases. **Discussion:** Despite MS is been frequently reported in association with other autoimmune diseases is rarely described in coexistence with systemic sclerosis. Systemic sclerosis is characterized by immune dysregulation which includes also interferon inducible genes. As is known from the literature some MS cases treated with interferon beta (INF-beta) subsequently developed systemic sclerosis. Maybe INF-beta precipitates immune-mediated abnormalities. **Conclusion:** INF-beta as treatment for MS coexistent with SSc should be avoided as it could result in significant deterioration of SSc.

MULTIPLE SCLEROSIS AND CELIAC DISEASE, CASE REPORT

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1. Background Multiple sclerosis (MS) is an immune mediated inflammatory disease of the central nervous system (CNS). The diagnosis was based on clinical, laboratory and radiological data according to Mc Donald's criteria. Based on etiology MS seems to be associated with other autoimmune diseases. A correlation between gluten intake and incidence of MS had been reported and a relationship of antigliadin antibodies and MS was debated. The research studies found an increased prevalence of celiac disease (~11.1%) with MS. **Case Report:** We report the case of a 30 years old female, who was consulted in our clinic for the first time 15 years ago (2001) presented with: spastic paraparesis and paresthesias in upper and lower extremities. MS diagnosis was done. She had relapsing remitting episodes with the same symptoms, evaluated with EDSS 3.0 Kurtzke and was treated with intravenous methylprednisolone. The b1-Interferon is applied for three years. Episodic generalized tonic clonic seizures happened during the first years. During the last year the patient complains gastrointestinal disorders such as constipation, diarrhea and extremely weight loss. We suggested Celiac disease and autoimmune thyroiditis screening for autoantibodies and gastrointestinal endoscopy. The biopsy supports the celiac disease diagnosis. The patient was given gluten-free diet for celiac disease and she has a weight gain and gastrointestinal disorders improvement. 3. **Conclusion:** MS is known to be associated with other autoimmune diseases. Some studies revealed the association between MS and CD. MS patients with gastroenterological complaints should be tested for gluten sensitivity and other gastrointestinal autoimmune disorder.

IMPROVEMENTS IN PATIENT-REPORTED TREATMENT SATISFACTION WITH TERIFLUNOMIDE: RESULTS FROM THE PHASE 4 TERI-PRO STUDY

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Introduction: Teriflunomide is a once-daily oral immunomodulator for relapsing-remitting MS. The global, phase 4 study, Teri-PRO (NCT01895335), examined patient-reported outcomes, and the effectiveness, safety, and tolerability of teriflunomide treatment in routine clinical practice. **Methods:** Patients with relapsing forms of MS received teriflunomide 7 mg or 14 mg for 48 weeks, per local labeling. The primary outcome was Global Satisfaction at Week (W) 48, measured using the Treatment Satisfaction Questionnaire for Medication (TSQM, v1.4). TSQM scores were measured at baseline (for patients switching from prior disease-modifying therapy [DMT]), and at W4 and W48/end of treatment (all patients). **Results:** For 1000 treated patients, mean (SD) age was 47.1 (11.0) years; mean time since first MS symptoms was 13.2 (9.5) years. Mean (95% CI) TSQM scores were similar between W4 and W48: Global Satisfaction 72.3 (71.0,73.6)/68.2 (66.4,70.0); Side Effects 88.4 (87.2,89.7)/84.1 (82.5,85.7); Convenience 92.3 (91.6,93.1)/90.4 (89.4,91.3); Effectiveness 67.1 (65.8,68.4)/66.3 (64.7,67.9). In 594 patients who switched from a prior DMT within 6 months, improvements in all TSQM subscales were observed from baseline to W4, and maintained at W48 (P). **Conclusion:** Results from Teri-PRO showed high levels of treatment satisfaction with teriflunomide at W4 and W48 across all TSQM domains. Patients switching to teriflunomide from other DMTs reported a sizeable increase in treatment satisfaction at W48 vs baseline. Previously presented atECTRIMS 2016. Study supported by Sanofi Genzyme.

EFFICACY OF ALEMTUZUMAB IS DURABLE OVER 6 YEARS IN PATIENTS WITH ACTIVE RELAPSING-REMITTING MULTIPLE SCLEROSIS AND AN INADEQUATE RESPONSE TO PRIOR THERAPY IN THE ABSENCE OF CONTINUOUS TREATMENT (CARE-MS II)

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Background: Patients with active RRMS and inadequate response to prior therapy (≥ 1 relapse after ≥ 6 months of treatment) had improved outcomes with alemtuzumab versus SC IFNB-1a over 2 years (CARE-

MS II; NCT00548405). An extension (NCT00930553) demonstrated durable efficacy through 5 years in the absence of continuous treatment.

Goal: Evaluate 6-year efficacy and safety of alemtuzumab in CARE-MS II patients. **Methods:** Patients received 2 courses of alemtuzumab 12 mg (baseline: 5 days; 12 months later: 3 days) in CARE-MS II with as-needed alemtuzumab retreatment for relapse/MRI activity, or another DMT per investigator discretion, in the extension. Assessments: ARR; freedom from 6-month CDW (≥ 1 -point EDSS increase [≥ 1.5 -point if baseline EDSS=0]); 6-month CDI (≥ 1 -point EDSS decrease [baseline score ≥ 2.0]); NEDA; AEs. **Results:** Through 6 years, 344/393 (88%) patients remained on study. ARR remained low (Year 6: 0.15). 72% of patients were free from 6-month CDW; 43% achieved 6-month CDI. Mean EDSS increase from baseline was 0.10 (Years 0–6); 77% had improved or stable EDSS at Year 6. Most patients achieved annual NEDA (Year 6: 60%). 50% received no additional treatment after 2 initial courses of alemtuzumab. AEs decreased over time. Thyroid AEs peaked at Year 3 then declined. Infusion-associated reactions decreased with additional treatment courses. Serious AE rates, including infections, were low. **Conclusion:** Efficacy was maintained over 6 years with 50% of patients receiving no additional treatment after 2 initial alemtuzumab courses. Based on these findings, alemtuzumab may provide a unique treatment approach with durable efficacy in the absence of continuous treatment.

BRAIN VOLUME LOSS CORRELATES WITH LONG-TERM DISABILITY WORSENING IN PATIENTS WITH MS: SIENA ANALYSIS OF TEMSO MRI DATA

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Introduction: In TEMSO (NCT00134563), SIENA (structural image evaluation using normalization of atrophy) analysis determined that, vs placebo, teriflunomide significantly reduced brain volume loss (BVL), which was strongly correlated with disability worsening. Subgroup analyses showed that teriflunomide significantly slowed BVL vs placebo independently of disability worsening over 2 years. Here, we explore BVL and long-term disability worsening in TEMSO and its extension (NCT00803049). **Methods:** Blinded SIENA analysis of patient scans (n=969) determined BVL in Year 1 and Year 2. Percentage brain volume changes (PBVC) from baseline to Year 2 were categorized into quartiles (Q1–Q4) to evaluate probability of 12- and 24-week confirmed disability worsening (CDW) over 5 years in the extension. Probability of worsening was derived from Kaplan–Meier estimates. Quartiles were compared using a Cox proportional hazards model (covariates: PBVC categories, baseline Expanded Disability Status Scale strata, and region). **Results:** Patients with scans in Q1 (n=177; greatest BVL from baseline to Year 2) had a significantly higher risk of 12- and 24-week CDW after 5 years than those in Q4 (n=178; lowest BVL from baseline to Year 2): Q1 vs Q4 hazard ratios, 0.611 (95% CI: 0.432, 0.865; $P=0.0055$) and 0.566 (95% CI: 0.386, 0.830; $P=0.0036$) for 12- and 24-week CDW after 5 years, respectively. **Conclusions:** Results provide further evidence of the association between BVL and later disability worsening. Greater rates of BVL over 2 years are predictive of longer-term disability worsening at 5 years in the TEMSO extension. Study supported by Sanofi Genzyme. Previously presented at ECTRIMS 2016.

THE TREATMENT WITH NATALIZUMAB OF RELAPSING REMITTING MS IN CHILDREN: YES OR NO? THE HELLENIC EXPERIENCE

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Objective: To elucidate the efficacy and safety of Natalizumab in pediatric Multiple Sclerosis in all children from our cohort who were placed on Natalizumab per clinician's judgment. **Methods:** Clinical history and outcomes in 11 children with aggressive relapsing-remitting MS (2 boys, 9 girls), age of MS onset 13.3 years [range 10-16 years] were reviewed in our database. The first disease-modifying treatments for nine children were either IFN- β or Glatiramer Acetate. These children transitioned to Natalizumab after a year due to lack of clinical or radiological response. The 10th and 11th cases, were immediately started on Natalizumab due to a very aggressive disease presentation. Patients received between 5-40 monthly treatment infusions and were followed for between one and eight years. **Results:** With regards to treatment efficacy, the median annualized relapse rate (ARR) decreased from three to zero and disability measured through the EDSS scale decreased from a range between two and six to one after a year. There were no active lesions on MRI a year after treatment initiation. With regards to safety, there was no evidence of adverse events or hypersensitivity reactions. **Conclusion:** Multiple Sclerosis is not an adults privilege. Natalizumab is an effective and safe treatment for pediatric MS that is either of an aggressive nature or does not respond to common first line disease modifying therapies. Longer follow-up periods will allow better prediction of long-term safety and efficacy on degenerative disease features. There is less danger for PML in children. **References:** Chitnis T. Neurotherapeutics 2013 Jan;10(1): 89-96 Waldman A., Brenda Banwell et al Lancet Neurol. 2014, 13:936-48 Arnal-Gracia C. et al Eur. J. of Paed. Neurology 2013; 17:50-54 Ghezzi A. et al BMC Neurology 2015;15:174.

IDENTIFYING NEUROPATHIC BACK AND LEG PAIN IN PATIENTS WITH MULTIPLE SCLEROSIS

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Introduction and aim: The aim of this study was to investigate the prevalence of nociceptive or neuropathic low back pain (LBP) amongst patients with multiple sclerosis (MS). **Methods:** The study was conducted on 85 MS patients with LBP with or without leg pain. PainDETECT neuropathic pain screening questionnaire (PDQ) was used to identify likely pain mechanisms. Based on the PDQ scores, participants were classified into three groups: a neuropathic pain group, a nociceptive pain group, and an unclear pain group. Hospital Anxiety and Depression Scale was used to measure depression and anxiety. The degree of disability was based on the Expanded Disability Status Scale (EDSS), whereas the severity of pain was measured using a visual analogue scale. **Results:** A total of 31.8% of participants (n=27) reported nociceptive pain, 32.9% (n=28) unclear, and 35.3% (n=30) neuropathic pain. Among them, patients with clear nociceptive and neuropathic LBP were selected. Patients in the neuropathic pain group had significantly higher pain intensity (t=3.569, p=0.001) and higher prevalence of anxiety (t=1.417, p=0.5). There were no statistically significant between-group differences according to age (t = 1.557, p=0.125), sex (t=1.51, p=0.5), EDSS score (t=0.009, p=0.993), MS course (t = 1.041 p = 0.303), disease duration (t=1.250, p=0.217) and prevalence of depression (t=0.29, p=0.5). **Conclusion:** Based on screening test results, MS patients suffer from either neuropathic or nociceptive LBP, which has implications for the choice of treatment strategy. **Key words:** Multiple sclerosis, low back pain, PainDETECT questionnaire.

HEALTHY CHILDREN AND DISEASE STABLE MOTHERS WITH MULTIPLE SCLEROSIS

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Background: Multiple sclerosis (MS) affects fertile women who ask for a safe pregnancy. **Goals:** To find the most efficient strategy to shorten the preconception period and the proper time to return to disease modifying treatment (DMT). **Methods:** Our strategy used in 38 women with MS receiving DMT and planning their pregnancy resulted in the birth of 34 healthy children (also a pair of twins) and a minimal risk for disease worsening. Patients were psychologically supported and educated to plan pregnancy, after stopping DMT, birth control pills and other contraceptive methods used 3 months prior to conception, in order to have a regulate menstrual cycle. They performed gynecological clinical and ultrasound examination to exclude local problems, tests to exclude local or general infections, specific hormonal tests and anti Mullin Hormone test. All treatable problems were solved before stopping DMT. Sperm grams of their partners were performed. Intercourse occurred in the ovulation days (3-4 times), after 3 days of male abstinence. No toxics or drugs were used. **Results:** DMT safely discontinued had a high percent of rapid pregnancies and healthy children. They returned to the same DMT no later than 8 weeks after delivery, initial breastfeeding being possible and no/minimal neurostatus worsening was observed. Patients were permanently monitored by the neurologist and obstetrician-gynecologist. **Conclusions:** The patient should remain uncovered by DMT for as little time as possible and this goal can be reached by planning and performing specific tests and treatments for the couple before stopping DMT and returning to DMT treatment.

CLINICIANS' PERCEPTIONS OF HOW CURRENT PRACTICE MEETS MULTIPLE SCLEROSIS PATIENT NEEDS: RESULTS FROM A QUALITATIVE SURVEY

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Background: The MS in the 21st Century initiative is led by a steering group (SG) of international multiple sclerosis (MS) specialists and patient advocates with the current focus to improve communication and education between physicians and people with MS. **Objective:** To understand the views of the MS clinical community on unmet patient needs, with emphasis on patient support, treatment decisions, and the concept of disease progression. **Method:** Across two workshops, the SG of MS specialists and patient advocates developed an electronic survey piloted at the European Committee for Treatment and Research Congress in MS (ECTRIMS), 2016. Multiple answers were solicited in response to six questions. **Results:** All respondents (n=57) reported at least one challenge at diagnosis, including lack of time to explain progression (33%) and offer emotional support (39%). Approaches to discussing progression varied: 32% rely on patient-led discussion and 39% use analogies to explain difficult concepts; 46% would like more resources to aid discussion. Patient participation in treatment decisions (67%) varied; 21% reported lack of time or resources to accommodate involvement, 56% explain treatment side effects and benefits and 23% would like more 'risk versus benefit' written/online information. There was no consensus on the most important factor for patients making treatment decisions. **Conclusion:** Clinicians recognised a lack of time and resources, particularly at diagnosis; there was not enough time to offer the emotional support patients needed. However, variation in clinicians' perceptions of patient's priorities, and the disparity in discussing disease progression, suggests a need for understanding the patient perspective.

ALEMTUZUMAB DURABLY SLOWS BRAIN VOLUME LOSS OVER 6 YEARS IN THE ABSENCE OF CONTINUOUS TREATMENT IN PATIENTS WITH ACTIVE RRMS WHO WERE TREATMENT-NAIVE (CARE-MS I) OR HAD AN INADEQUATE RESPONSE TO PRIOR THERAPY (CARE-MS II)

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Background: Alemtuzumab significantly slowed brain volume loss (BVL) over 2 years versus SC IFNB-1a in active RRMS patients who were treatment-naive (CARE-MS I; NCT00530348) or had inadequate response (≥ 1 relapse) to prior therapy (CARE-MS II; NCT00548405). Efficacy was durable through 5 years in an extension (NCT00930553) in the absence of continuous treatment. **Objective:** Evaluate effect of alemtuzumab on BVL over 6 years. **Methods:** Patients received 2 courses of alemtuzumab 12 mg (baseline: 5 days; 12 months later: 3 days), with as-needed alemtuzumab retreatment for relapse or MRI activity, or another DMT per investigator discretion, in the extension. BVL was derived by relative change in brain parenchymal fraction. **Results:** Through 6 years, 325/349 (93%) CARE-MS I and 344/393 (88%) CARE-MS II patients remained on study. Alemtuzumab slowed median yearly BVL over 2 years, maintaining low BVL in Years 3–6 in CARE-MS I (Year 1: -0.59%, Year 2: -0.25%, Year 3: -0.19%, Year 4: -0.14%, Year 5: -0.20%, Year 6: -0.17%) and CARE-MS II (Year 1: -0.48%, Year 2: -0.22%, Year 3: -0.10%, Year 4: -0.19%, Year 5: -0.07%, Year 6: -0.10%) patients. 63% (CARE-MS I) and 50% (CARE-MS II) of patients received no additional alemtuzumab and no other DMT after 2 initial alemtuzumab courses. **Conclusions:** Slowing of BVL with alemtuzumab was maintained over 6 years in RRMS patients, with median annual BVL $\leq 0.2\%$ in Years 3–6 in both studies. Based on these findings, alemtuzumab may provide a unique treatment approach with durable efficacy in the absence of continuous treatment.

DIVERSE ROLE OF MACROPHAGES IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS: A CONTROVERSY

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Organ specific central nervous system (CNS) autoimmune diseases including experimental autoimmune encephalomyelitis (EAE), a model of human multiple sclerosis, has been known to be caused by autoreactive T cells and bystander macrophages. The inflammatory lesions are characterized by the infiltration of T cells and monocyte originated macrophages, followed by reactive microgliosis and astrogliosis. There is a general agreement that classically activated M1 macrophages play an important role in the initiation of CNS tissue damages. Recently alternatively activated M2 macrophages has been found in the EAE lesions with concurrent remission of paralysis in Lewis rats. The source of M2 macrophages in rat EAE lesions remains

controversial whether they are originated from either monocytes or microglial cells, or both. As for the phenotypic switch of macrophage or microglia, in vivo EAE study shows that phenotypic switch occur in Iba-1 positive macrophages (monocyte and/or microglia) because either inducible nitric oxide synthase⁺(M1 marker), arginase-1⁺ (M2 marker), or both –positive macrophages were found in EAE lesions. It is postulated that spontaneous recovery of EAE paralysis in rats is closely related with the relative prevalence of M2 milieu of inflammatory lesions, in which M2 macrophages secrete tissue protective molecules including heat shock protein and TGF beta. The control of macrophage phenotypes would be an alternative therapeutic strategy in organ specific autoimmune diseases. This research was supported by the Basic Science Research Program of the National Research Foundation of Korea (NRF), funded by the Ministry of Education (Grant number: NRF-2014R1A1A2055965).

LOWER URINARY TRACT SYMPTOMS IN PATIENTS WITH MULTIPLE SCLEROSIS

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Background: Patients with multiple sclerosis (pwMS) commonly report overactive bladder (OAB) symptoms of urinary urgency, incontinence and frequency, as well as the inability to void to completion. The aim of this study was to evaluate lower urinary tract symptoms (LUTS) and their impact on quality of life (QoL) in people with multiple sclerosis (pwMS). **Design/Methods:** This was a study conducted in tertiary care center over 10 months. LUTS and related QoL were evaluated using International Consultation on Incontinence Questionnaires (ICIQ): ICIQ-OAB, ICIQ-UI (urinary incontinence) and ICIQLUTS-QoL. Data were analysed and interpreted using descriptive statistics (IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA)). **Results:** Hundred and one consecutive pwMS (75 female, 26 male, mean age 42.09 (range 19-77 years), mean Expanded Disability Status Scale (EDSS) score 3.1 (range 0.0-7.0)) participated in this study. On ICIQ-OAB 35.6% (N=36) pwMS report increased daytime frequency, and 23.8% (N=24) borderline symptoms (7-8 times a day). 82% (N=82) report nocturia, 90.9% (N=90) urgency, with urge UI present in 72.4% (N=71). On ICIQ-LUTSQoL 91% (N=91) report feeling drowsy and sleepy during the day due to LUTS. 87% (N=87) had to plan to use a public washroom. In 56.7% (N=55) LUTS caused an issue with their partner of spouse. **Conclusion:** Lower urinary tract symptoms may be present in pwMS and may have an influence QoL. This must be considered when managing pwMS.

NEUROMUSCULAR DISEASES

GENETIC ANTICIPATION - TRUE OR FALSE?

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Background: The phenomenon in which a genetic disease has an earlier onset and a more aggressive evolution with each succeeding generation was controversial. However, anticipation has now been proven to occur in a large number of important genetic disorders, including myotonic dystrophies. **Case report:**

A 41-year-old man has had locomotor difficulty since he was 18 years old. Later, he noticed difficulties in vowel pronunciation and recently, a slowed relaxation following a normal muscle contraction. Neurological examination reveal hypertonic hands and feet muscle, atrophy in the masseter, temporalis, sternocleidomastoid muscles and distal legs muscles, distal motor deficit in wrist extension, walking without aid, early balding, triangular facies. Genetic tests revealed on a chromosome (allele) 5 ± 1 CTG repeats and on the other chromosome (allele) more than 300 CTG repeats. The pattern is characteristic for DM (muscular dystrophy) type 1 (Steinert's disease). His parents were apparently healthy, but his father has early baldness and cataracts, without any complaints. The patient has two girls, 8 and 15 years old. The older one has had signs and symptoms of DM1 disease for 4-5 years and EMG and genetic test confirmed it, with an increased number (over 300) of the CTG trinucleotide repeat in DMPK gene. **Conclusion:** This case report represents an example of a real genetic anticipation. Grandfather, father and daughter associate mild, classic and congenital phenotypes, respectively. Thus, genetic counseling and prenatal testing is mandatory for pregnancies at increased risk when the diagnosis of DM1 has been confirmed in an affected family member.

ALTERATION OF THE MOTOR UNIT POTENTIAL (MUP) IN MYASTHENIA GRAVIS (MG)

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Aim: The MUP in the MG are controversial and based on insufficient number of patients investigated. The series of investigations were carried out, in which detailed analysis of the MUP parameters in the MG patients was made and their alterations in respect to the muscles' functional state were studied. **Methods:** Electromyographic (EMG) investigations were carried out in 400 muscles of 104 patients with serious forms of MG. The abductor muscle of the fifth finger and other various muscles were investigated. The data obtained assessed the students t-criteria. **Results:** The MUPs of the MG patients are characterized with decreased mean duration of the potential and pronounced drop of the amplitude. High value of the polyphasic and spontaneous activity is not revealed. Manifestation of the spontaneous activity MG is concerned with denervation alterations, confirmed by: practical absence of the fibrillation potentials and the positive spiky waves in the patients with reversible damages of the neuromuscular transmission; higher manifestation of spontaneous activity in muscles, where an adequate dose of Neostigmine does not elevate the mean duration of the MUPs. **Conclusion:** All the above-mentioned indicate high diagnostic value of recording of the MUPs and spontaneous activity during MG. Both the Neostigmine test and the EMG investigations provide for the assessment of the depth of neuromuscular transmission infringement as well as for reversibility of the process in a separate muscle. Advantage of the method for investigation of MUPs and spontaneous activity of the motor units in the MG diagnostics has been determined in testing of any kind of muscle.

A PRACTICAL APPROACH TO ACUTE FLACCID PARAPLEGIA: A CASE SERIES

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Introduction: Acute flaccid paraplegia is a clinical occurrence of extreme importance, due to the dramatic presentation, the severity of the underlying disorder, and the generally poor prognosis that follows such

a condition. **Materials and methods:** During 2014, we dealt with eleven cases of acute non-traumatic paraplegia, in our neurological facility. A thorough electrophysiological, serological and imaging study has been performed in all cases. An ad hoc therapy was implemented as well, within the best standard of care as of actual. The majority (8/11) were warranted a diagnosis of polyradiculoneuritis. **Discussion:** Among etiological factors, the traumatic events are of particular interest, with the treating clinical dealing with a severely ill patient, following fall from height, motor vehicle collisions, and direct shocks applied over the vertebral column. The non-traumatic list is more numerous; however the severity of the acute paraplegia is not necessarily of a lesser degree. Viral infections, autoimmune disorders, and ischemic events involving feeding spinal arteries have been imputed. Chemical and medications injected intrathecally during procedures or accidentally can produce acute flaccid paraplegia. In spite of the poor prognosis, different therapeutic options have been proposed and applied. **Conclusions:** Surgery interventions are often necessary when trauma is present, with high dose glucocorticoids treatment preceding the intervention, aiming to decrease edema-related compression over the spinal cord. Immunoglobulins and plasmapheresis are logical and helpful options when a polyradiculoneuritis produces such a clinical picture. With the casuistics suggesting that even intra or extra axial tumors invading the spinal canal are able to imitate this event, the role of decompression seems by far of a particular significance.

NEUROPSYCHIATRY

EFFECT OF FLICKERING OF LED LIGHT ON COGNITIVE EVENT-RELATED POTENTIALS

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Purpose: It has been well established that light condition affected the brain function including cognitive processes. However, exact mechanisms of these effects have not been fully understood. Development of light-emitting diode (LED) allowed us to control light conditions in more detail. In this study, we examined the effects of LED light flicker on working memory by using event-related potential (ERP). **Materials and Methods:** Twenty-six healthy subjects participated in this study (mean age, 30.4 years; men 66.7%). Sixty-channel scalp EEG was recorded under two different conditions: control flicker (40%) light and flickerless (1%) light. Color temperature and brightness were set as 4,000 K and 500 lux in both conditions. Each light condition consisted of four blocks: 3 min in a dark condition (resting block), 4 min in one of the light condition (EEG block), 15min with working memory task (ERP block), and 3 min in a relaxed state (relaxation block). Data were epoched from 200ms prestimulus and 1,200ms poststimulus. We analyzed ERP component, time-frequency, functional connectivity data by using Matlab (MathWorks, USA). **Results:** Among ERP component, P2 component (from 160 ms to 200 ms) tended to increase in parietal and occipital areas under flickerless condition ($p = 0.038$ and 0.021 , respectively). However, P3 component did not differ between two light conditions. Time-frequency analysis revealed no significant difference in all frequency bands. Regarding functional connectivity, flickerless light increased theta-band connectivity in both item 2 and 3 conditions ($F_{1,18} = 8.633$, $p = 0.009$). In addition, theta-band connectivity was significantly correlated with refreshing and comfort scores ($p = 0.012$ and 0.040 , respectively). **Conclusions:** This ERP study demonstrated that flickerless light enhanced the theta-band functional connectivity during the working memory process compared to control flicker light.

ANTIDEPRESSANTS FOR POST-TRAUMATIC BRAIN INJURY DEPRESSION: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Introduction: Patients with traumatic brain injuries (TBIs) suffer from depression at a frequency varying between 16-60%. Considering that brain injuries afflict mainly young individuals, the need for effective treatment is imperative. **Methods:** We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) from January 1990 until November 2016 comparing the efficacy of antidepressants with placebo in the treatment of post-TBI depression. We searched MEDLINE, SCOPUS and the CENTRAL Register of Controlled Trials. **Results:** Four placebo-controlled RCTs investigating the Selective Serotonin Reuptake Inhibitors (SSRIs) citalopram and sertraline complied with the eligibility criteria of our search. Even though at the end of the follow-up period the rate of non-responders was found to be lower in the treatment groups compared to placebo (OR=0.42, 95% CI=0.15-1.17), this difference was not statistically significant (p=0.10). In the subgroup analysis of the studies that reported mean Hamilton Depression Scale for Depression between treatment and control patients on both the baseline and endpoint evaluations, the pooled mean difference was reduced from 2.11 (95% CI=-1.25-5.46) to -2.36 (95% CI=-5.59-0.87) in favor of the treatment group. Despite this reduction, statistical significance was marginally unattainable (p=0.06). No evidence of heterogeneity or publication bias were observed among the included studies. **Conclusion:** Citalopram and sertraline seem to be effective in treating patients with post-TBI depression. Due to the lack of high quality data on this devastating problem of public health, there is an urge for appropriately designed and adequately powered RCTs extending to other newer antidepressants.

PREVALENCE IN DEPRESSION AFTER STROKE

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Aim: To determine the prevalence of depression after stroke; To determine differences in prevalence of depression between the sexes and between age. **Methodology:** 186 (83Fand103M) patients admitted at University Clinic of Neurology in UHC "Mother Teresa", Tirana, Albania; diagnosed for ischemic stroke were assessed initially, by examination and interview. This patients are followed from 4 to 12 months by the psychosocial staff of our center in their houses. back inventory of used to measure the degree of depression clinical interviews. For each patient was prepared a folder to compare changes in time as a result of intervention of psychosocial. **Results:** The prevalence of depressive illness 4 months after stroke in 186 patients was 28%, major depression and 12% minor depression. There were small differences between the sexes and small difference from the ages. With a non-hierarchical approach to diagnosis of those with depression, 43% of men and 31% of women had an associated anxiety disorder. 12% of male and 15% of female patients interviewed had evidence of depression at the time of stroke. 12 months after stroke 42% of the men were still depressed, as were 26% of the woman and 22% youngest patients were still depressed and 37% older. **Conclusion:** The prevalence of depression after stroke was comparable with that reported from other studies. They have small differences between sexes was revealed and small differences for ages.

THE “FACE OF THE GIANT PANDA” IN A PURELY NEURO-PSYCHIATRIC PRESENTATION OF WILSON’S DISEASE

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38 year old male referred by his GP with 6 months history of progressive ataxia, changes in his demeanour, and tremor. The neurological examination revealed fine bilateral hand and leg tremor, side to side head tremor, finger nose hypermetry, dysdiadochokinesis and choreiform tongue movements. On the Addenbrooke’s cognitive test he showed marked deficits in memory and visual-spatial skills. Ophthalmic examination revealed Kayser–Fleischer rings. The brain MRI depicted extensive symmetrical high signal changes involving the corticospinal tracks at the level of the basal ganglia extending to the brainstem. Furthermore diffuse signal abnormalities were noted, affecting the cerebellar white matter, the midbrain, pons and thalami. As seen on the MRI the red nucleus and substantia nigra produce lower signal compared to the surrounding tissue forming ‘the face of the Panda’, as seen in less than 3% of the neuropsychiatric presentations. A challenging diagnosis as the patient presented in his late thirties without any hepatic involvement. It is highly didactic as it teaches the importance of broad differential and the need for early recognition of possible reversible causes. Prompt involvement of the Neuro-Radiology MDT and Discussion in Grand rounds is always beneficial towards achieving correct diagnosis.

PARKINSON’S DISEASES AND OTHER MOVEMENT DISORDERS

DEEP BRAIN STIMULATION IN PARKINSON’S DISEASE AND X-LINKED DYSTONIA-IMPACT ON QUALITY OF LIFE: A DESCRIPTIVE STUDY

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Deep brain stimulation has been recently introduced in the Philippines as a procedure to control or alleviate symptoms of movement disorders such as X-linked Dystonia and Parkinson’s Disease. In our institution, a total of 11 patients (X-linked Dystonia and Parkinson’s disease) have been granted and are being followed up for their neurostimulators. This study describes the quality of life of these patients after deep brain stimulation in terms of physical and psychosocial domains. It was limited to the patients who have active neurostimulator. Sickness index profile (SIP), a 136 item questionnaire, was used. Seven patients consented to be part of the study, 2 of whom are PD patients and 5 are XDP patients. The mean sickness index score obtained was 38.85 (28%) with more impairment of psychosocial functions. Adapting a validated cut - off score (SIP score of 33 +/- 13) from Volkmann et al, our results translates a poor quality of life among these patients.

IMPACT OF PAIN AND PAIN SUBTYPES ON THE QUALITY OF LIFE OF PATIENTS WITH PARKINSON'S DISEASE

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Background: Pain is a frequent and troublesome non-motor symptom in Parkinson's disease (PD) and has a negative impact on QoL of PD patients. The aim of this study is to investigate the relative impact of pain or a specific pain subtype on the QoL of the PD patients. **Methods:** We included 161 PD patients. Pain was assessed using the patients' descriptions, a structured interview, a detailed neurologic examination, and the visual analogue scale (VAS). QoL was assessed using the 39-item Parkinson's disease questionnaire (PDQ-39). **Results:** One hundred and twenty (74.5%) PD patients had chronic pain. Musculoskeletal pain was the most prevalent type, followed by radicular/neuropathic, dystonic, and central. PD patients with pain, regardless of pain subtype, had a higher PDQ-39 score than PD patients without pain. Multivariate regression analysis showed that the high score of PDQ-39 was related to PD onset age, UPDRS-II score, Beck depression inventory (BDI), and VAS score. **Conclusion:** Pain along with depression, poor ADL, and younger PD onset age is associated with poor QoL and all subtypes of pain affect QoL of PD patients.

CIGARETTE SMOKING, COFFEE INTAKE AND ALCOHOL CONSUMPTION PRECEDING PARKINSON'S DISEASE: A CASE-CONTROL STUDY

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Background: Although genetic factors play a role in the development of Parkinson's disease (PD), the lack of a clear genetic underpinning has led to investigation of the role of environmental factors in the etiology of PD. **Objective:** A case-control study was performed in Belgrade in order to investigate the association between PD and smoking, coffee and alcohol consumption. **Methods:** 110 new PD cases and 220 hospital controls were interviewed. Cases and controls were matched by sex, age and place of residence. Conditional univariate and multivariate logistic regression methods were used. **Results:** With PD were associated, independently from each other, current smoking [odds ratio (OR) = 0.44; 95% confidence interval (CI) = 0.23-0.82], alcohol consumption (OR = 4.78; 95% CI = 2.67-8.55) and coffee consumption (OR = 2.54; 95% CI = 1.36-4.75). In ever smokers the risk for PD significantly decreased with the increasing number of cigarettes smoked and with increasing duration of smoking. The risk for PD significantly increased with the increasing quantity of alcohol consumption. PD risk was significantly higher in subjects whose average daily consumption of coffee was 1 and 2-3 cups, and it was lower (but not significantly) in those whose daily coffee consumption was 4+ cups. The results of multivariate analyses did not substantially change after adjustment on family history positive on PD. **Conclusion:** The findings of this study support the hypotheses of inverse association of smoking with PD, but an inverse association with coffee was not confirmed. PD was found to be positively associated with increased alcohol consumption.

THE CHOLESTEROL OXIDATION DERIVATIVE 27 HYDROXYCHOLESTEROL REGULATES A-SYNUCLEIN TRANSCRIPTION-IMPLICATIONS IN SYNUCLEINOPATHIES

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Accumulation of α -synuclein protein is a common hallmark of a group of brain disorders collectively known as synucleinopathies. These disorders include Parkinson's disease, dementia with Lewy bodies, multiple system atrophy and Alzheimer's disease. The causes of synucleinopathies are likely multi-factorial with several factors including genetic susceptibility and environmental agents, potentially participating in the pathogenesis of these diseases. 27-hydroxycholesterol (27-OHC) is an oxysterol produced from oxidation of cholesterol by the mitochondrial enzyme CYP 27A1. Cholesterol oxidation to 27-OHC is accelerated not only by diets rich in cholesterol but also by oxidative stress and aging. When formed in excess, 27-OHC has the ability to cross lipophilic membranes of the blood brain barrier and migrate into the brain where it can increase α -synuclein levels through over-activation of its cognate receptor, liver X receptor (LXR). We have incubated human neuroblastoma (SHSY5Y) cells, mouse dopaminergic neurons differentiated from embryonic stem cells, and human dopaminergic neurons differentiated from human normal dopaminergic neuronal precursor cells with 27-OHC and examined the effects of increased 27-OHC on the expression levels of α -synuclein. Our results show that 27-OHC dose-dependently increases the transcription of α -synuclein through modulation of LXR in the three different cell types. Identification of the oxysterol 27-OHC and the LXR as the underlying cellular mechanisms by which 27-OHC increases α -synuclein levels may help in designing therapeutic agents that can prevent, reverse, or stop the over-production of α -synuclein and ultimately may protect against *synucleinopathies*.

OPTIC NERVE AND MACULA MORPHOLOGY IN PATIENTS WITH PARKINSON'S DISEASE USING OPTICAL COHERENCE TOMOGRAPHY

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Purpose: To investigate optic nerve and macular morphology in patients with Parkinson's disease (PD) using spectral-domain optical coherence tomography (SD-OCT). **Methods:** 25 participants with PD (19-males and 6-females; mean age 60.79; SD \pm 9.24) and 25 gender-, age-, ethnicity- and refraction-matched healthy controls where enrolled in a prospective, cross-sectional, observational study. High-resolution SD OCT (Copernicus, 3 μ m resolution) was used to acquire scans centred on the optic disc and fovea. Main outcome measures: Optic nerve head parameters (disc/cup diameters/areas, cup/rim volumes, cup depth, cup/disc ratio; peripapillary retinal nerve fibre layer (ppRNFL) thickness, retinal thickness and thickness of individual retinal layers. **Results:** Our study showed significant ppRNFL thinning in PD patients in all quadrants (p<0.05) associated with a shallower optic cup (p=0.03) as compared to healthy controls. Foveal remodelling with retinal thinning (nasal and temporal segments in both annuli; and superior segment in outer annulus; p<0.05), foveal pit widening (p=0.05), central OPL thickening (p<0.001) and nasal RPE thinning (p<0.001) was also found in PD. Changes were more pronounced in advanced stages of PD and with longer diseases duration. **Conclusions:** Optic nerve changes in PD are likely to be caused by primary neurodegeneration and are different to ON changes described in glaucoma. Central retinal thinning, pit widening, central OPL

thickening and RPE thinning indicate that remodelling of the fovea occurs. Specific changes of the fovea and thinning of individual retinal layers, correlating with disease severity and duration indicate that ON and retinal changes have potential to be used as biomarkers for PD.

NON-MOTOR SYMPTOMS OF PARKINSON'S DISEASE: GENDER AND AGE FEATURES AND THEIR DEPENDENCE ON THE STAGE OF THE DISEASE

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In recent years increasing attention is paid to non-motor symptoms (NMS) of Parkinson's disease (PD) as their manifestations are significantly different in patients of various age and gender groups. The goal of our research was to investigate the expression of PD NMS, depending on the age and gender of patients and stage of the disease. The study involved 255 patients with PD, 56.9% of which were men, 43.1% were women. The course of the disease, including NMS in daily life, was evaluated according to unified PD rating scale. The stage of the disease was determined by Hoehn and Yahr scale. We found growth rate of PD NMS in a group of women. In senile age patients this index was significantly increased compared with groups of young ($p=0.036$) and average age women ($p=0.016$). Also direct correlations were observed between age ($r=0,33$; $p=0.021$), stage of the disease ($r=0,37$; $p=0.028$) and severity of NMS. Index of PD NMS in a group of men was also increased. But in senile age men this index significantly reduced compared to a group of women of the same age ($p=0.038$). Also directly proportional dependence was observed between stage of the disease and its NMS ($r=0,32$; $p=0.023$). The data of our research indicate that NMS of PD are the most pronounced in senile age women, and their direct dependence with the stage of PD according to the Hoehn and Yahr scale was observed.

AMELIORATING EFFECTS OF NEW NEUROTENSIN ANALOGUE AND VASOACTIVE INTESTINAL PEPTIDE IN PARKINSON'S DISEASE MODEL

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Parkinson's disease (PD) results in progressive loss of dopamine neurons and leads to movement disorders such as tremor at rest, slowness of voluntary movements, rigidity, postural instability. Using rat experimental model of PD via unilateral injection into striatum (target coordinates AP = +0.2; LR = -3.0; H = -5.6 according to stereotaxic atlas) of 6-hydroxydopamine we aimed to study: i) effects of new neurotensin analogue (NT2) on rat motor performance and brain activity; ii) effects of vasoactive intestinal peptide on the levels of glutathione reductase activity and lipid peroxidation in rat brain. Our results demonstrated gradual improvement in the motor performance of NT2-treated animals as compared to control PD-rats treated with saline. At the same time cortical EEG showed differences in spectral composition and patterns above the lesioned areas and their hemispheric counterparts in the PD-rats treated with NT2 as compared to saline treated PD-animals. Our experiments also demonstrated that vasoactive intestinal peptide decreased the activity of enzyme glutathione reductase and inhibited lipid peroxidation in the experimental model of Parkinson's

disease counteracting in such way against membrane damage and ameliorating the cell viability. In conclusion the beneficial effects of vasoactive intestinal peptide and new neurotensin analogue outlined in the present investigations may represent a new therapeutic option for control of some Parkinson's disease disorders.

DOPAMINE TRANSPORTER IMAGE IN NIEMEN-PICK DISEASE TYPE C

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Niemann-Pick disease type C (NP-C) is a rare autosomal recessively inherited lysosomal storage disorder characterized by progressive neurological symptoms and various degrees of visceral involvement. The patient was a 24-yr-old male presented with psychosis, abnormal posturing, and gait disturbance. His birth and development had been unremarkable. At the age of 18, He started to develop delusion and abnormal posturing on both hands. At 21, He had to be hospitalized in department of psychiatry because of troublesome psychosis such as visual and auditory hallucinations, aggressive and impulsive behavior. He also developed gait disturbance and cognitive impairment around that time. Despite of symptomatic treatment, all symptoms were gradually aggravated, so at the age of 24, he became completely dependent on caregivers and wheelchair bound. Family history revealed that his younger sister had similar symptoms. On neurologic examination, He showed generalized dystonia that is prominent in both upper limbs, severe ataxic gait, VSGP and severe dysarthria. Brain Magnetic resonance image (MRI) showed no definite signal change, but mild atrophy of posterior part of brain was seen and ¹⁸F-FP-CIT positron emission tomography (PET) scan showed mildly decreased uptake in right caudate and anterior putamen. NPC1 gene sequencing revealed a compound heterozygote mutation which was already known as a genetic cause of NP-C, one in exon 9 (c.1552CT [R518W]) and one in exon 18 (c.2780CT [A927V]). Filipin staining test of cultured fibroblasts from skin, which is another key diagnostic test for NP-C, was done and the result was positive. There has been no systematic study in NP-C using ¹⁸F-FP-CIT scan that demonstrate presynaptic dopaminergic neuronal loss. Our case had decreased dopaminergic uptake in ¹⁸F-FP-CIT scan, but the pattern was much differ from parkinson's disease, in which deficit is predominantly in dorsal, posterior putamen.

5'-CHLORO-5'-DEOXY-(±)-ENBA, A POTENT AND SELECTIVE ADENOSINE A₁ RECEPTOR AGONIST, INHIBITS THE HARMALINE-INDUCED TREMOR AND ZIF-268 MRNA EXPRESSION IN RATS

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Harmaline is commonly used to model essential tremor (ET) in animals. The main cause of harmaline-induced tremor is abnormal activation of the olivo-cerebellar glutamatergic climbing fibers, elevation of glutamate release and increase in complex spike discharges of Purkinje cells of the cerebellar cortex. Adenosine A₁ receptors are present in all the brain structures associated with the harmaline-induced tremor (inferior olive, cerebellum, thalamus and cerebral cortex). Furthermore, an intrathalamic infusion of an A₁ agonist decreased the harmaline tremor in mice.

The aim of this study was to examine the role of A₁ receptors in the harmaline-induced tremor in rats

using 5'-chloro-5'-deoxy-(±)-ENBA (ENBA), a potent and selective A₁ agonist. Harmaline-induced tremor (15 mg/kg *ip*) was measured automatically in Force Plate Actimeters. The zif-268 mRNA expression was additionally analyzed by *in situ* hybridization in several brain structures. ENBA (0.05-0.5 mg/kg *ip*) dose-dependently reduced the harmaline-induced tremor and the effect of ENBA (0.1 mg/kg *ip*) was reversed by DPCPX, a selective A₁ antagonist (1 mg/kg *ip*). Harmaline increased the zif-268 mRNA expression in the inferior olive, cerebellar cortex, ventroanterior/ventrolateral thalamic nuclei and motor cortex. ENBA reversed those increases in all the above structures and DPCPX reduced the ENBA effect only in the motor cortex. The present study suggests that adenosine A₁ receptors may be a potential target for the treatment of ET. *Supported by statutory funds and National Science Center grant no. 2013/11/B/NZ4/04565. B. Kosmowska is a holder of scholarship from the KNOW funds sponsored by Ministry of Science and Higher Education, Poland.*

PAINFUL LEG AND MOVING ANKLE SYNDROME

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Background: Painful leg and moving toe syndrome is characterized by pain in the feet or lower limbs and spontaneous movement of the toes. The variants of this syndrome include phenotypes affecting the upper limbs, with symptoms such as painful hands and moving fingers. We present a case of chronic leg pain associated with involuntary ankle movements. **Case Report:** A 43-year-old woman presented with a 3-month history of involuntary movements of the left ankle, which appeared insidiously and an 18-month history of left leg pain and paresthesia. The involuntary movements of the left ankle had a roving pattern with some jerky components. No spontaneous toe movements were observed. The pain did not respond to various analgesics. Lumbar spinal magnetic resonance imaging revealed left-sided disc protrusions at the L3-4 and L4-5 levels. Nerve conduction studies showed left peroneal and lateral femoral cutaneous neuropathy. The ankle movements did not respond to clonazepam, baclofen or anti-dopaminergic agents. The ankle movements resolved when the pain subsided spontaneously 6 months later. **Comments:** Involuntary ankle movements can be associated with moving toe syndrome. However, to the best of our knowledge, isolated movement of the ankle in association with proximal leg pain has not been described previously. The present case illustrated a rare type of involuntary distal movement associated with neuropathic leg pain.

ROLE OF KININS RECEPTOR B2 IN THERAPY OF PARKINSON'S DISEASE IN ANIMAL MODELL

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Parkinson's disease (PD) a neurodegenerative disorder, is characterized by the loss of dopaminergic neurons in the substantia nigra and its projections into the striatum causing various motor deficits. Nowadays, treatment mostly relies on L-DOPA administration; however, effects produced by this drug are limited and cause diverse side effects. Treatment of PD is initiated at progressed stages of PD, since symptoms only become evident after a loss of at least 50 % of dopaminergic neurons in the substantia nigra accompanied by a drastic reduction of dopamine content in the striatum. The slow and progressive death of dopaminergic neurons let to suggest therapeutic strategies aiming at protection of the remaining ones against apoptosis and stimulation of neurogenesis for replacement of lost neurons. In view of that, the exploration of neuroprotective, self-renewal of stem cells inducing and neuroregenerative properties of bradykinin may help

to substitute lost dopaminergic neurons in addition to enhance the survival of reminiscent neurons. The bioactive peptide bradykinin obtained from cleavage of precursor kininogens activates the kinin-B2 receptor functioning in induction of inflammation and vasodilatation. Recent evidence suggests that bradykinin participates in kidney and cardiovascular development and neuronal differentiation. Here we show that kinin-B2 receptors and the participation of bradykinin in neuroregeneration in a rat model of PD induced 6-OH-dopamine injection. Bradykinin injection following establishment of PD symptoms resulted in improvements in the lesioned areas as studied by tyrosine hydroxylase immunostaining and motor functions.

WOLFRAM SYNDROME PRESENTING WITH UPBEAT NYSTAGMUS

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Wolfram syndrome (WFS) is a rare autosomal recessive genetic disorder characterized by diabetes insipidus, diabetes mellitus, optic atrophy and deafness. Imaging studies revealed atrophy of brainstem and cerebellum in WFS but its clinical significance remained unclear. A 18-year-old woman visited to our hospital for anosmia which had developed two years before the admission. She had been diagnosed with diabetes mellitus at the age of 3 and bilateral optic atrophies at the age of 11. On admission, the patient was totally blind and video nystagmography revealed upbeat nystagmus in central gaze both with or without fixation. MRI of the brain demonstrated diffuse atrophy of brainstem and cerebellum. Diagnostic exome sequencing test revealed two distinct variants (c.1232_1233delCT; p.Ser411Cysfs*131 and c.2168TC; p.Leu723Pro). WFS is associated with smaller intracranial volume with specific abnormalities in the brainstem and cerebellum even at the earliest stage of clinical symptoms but there is a variable degree of mismatching between clinical and radiologic findings in brainstem and cerebellum of WFS patients. Pendular nystagmus and gaze-evoked nystagmus have been described as the corresponding neurological deficit. Upbeat nystagmus is commonly localized to the caudal medulla, more rostral brainstem lesions with interruption of the ventral tegemental tract, or brachium conjunctivum in the rostral pons and medulla. Although the specific neural substrate for the abnormality is not clear, it is possible that brainstem and cerebellar abnormality in WFS present with upbeat nystagmus in this case.

DOCUMENTATION OF A STRIATAL GLUTATHIONE DEFICIT *IN VIVO* IN PARKINSON'S DISEASE DIRECTLY IMPLICATES OXIDATIVE STRESS IN DISORDER PATHOPHYSIOLOGY

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Background. *Postmortem* studies of Parkinson's disease (PD) brain have consistently reported deficits of nigrostriatal glutathione (GSH) – the primary living tissue antioxidant – of up to 40% compared to normal brain, strongly implicating oxidative stress in the pathophysiology of PD. However, direct evidence corroborating a striatal GSH deficit in PD brain *in vivo* is currently lacking. This study assessed whether there is a GSH deficit in living PD brain by directly measuring cortical levels of the antioxidant *in vivo* with MRS. **Methods:** For this pilot study, 22 patients diagnosed with idiopathic PD per the United Kingdom Parkinson's

Disease Society Brain Bank criteria, and 27 medically healthy volunteers (HV) were recruited. *In vivo* spectra of GSH were measured in 15 min with proton MRS on a 3T GE MRI system from voxels of interest in the left striatum and the occipital cortex (OCC). **Results:** In the striatum, the region of primary interest, GSH in PD patients was 15% lower ($p=0.04$) than in the HV group. In the OCC, a region not directly implicated in PD, there was a trend-level lower GSH ($p=0.08$) in PD patients than in the HV group. **Conclusion:** This study has obtained what may be the first *in vivo* evidence of a nigrostriatal GSH deficit in PD compared to healthy subjects, a finding that corroborates *postmortem* PD brain results that have consistently shown striatal GSH deficits and are the basis for a pathophysiological model of PD that places oxidative stress centrally in disorder pathogenesis.

RBD AND OTHER SLEEP DISORDERS IN A COHORT OF p.A53T SNCA MUTATION CARRIERS

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REM sleep behavior disorder (RBD), defined as REM sleep without atonia (RWA) plus either dream enactment behavior, sleep related injuries, potentially injurious or disruptive behaviors, documented by medical history, or polysomnography (PSG), may occur in association with neurodegenerative diseases, mainly α -synucleinopathies. In idiopathic Parkinson's Disease (PD) RBD may precede the motor manifestations of the disease. There is a general question whether PD due to defined genetic causes, transmitted through Mendelian inheritance, is similar to idiopathic PD. In this regard, it is especially interesting to assess whether RBD and other sleep abnormalities occur in carriers of the p.A53T alpha-synuclein gene (SNCA) mutation, the prototypical genetic synucleinopathy. Such a systematic study has not been performed previously. We have accordingly assessed 10 p.A53T carriers with PSG, Epworth Sleepiness Scale, RBD Screening Questionnaire (RBDSQ), UPDRSIII and MOCA. Three of the p.A53T carriers were asymptomatic, had no evidence of RBD in PSG and scored ≤ 5 in RBDSQ. All 7 symptomatic p.A53T carriers had evidence of sleep disorder in PSG. Three were diagnosed with RBD in PSG, however 2 of them were treated with antidepressants and only 1 of them scored 5 in RBDSQ. In three others, PSG showed RWA, but only 1 of them scored 5 in RBDSQ. The last one was diagnosed with PLM in PSG, was not treated with drugs and scored 5 in RBDSQ. We conclude that RBD or RWA occur in the majority of PD p.A53T manifesting carriers, possibly at a higher percentage compared to idiopathic PD.

IS IT POSSIBLE TO DEVELOP A PRECLINICAL DIAGNOSIS OF PARKINSON'S DISEASE, BASING ON A SEARCH FOR BIOMARKERS? IS THERE AN ALTERNATIVE APPROACH?

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Motor symptoms first appear in Parkinson's disease (PD) years after beginning of degradation of the nigrostriatal dopaminergic system at loss of threshold amount of dopamine (DA) in the striatum (70%), which explains low efficiency of treatment. Therefore, the development of preclinical diagnosis of PD is a high priority. Considering the systemic pathogenesis of PD, current methodology is based mainly on finding biomarkers, such as non-motor clinical symptoms and changes in body fluids (blood, CSF) and blood

cells. A number of weak points makes this methodology doubtful: (i) there is no guarantee that biomarkers found in body fluids of patients at clinical stage are also characteristic of patients at preclinical stage; (ii) considering that individual biomarkers (non-motor symptoms, changes in body fluids) are semi-specific, it is necessary to use a battery of biomarkers; (iii) the diagnostic procedure should be too expensive for mass examinations. This methodology can be improved by additional searching biomarkers in animals at modeling preclinical PD, although it will always remain nonspecific. Importantly, the alternative approach, the provocative, or challenge test can be successfully used for specific preclinical diagnosis of chronic internal diseases. Provocative test is used to specifically and reversibly enhance latent failure of a defective organ to the threshold level, thereby causing a short-term appearance of specific symptoms. We have proven the validity of this methodology for the development of preclinical diagnosis of PD by systemic administration of a reversible inhibitor of dopamine synthesis to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated mice at the presymptomatic stage of parkinsonism. **Principal publication:** Khakimova GR, Kozina EA, Kucheryanu VG, Ugrumov MV, Reversible pharmacological induction of motor symptoms in MPTP-treated mice at the presymptomatic stage of parkinsonism: Potential use for early diagnosis of Parkinson's disease. *Mol Neurobiol.* 2016 May 19. [Epub ahead of print].

DOPAMINE SYNTHESIS BY NON-DOPAMINERGIC NEURONS IN THE STRIATUM AT PARKINSONISM – A PARADOXICAL REALITY

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Parkinson's disease (PD) is developed for a long time at preclinical (asymptomatic) stage, despite the loss up to 70% dopamine in the striatum that is due to neuroplasticity. Neuroplasticity in the striatum is manifested in stimulation of functional activity of survived dopaminergic neurons and an increase of sensitivity of target neurons to dopamine. In addition to the dopaminergic axons, ascending from the substantia nigra, striatum contains intrinsic non-dopaminergic neurons expressing one of the enzymes of dopamine synthesis – tyrosine hydroxylase (TH) or aromatic L-amino acid decarboxylase (AADC). Among mammals, the number of these monoenzymatic neurons is especially large in primates, and it increases significantly in PD. When modeling PD at preclinical and clinical stages in mice with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), we have shown for the first time that: (i) monoenzymatic neurons expressing complementary enzymes of dopamine synthesis produce this neurotransmitter in cooperation in MPTP-treated mice, but not in intact animals, (ii) the proportion of dopamine synthesis by monoenzymatic neurons in the striatum increases at the progression of neurodegeneration. Cooperative synthesis of DA was proved using the original model of inhibition of DA synthesis in striatal slices by blocking transport of L-DOPA, produced in monoenzymatic TH neurons, to AADC neurons by means of L-leucine, a competitive inhibitor of the membrane transporter of large neutral amino acids, and L-DOPA. Thus, the cooperative synthesis of dopamine in the striatum under dopaminergic deafferentation is an up-regulated compensatory reaction, which is among the principal mechanisms of neuroplasticity in PD. **Principal publications:** M. Ugrumov (2009) Non-dopaminergic neurons partly expressing dopaminergic phenotype: Distribution in the brain, development and functional significance. *J Chemical Neuroanat.*, 38, 241-256. Kozina, A. Kim, A. Kurina, M. Ugrumov. (2017) Cooperative synthesis of dopamine by non-dopaminergic neurons as a compensatory mechanism in the striatum of mice with MPTP-induced Parkinsonism. *Neurobiology of Disease* 98, 108-121.

PERIPHERAL NEUROPATHY

CASE AND CONTROL STUDY: HIGHER PREVALENCE OF NEUROPATHY IN PATIENTS WITH SECONDARY HYPERPARATHYROIDISM

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Background: Diabetic neuropathy is frequent in the population with diabetic nephropathy (DN); however, there is no information about whether secondary hyperparathyroidism increases its incidence. The purpose of this study was to determine, through symptoms and signs, if there was neuropathy increased frequency in a group of patients with DN with hyperparathyroidism, compared to a control group. **Methods:** This is a case and control prospective observational study that was composed of patients with DN having 60 pg/ml serum parathormone (PTH) values, named control group (CG). The Hyperparathyroidism group (HG) was formed by patients with DN and ≥ 60 pg/ml PTH values. The variables were: body-mass index, diabetes evolution time, and presence of diabetic neuropathy (Michigan Test). The minimum calculated sample consisted of 60 cases in each group. The variables on scale were compared to the Student's t-test and the percentages to Chi2.

Results: There were 60 cases in each group: 35 (58.3%) men in CG versus 33 (55.0%) in HG ($P = 0.713$). The age for CG was 67 ± 11.0 years vs 72 ± 11 for HG ($P = 0.009$). The glomerular filtration in CG was 53.82 ± 25.13 , and in HG, it was 35.34 ± 18.43 ml/min/1.73 m² ($P 0.001$). The PTH in CG was 38.02 ± 15.32 pg/ml, and in HG, it was 119.07 ± 84.33 pg/ml ($P 0.001$). The neuropathy through symptoms in CG was 28.3 % while in HG, it was 36.6% ($P = 0.330$). The neuropathy through signs in CG was 38.3%, and in HG, it was 83.3% ($P = 0.001$). The odds ratio for HG to present neuropathy through signs was 8.044 (IC95% 3.42 – 18.92).

Conclusion: In the subjects suffering from diabetic nephropathy who were studied, neuropathy had more prevalence in the group affected with secondary hyperparathyroidism. Therefore, statistical association was evident between secondary hyperthyroidism and the presence of diabetic neuropathy in patients with DN. **Key words:** Secondary hyperparathyroidism, complications, diabetic neuropathy, renal failure, adult.

CHARACTERISTICS OF THE RESTLESS LEG SYNDROME IN PATIENTS WITH DIABETIC POLYNEUROPATHY

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The clinical picture of Restless Legs Syndrome (RLS) is diverse with the wide range of common symptoms of diabetic polyneuropathy (DPN), such as unpleasant feelings, pain, burning sensation, cramps, crawling that might disappear during the movement of the legs. The aim of the study was to examine the efficacy of pramipexole in patients with DPN resistant to standard therapy. The study involved 84 patients with type 2 diabetes mellitus complicated with DPN. In 25 (29.76%) patients, (main diagnostic criteria used), RLS was found. There were 2 groups: I group - 13 patients received gabapentin with dose titration up to 2.4g per day; II - 12 patients received pramipexole 0.750 mg once a day. Patients were interviewed on a quality of life at RLS scale before and 30 days after the treatment. Social function was $9,51 \pm 0,05$ points; after the treatment, the average score in the first group was $18,21 \pm 0,12$ points ($p0.05$). In the second group, the patients proved a more positive trend, which was $21,51 \pm 0,11$ points ($p0.05$). Sleep violation bothered all patients (15.21 ± 0.14 points). In the first group, it was 19.03 ± 0.17 points ($p0.05$) after the treatment, whereas the patients of the second group indicated a significant improvement ($26,15 \pm 0,18$) ($p0,05$). Con-

clusions. In patients who were resistant to treatment with gabapentin, RLS should be suspected, because of the similarity of symptoms with DPN and pramipexole therapy must be assigned.

A CASE OF ACUTE OPHTHALMOPLÉGIA WITHOUT ATAXIA ASSOCIATED WITH ANTI GD1b IGG ANTIBODY

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It is known that acute ophthalmoplegia without ataxia was reported to be mostly elevated anti-GQ1b antibody titer. It is very rare that anti-GQ1b antibody is negative but another ganglioside antibody-positive such as anti-GM1b, GD1b antibodies. In previous cases, high anti GM1 antibody alone or GM1, GD1a and GD1b antibodies in acute ophthalmoplegia without ataxia were reported. We reported case that only elevated anti GD1b antibody titer in acute ophthalmoplegia without ataxia. A 53-year-old male presented ptosis of the left eye with progression of the ptosis in both eyes 2 weeks ago admission to our department of neurology. On the next day of admission, he presented bilateral ophthalmoplegia. Pupil light reflex, deep tendon reflex were normal and ataxia were absent. Other neurologic examination were unremarkable. Brain MRI showed no ischemic or hemorrhagic lesions and nerve conduction test and anti acetylcholine receptor antibody test were normal. In cerebrospinal fluid analysis, protein was elevated (82.0 mg / dl) and other index were unremarkable. The oligoclonal band was negative and thyroid function tests was normal. Anti-GD1b IgG antibody titer was increased mildly to 38.62 (normal value 30) but other anti ganglioside antibodies were normal ranges. He was given intravenous methylprednisolone 1g/day for 7 days and oral prednisolone tapered. After 1 month, ophthalmoplegia and ptosis were undergoing some improvement without ataxia or areflexia. We experienced rare case of acute ophthalmoplegia associated with isolated elevated anti GD1b antibody titer. Further researches for correlation of ophthalmoplegia with antiganglioside antibody other than anti GQ1b antibody.

A TRICKY PROGRESSIVE WEAKNESS

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A 63 years old man, presented with 10 days story of lower limbs weakness, he reported a previous pneumonia treated with antibiotics. Symptoms have been worsened and forced him to use a stick before admission. Neurological examination showed pure motor paresis of lower limbs, with proximal strength graded 3/5 while spared distal movements, conserved flexion plantar reflexes and brisk tendon reflexes. He presented a marked increase of CPK (14799), GOT (741) and GPT (266). Electrophysiological studies showed normal amplitude of motor and sensor nerve action potential and distal conduction velocity, EMG showed a reduced recruitment in ileopsoas and deltoid muscles but no myositic signs. Suspecting a miopathy, he was treated with intravenous infusion of 1 mg metilprednisolone for 5 days. On hospital day 3, the paresis became worse: consisting in inability to lift legs from the bed and areflexia. His CSF examination revealed 130 protein and cell count of 2. Viral-bacterial tests and serological tests for self-directed and paraneoplastic antibodies were negative. Further ENG study showed prolonged F-wave latencies, poor F-wave repeatability and prolonged distal latencies, consistent with demyelination of nerve roots; normal recruitment muscle pattern, no fibrillation. He was treated with immunoglobulins 0.4 mg/kg for 5 days. During the first 5 days of therapy the weakness was spreading to the arms: proximal inability to keep arms lifted, conserved grasp strength; areflexia of upper limbs. Later he started a slow recovery, and 15 days after therapy neurological examination showed no strength deficit in upper limbs and ability to lift lower limbs up for few seconds.

This is an example of GBS associated with myopathy; few cases are reported in literature with such increase in CPK. This case should teach to think about GBS even if the clinical pattern is uncommon, in case of prolonged F waves and albumino-citological dissociation.

TABES DORSALIS SHOWING ABNORMAL SOMATOSENSORY EVOKED POTENTIAL WITH NORMAL SPINE MRI FINDING

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Background: Tabes dorsalis is a late manifestation of untreated syphilis that is characterized by sensory ataxia, lancinating pains, and urinary incontinence. Pathologically, there is degeneration of the posterior roots and column of the spinal cord. **Case report:** A 43-year-old man presented with progressive difficulty in walking and tingling paresthesia in the lower limbs for 5 months. On examination he showed hypesthesia on below T12 level, sensory ataxia, generalized hyporeflexic deep tendon reflex and Argyll Robertson pupil. Serum FTA-ABS was positive and serum RPR was reactive (1:64). Both CSF FTA-ABS and CSF VDRL were positive. CSF examination also manifested WBC count 90/mm³ (lymphocyte 93%), protein 72mg/dl, glucose 53mg/dl. HIV ELISA was negative and serum vitamin B12 level was within normal limit. Genetic study for spinocerebellar atrophy was negative and nerve conduction study was also negative. Magnetic resonance imaging (MRI) of the whole spine showed no definite intramedullary abnormal findings. MRI of the brain also showed normal result. Median somatosensory evoked potential (SEP) was normal, but posterior tibial SEP revealed increased lumbar to cortical central conduction time, suggesting a spinal defect mainly below the cervical region. He was treated with aqueous crystalline penicillin G, 3 million units intravenously every 4 hours for 14 days, which relieved his ataxic gait. Follow up posterior tibial SEP after 6 months documented shortening of lumbar to cortical central conduction time. **Conclusion:** This is the first case report of tabes dorsalis with normal spine MRI finding but abnormal SEP result, correlating with patient's symptom.

REHABILITATION

C10MPUTER MOUSE DRAWING AND MOTOR PATTERN DEVELOPMENT

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The idea of the study was based on observations collected during daily-life of our family. We analyzed two sources of data. The first one was the set of sketches made by a 7-year-old girl during her natural drawing activity, and the other one was experience of one of the authors in drawing with the use of a traditional computer mouse. Observations of motor task execution after changing the tool for a new one were analyzed in the context of data from two lectures regarding human motor pattern development that were delivered by other authors. Changing the drawing tool for a new and more difficult resulted in new ideas and topics, as well as in increased creation abilities and imagination. After a change in the technique of drawing, we observed the consecutive three stages of motor pattern development. We noted an effect

of motor pattern changing on fine art creation, which can be useful for practicing art (especially by hand-capped artists) or for art teachers. By an analogy between tool changing and the appearance of disability, our findings could be also useful in rehabilitation.

CAROTID ARTERY DISSECTION AND DELAYED ONSET STROKE CAUSED BY A MINOR BLUNT TRAUMA IN DAILY LIFE

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Objective: We present a case of traumatic CCA dissection and delayed onset stroke caused by a minor blunt trauma in a young office worker. **Case Description:** A 29-year-old woman slipped down and bumped against the corner of a table in her workplace. After the trauma, she felt dull pain in the neck without a bruise. Next day, she had mild headache and saw a black spot in front of her eye fields intermittently. However, symptoms got improved immediately. On the third day, dysarthria and left hemiplegia were developed suddenly. Neck CTA showed nearly total long segmental occlusion of right mid to distal CCA. Brain MRI and MRA displayed acute cerebral infarction on right basal ganglia, partial embolic occlusion at distal M1 segment of right MCA, decreased flow related enhancement in right ICA and no visualization of flow related enhancement in right CCA. TFCA revealed thrombotic occlusion of right proximal CCA. There were no abnormal laboratory findings but slightly increased LDL cholesterol and triglyceride. She was diagnosed as CCA dissection and delayed-onset cerebral infarction caused by blunt trauma. She took medication and received occupational therapy for 2 months and showed significant functional improvement except slightly decreased fine motor control of left hand. **Conclusion:** Even a minor blunt trauma that can be accidentally occurred in daily life may cause serious vascular events or stroke. In this case, the probable injury mechanism to the carotid artery might be direct blow and the stretch of carotid artery by neck hyperextension posture.

QUADRIPARESIS AND SEVERE COGNITIVE DEFICITS AFTER ACUTE CARBON MONOXIDE (CO) POISONING - REHABILITATION OUTCOMES

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Introduction: Acute carbon monoxide (CO) poisoning occurs after breathing in too much CO and may result in serious neurological manifestations, such as cognitive defects, especially affecting memory and learning, and movement disorders. These disorders are typically related to damage to the cerebral white matter and basal ganglia. **Case Report:** A young 23-year-old man was admitted to emergency department on 28/02/2013 after poisoning with CO, being comatose [GCS: 5/15 (1-1-3)]. He was intubated and admitted to the ICU, on mechanical breathing support. Initial investigations revealed: metabolic acidosis (pH 7.32), CPK: 21000, rhabdomyolysis and acute renal failure. Tracheostomy was performed on 06/03/2013 and removed on 31/03/2013. Brain MRI showed findings consistent with diffuse ischemic leukoencephalopathy and demyelination foci in the corpus callosum. On admission to our Center (01/04/2013), he presented with GCS: 10/15, quadriplegia and left peroneal neuropathy. He had a nasogastric feeding tube and urinary catheter. His initial FIM+FAM score: 58/210. He followed an intensive rehabilitation program

including physical therapy, speech therapy, occupational therapy, hydrotherapy, robotic gait training and psychological support. **Results:** During his stay, he remained hemodynamically stable and afebrile. He showed significant improvement of neurological status, swallowing disorders and cognitive deficits (MMSE score: 30/30). On discharge (06/08/2013), he was walking without aids, was independent in all ADLs (FIM+FAM score: 200/210). **Conclusion:** Timely diagnosis, effective treatment and early rehabilitation can improve outcomes for patients with CO poisoning and prevent its complications.

BOTULINUM TOXIN INJECTION INTO SALIVARY GLANDS FOR PROMOTING SWALLOWING REHABILITATION, COMMUNICATION AND QUALITY OF LIFE IN A PATIENT WITH TRACHEOSTOMY AND SEVERE SWALLOWING DISORDERS POST STROKE

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Introduction: Swallowing disorders (SD) post stroke may lead to serious respiratory complications and tracheostomy. Botulinum toxin type A injection in salivary glands (BTISG) is a treatment option for sialorrhea, a sign of SD. **Purpose:** To present a case of a stroke patient with tracheostomy, severe SD and sialorrhea, treated with BTISG. **Case report:** A 73-year-old man with stroke, admitted to our Center on 25/06/2015, presented with tetraparesis, a tracheostomy tube (TT) and PEG tube due to severe SD. GCS score: 11/15. He followed intensive rehabilitation program, but had several episodes of serious respiratory infections, treated in ICU. Fiberoptic Endoscopic Evaluation of Swallowing (FEES) showed absent gag reflex and aspiration. Chest CT scans revealed trachea dilatation, endoscopically confirmed. A TT of adjustable length with cuff was placed (January 2016). No respiratory infection occurred after March 2016. Mental, physical and mobility status improved significantly. His main complaint was the inability to speak and communicate. Following intensive speech therapy and FEES, a speaking TT was placed (July 2016). Saliva and bronchial secretions remained excessive, but were managed effectively by coughing. Anticholinergics initially used had no results. After BTISG (August 2016), saliva and bronchial secretions reduced significantly, allowing deflating the cuff initially and, finally, capping the tracheostomy for almost 10 hours daily, with no complications, enabling speaking, communicating, participating; improving his mood and quality of life (QoL). **Conclusions:** BTISG combined with an intensive rehabilitation program resulted in significant improvement of SD, enabling the patient to communicate and participate, thus improving QoL.

CAN PATIENTS WHO UNDERWENT NEUROSURGERY FOR GLIOMAS GET A SIGNIFICANT IMPROVEMENT FROM REHABILITATION?

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Introduction: Patients who underwent neurosurgery are a strong test for rehabilitation units (high length of stay, high resource consuming, poor prognosis). It is still controversial if such patients (most patients

with neoplastic disease) can get a significant improvement from rehabilitation. The aim of the study was to evaluate outcome comparing malignant and non malignant patients hospitalized in our rehabilitation unit. **Material and Methods:** We considered 55 patients hospitalized in our rehabilitation unit between March 2011 and July 2016 with who underwent intracranial surgery. Their age was between 20 and 84, with an average of 55.1, SD 14.4. In 34 patients out of 55 (61%) there was no malignancy. 11 (20%) were affected with neoplastic disease with poor prognosis, the remaining with low malignancies. **Results:** The mean length of stay was 60 days \pm 61. The mean delay between surgery and admission was 32 days. Mean modified Rankin Scale ad admission was 4.3 \pm 0.7. At discharge 3.3 \pm 1.3. 32 patients (58.1%) were discharged at home, 2 deceased, 7 were sent to other rehabilitation facilities, the others went back to neurosurgery, neurology or intensive settings. People who went back home had a higher mean GOS: 4 \pm 0.9 (in the others 3 \pm 0.7). Po.oo1, two tails t test. Modified Rankin Scale at discharge was lower in patients who were discharged home. There was no significant relation between discharge at home and malignancy (chi square test). **Discussions and conclusions:** Our patients can get a significant improvement from rehabilitation, no matter if affected with malignancies or other intracranial pathology.

CAVUM SEPTUM PELUCIDUM IN NEUROLOGIC PATIENTS

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Cavum septum pellucidum (CSP) is a normal variant CSF space between the leaflets of the septum pellucidum. The aim was to evaluate its occurrence with neurologic nosologies. Methods Intrigued by this casually radiological finding we retrospectively analyzed fourteen patients with cavum septum pellucidum among patients admitted with neurological emergencies. Among them 64% were male while 36% female aged from eighteen to eighty years old with mean age of 56. Results Neurologic diagnosis raised commonly were stroke in 42% (recurrent ischemic, lacunars 17% similarly ; 8% pontine lacuna in vasculitis from Bexhet disease), epilepsy in 24% (TLE, epilepsy -dementia, new onset SE Status Epileptic in herpetic temporal encephalitis with 8% respectively), 16% CDH chronic daily headache ; migraine with visual aura or chronic psychosis identically) PD Parkinson Disease 8%, MS (Multiple Sclerosis) 8%. Neurologic objective examination was normal 13%, frontal syndrome 13%, motor impairment 50%, Parkinsonism, psychomotor agitation equally with 8%. (CSP) in imaging resulted associated with 24%, thalamic, basal ganglia and pontin lacuna 24%, cortical atrophy 14%, CSP only 14%, frontal agenesis, left frontal hygroma, white matter demielinising plaques, temporal posterior brain edema in encephalitis 6% simultaneously. EEG performed in 24% of patients revealed; normal generalized alfa in CDH case, FIRDA in TLE and diffuse intermittent delta in SE case with identical prevalence. Conclusions; CSP resulted coincidentally associated with diverse neurological diseases imaging's frequently observed with in stroke 42%, less subsequently with epilepsy 24%, followed by CDH 16% and lastly concurrently occurred with post-trauma, MS, PD, or vasculitis.

FALLS AFFECTING QUALITY OF LIFE

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Objectives: Falls are important causes of hospital admissions, injury and even death among the elderly population; people don't fall because they get older. There is more than one underlying cause involved in a fall and often incompletely investigated and treated, affecting the quality of life (QoL) of patients and

caregivers. **Methods:** We conducted a prospective study on 71 consecutive patients which were admitted in our clinic as a result of a fall. The mean age was 77 years (61-93). We tried to identify the leading cause for falling and the consequence on QoL. **Results:** The causes for our patients' falls were: stroke, vertigo and balance difficulties, Parkinson's disease, polyneuropathy, vision problems, arthritis and other orthopaedic problems, seizures, postural hypotension, environmental factors. Only 34 patients had a single cause for falls, 37 of them had 2 or more factors that caused falls. Almost all the patients needed a multidisciplinary medical team to pass the consequences of their fall. **Conclusion:** Most falls are caused by a combination of risk factors. Falls, even without any injury, have a psychological impact on patients. They become afraid of falling again. The fear was increased by the number of falls. QoL is affected in the same proportion by the physical consequence of falls (trauma, fractures, haematomas, pain) as well as by anxiety, reducing the motility and activity of the patients and increasing their dependence on caregivers. A multidisciplinary team is necessary to prevent and treat consequences of falls in elderly.

THE EXOSKELETON EXPERIENCE IN GAIT TRAINING OF NEUROLOGICAL PATIENTS

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The evolution of technology and its use in the rehabilitation field provide us with new sophisticated tools to achieve the rehabilitation goals. Some of the most innovative systems are the robotic technology systems which help us to use in the best way the patients' abilities. They are usually specialized for gait training. One of the most innovating system for robotic gait training is EXOSKELETON. This system has been used in the facilities of <> Rehabilitation Center for promoting walk abilities of neurological patients. The patients are following a multidisciplinary rehabilitation approach and use of EXOSKELETON is combined with the rest of the program. We have the experience of 4 patients following this combined program (3 stroke and 1 MS patient). They used EXOSKELETON for gait exercise twice a week for 6 weeks. In the advantages are the correct step pattern learned, the faster speed achieved than the conventional therapy, the natural fully weight bearing gait, the task specific gait training and the more customized and intensive (high-dosage and high intensity) gait training. In the disadvantages are the time consuming fit and adjustment of the robotic system, the need for good patient's cooperation and perception, the high cost of the system and the restrictions (spasticity, floor specifications, length limb discrepancy >4 cm, body weight >100 kgr).

QUALITY OF COMMUNICATION IN THE REHABILITATION OF PERSONS WITH APHASIA AND/OR DEMENTIA: THE CAREGIVERS PERSPECTIVE

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We propose that performance on a quality of communication scale for caregivers primarily reflects the communication underpinnings that tap the communication effectiveness of persons in rehabilitation with stroke and/or dementia. Demographic differences as related to illness, sex, age, time of disease and communication disorder were studied. These results support the hypothesized associations between caregivers' perspectives for: 1. daily routines and autonomy, 2. self-perception and personality, 3. social life and and

interaction and 4. Cognitive and communication skills and 5. other general questions. Individuals for stroke (Mean=2.94, $p=0.009$ 0.05) as compared to individuals with dementia (Mean=3.37) showed statistically significant differences with regard to self-perception and personality. Moreover, for both groups social life and interaction (3.) was found to be significantly worse, especially for females (Mean=3.96, $p=0.0150$.05) as compared to males (Mean=3.44). Both groups with more than 11 years of having either stroke or dementia showed statistically significant differences mean=3.43 ($p=0.0280$.05) in the area of cognitive and communication skills however if the speech and language is not effected this result is also significant (Mean=3.27, $p=0.0220$.05). Moreover, an analysis of the statistically significant differences between the two groups revealed an intriguing association for two groups of caregivers. Results of this demographic analysis suggest that examining quality of communication from the caregivers' perspective can provide a useful way to bring undefined views of caregivers into closer alignment with the rehabilitation outcomes of communication quality.

THE INFLUENCE OF ION-REFLEX IMPULSIVE MAGNETIC ELECTROPHORESIS ON BIOELECTRIC ACTIVITY OF THE BRAIN

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In recent years, more and more attention of researchers attracted neurostimulatory effect of pulsed magnetic fields, such as transcranial magnetic stimulation. There is information about the increase of the functional activity of clock mechanisms of the brain under the influence of short-term local alternating magnetic field. **The aim:** To study the effect of ion-reflex impulsive magnetic electrophoresis on bioelectric activity of the brain. **Materials and Methods:** There was study of bioelectrical activity of the cerebral cortex of 30 relatively healthy volunteers aged 21 to 61 years with the help of electroencephalography recording. The study was carried out three times: before the experiment, after the first magnetic electrophoresis session, third record - at the end of 5 sessions. **Results and Discussion:** The decrease in the asymmetry of alpha rhythm in the dynamics on the background of magnetic therapy sessions with magnetic electrophoresis. Also an improvement in the frequency parameters of the alpha rhythm from 7.0 to 11.6 Hz is observed in the dynamics. Over both hemispheres, mainly in the fronto-temporal leads registered low- and high-frequency beta rhythm. The activity of beta rhythm by frequency remained 14-35 Hz (prior to treatment 12 to 35 Hz), by amplitude was modulated over 8-35 μ V. Volunteers noted improvement in general well-being, increase in efficiency, improvement of memory, attention, synchronization of circadian rhythms of sleep. **Conclusions:** The study showed a positive effect of ion-reflex impulse magnetic electrophoresis on the functional state of the brain, as evidenced by the the results of our study that can be used in neurorehabilitation and requires further study.

STROKE

AGE AND GENDER CHARACTERISTICS OF THE CEREBROVASCULAR DISEASES AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Background: Type 2 diabetes mellitus (2DM) is a major risk factor for cerebrovascular diseases (CVD). **Aim.** To study clinical and epidemiological features of CVD prevalence in patients with 2DM. **Material and methods.** 810 patients (31.2% men, 68.8% women) aged 30 to 69 (with the mean age 53.9 ± 0.4 year) were involved to the research. They answered the questions in the "ARIC" international questionnaire, which was prepared by experts of World Health Organization for using in clinical and epidemiological studies. All patients were examined by a neurologist. A carotid dopplerography was implemented and the level of glucated haemoglobin (HbA1c) was identified by express method for all the patients. **Results:** The questionnaires analysis showed that 12.8% parents of the patients with type 2DM had cerebral stroke under the age of 55 (females – 7.3%, males – 5.5%, $p < 0.05$). Carotid artery stenosis degree was about 40% in 30.1% of patients (males – 2.7%, females – 27.4%, $p < 0.01$), about 50-59% in 57.5% of patients (males – 16.4%, females – 41.1%, $p < 0.05$) and more than 60% in 12.3% of patients (males – 2.7%, females – 9.6%, $p < 0.05$). Carotid intima-media coefficient (IMC) was 1.2 ± 0.5 mm (95% CI 0.4-3.2) on the right side and 1.4 ± 0.6 mm (95% CI 0.6-3.5) ($p < 0.05$) on the left side. The average level of HbA1c was $8.5 \pm 0.3\%$ (men $8.2 \pm 0.3\%$, women $8.8 \pm 0.4\%$) ($p < 0.05$). Inadequate glycemic control was considered as the reason of IMC increase ($p < 0.05$). **Conclusion:** Frequency of CVD prevalence in 2DM was significantly higher among women than men and it can be explained with non adequate glycemic control.

HOW MANY CONTROVERSIES FIT IN A STROKE CASE?

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Introduction: Stroke is a major cause of death and prolonged disability. Common causes of an ischemic stroke are thrombosis from stenosis or occlusion of large arteries or embolism mainly from cardiogenic sources. Identification of etiology is fundamental in planning treatment strategy and secondary prevention. **Case report:** A 61-year-old right handed man was admitted eight hours after the onset of right side hemiparesis, right hemianopsia and also expressive aphasia. He was getting dabigatran 110mg twice per day for atrial fibrillation. Computer tomography (CT) showed large infraction as a low density lesion in the territory of anterior, middle and at a less degree of posterior cerebral artery with surrounding edema and mass effect. CT angiography revealed an anatomic variant with the left anterior artery to be branch of middle artery and the left posterior to be hypoplastic. Furthermore a severe stenosis, almost 80% of the left internal artery in the neck was detected. He decided to continue his anticoagulation therapy with rivaroxaban 20mg once daily and to perform interventional treatment for the internal carotid stenosis three months later. **Discussion:** This case includes many dilemmas. Firstly should be expanded the laboratory and imaging work up despite the obvious cause of ischemic stroke? In which cases they should decide so? Moreover a patient under Noacs for atrial fibrillation and a new severe ischemic stroke should continue the same therapy or change with warfarin? Finally what is the best timing and also the best procedure for a severe carotid stenosis in the neck after a major stroke?

A CASE OF WIDESPREAD CAVERNOUS ANGIOMAS OF THE CENTRAL NERVOUS SYSTEM ASSOCIATED WITH ACUTE NEUROLOGIC DEFICIT

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Background: Multiple cavernous angiomas (CA) in the central nervous system (CNS) are commonly associated with family history of CAs or previous radiation therapy on the CNS. In addition, neurologic deficit by spinal cavernous angioma more chronically appears in the adults compared than the children in which a rapid progression of the neurologic deficit associated with bleeding of CAs. Here in, we introduce a rare case in which a woman without familial or radiation history appeared with acute neurologic symptoms resulted from multiple CAs. **Case Report:** A 45-year-old female visited our clinic due to sudden right leg weakness and sensory loss. Brain and spinal cord magnetic resonance imaging showed widespread CA. CA in L1 spine level was accompanied by a hematoma of subacute stage with perilesional edema. Sensory loss was subsided after corticosteroid therapy. **Conclusion:** Diffuse involvement of CNS of CAs is rare condition without family history of CA and previous radiation therapy on the CNS. In conclusion, as in the present case, acute neurologic deficit can be associated with diffuse CAs in the CNS and extensive neuroimaging evaluation is needed to identify symptomatic CAs.

CEREBRAL HYPERPERFUSION SYNDROME: A PREVENTABLE AND TREATABLE CAUSE OF SEIZURES

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Introduction: Cerebral hyperperfusion syndrome (triad of headache, seizures and focal neurological deficits), which occurs in 0.2 to 18% post-carotid endarterectomy, is a preventable complication. **Case report:** A 63 yr old female with hypertension, hyperlipidemia and diabetes mellitus presented with acute left lower limb weakness. Home BP ranged from 104-146/43-94 mm Hg. Neurological examination revealed left lower limb monoparesis. MRI Brain showed acute right parasagittal frontoparietal infarcts. CTA neck showed severe stenosis at the proximal right ICA with tiny right ACA / PCA and watershed infarcts. She underwent successful carotid endarterectomy ten days later. Postop BP ranged from 114-154/65-102 mm Hg. A week later during rehabilitation, she developed recurrent left focal seizures. This was preceded by severe headaches the night before. CTA / CT perfusion revealed increase in perfusion in the right MCA territory secondary to postop hyperperfusion. The operated ICA site was patent and there were no new infarcts. EEG revealed right PLEDS. She was treated with anticonvulsants and BP control was achieved with IV labetalol, captopril and atenolol (kept less than preop BP). To-date she remained well with no complications. **Discussion:** Cerebral hyperperfusion syndrome can occur immediately postop to one month later. Pathophysiology involves impaired cerebral blood flow autoregulation with elevated systemic hypertension and vasogenic white matter edema. Prevention is key and numerous risk factors (preop, perioperative and postop) for development of this syndrome have been identified. Close hemodynamic monitoring is needed in patients with risk factors. TCD may be used for monitoring. **Conclusion:** Clinicians should be aware of this potentially preventable post carotid endarterectomy complication

DRIVING RISK AFTER STROKE

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Abstract: [Purpose] The aim of this study is to evaluate patients with confirmed stroke, using the DriveABLE Cognitive Assessment Tool (DCAT) to predict their driving risk. **Subjects and Methods:** A total of five hundred and fifteen patients were tested from July 1st, 2015- June 30th, 2016, out of five hundred and fifteen patients, one hundred and eight confirmed stroke patients participated in this study. A 1-year retrospective study was conducted in a Neurology clinic. A medical student, attending physician and staff, conducted DCAT evaluations, data gathering and statistical analysis. All participants were classified into the safety or risk groups based on the DCAT results. **Results:** Seven patients (6.48%) were within range of normal, 17 (15.74%) patients' cognitive abilities maybe affected, 22 (20.37%) cognitive abilities of driving are affected and 62 (57.4%) were outside the normal range and are not suitable to drive. **Conclusion:** The DCAT is a helpful tool in assessing the driving risk of stroke patients. **Key words:** Driving, Stroke, DriveAble Cognitive Assessment Tool.

CONTROVERSIES OF THYROID DYSFUNCTION EFFECTS IN PATIENTS WITH ACUTE ISCHEMIC STROKE

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Background: Previous studies showed that thyroid dysfunction is associated with more stroke severity and poorer functional outcome. However, there are controversies about the effects of particular thyroid hormones. **Methods.** 124 adult patients with acute ischemic stroke were included in this study. Exclusion criteria were autoimmune thyroiditis or thyroid carcinoma. Concentrations of free T3 (fT3), free T4 (fT4), TSH, as well as stroke risk factors were assessed during 24h from symptoms onset. Levels of thyroid hormones below 25 and above 75 percentiles were accepted as low and high respectively. Neurological deficit was assessed by Scandinavian Stroke Scale (SSS). **Results.** Analysis showed that patients with high fT3 levels (≥ 5.35 pmol/l, 95% CI 5,01-5,61) had less severe stroke compared to other patients (SSS median 44.5 vs. 36, $p = 0,0418$). This effect was stronger in the subgroup of patients without prior stroke or TIA (SSS median 48 vs. 37, $p = 0,0148$). Multiple regression showed that fT3 level had influence on the risk of disabling deficit (mRs score ≥ 3 at 6 month after stroke) independently of gender, age, stroke risk factors and etiology (OR=0.6389, 95% CI 0,4173 to 0,9782). There was no connection between fT4 and TSH concentrations and stroke severity or functional outcome. **Conclusion.** This study confirmed that low fT3 levels are associated with greater neurological deficit and poorer outcome in stroke patients. Higher levels of fT3 seemed to play a protective role. Future studies should be aimed at assessing the possible positive effects of additional fT3 supplement during stroke.

ANTICOAGULANT THERAPY AND UNRUPTURED INTRACRANIAL ANEURYSM

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Introduction: Data on anticoagulant therapy (AT) in patients with cardioembolic stroke and unruptured intracranial aneurysm are scarce. Decision is predominantly made by calculation of spontaneous aneurysm rupture and risk of recurrent stroke. **Case report:** 69-years old female with a paroxysmal atrial fibrillation was admitted to our hospital due to acute left-sided hemiparesis. Head computed tomography (CT) showed two hyperdense lesions in right thalamus. CT angiography showed no neck vessels stenosis and a 4 mm unruptured aneurysm on a.communicans anterior. Preventive LMWH and Aspirin were initiated. Control CT scan 5 days latter showed haemorrhagic transformation (HT) of ischemic stroke in right parietotemporal lobe, which was confirmed also by MRI scan. Due to haemorrhagic transformation AT was postponed. CT scan 6 days latter showed progression of haemorrhagic transformation. Aspirin was ceased. She completely neurologically recovered during hospitalisation (NIHSS 0). CT scan 3 weeks latter showed complete resorption of HT. AT with dabigatran in a lower dosage was initiated. She was latter on admitted to a cardiologist for an opinion of left atrial appendage occlusion (LAA) placement. **Conclusions:** There are no guidelines on AT in patients with cardioembolic stroke and unruptured intracranial aneurysm. Data on higher probability of aneurysm rupture due to AT is unknown. Decision on AT initiation is made on calculation of probability of spontaneous aneurysm rupture and risk of recurrent stroke. Initiation of lower dosage AT or LAA placement could be treatment options in our patient.

CAN ISCHEMIC PRECONDITIONING MAKE SPINAL CORD RESISTANT TO INFARCTION?

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We present the longitudinal clinical and electrophysiological study of 41 patients with spinal stroke and 25 patients with vascular chronic myelopathy. Thirty healthy subjects were considered as a group of references. All cases were confirmed by MRI examinations. Electrophysiological examination included needle electromyography, sensitive and motor electroneurography, F-wave study, Hoffmann reflex and motor-evoked potentials. In spinal stroke patients three vascular syndromes were considered: anterior spinal artery syndrome, syndrome of complete transversal lesion and posterior spinal arteries (artery) syndrome. The patients with chronic ischemic myelopathy were divided in several groups according to dominant clinical syndrome: spastic, spastic-atrophic and atrophic. Clinical and electrophysiological findings were assessed in each case together with etiological factors and the level of ischemic spinal lesion. Electrophysiological abnormalities were founded in 100% of cases. Based on statistical analysis of the results, electrodiagnostic criteria were elaborated for the discrimination of each syndrome of spinal stroke and chronic ischemic myelopathy. In addition to this data were founded that chronic ischemic damage of spinal cord tissue causes functional reorganization of motor units. Moreover, as a result of ischemic preconditioning and neuronal plasticity at the level of spinal cord new program of motor function was established. The general conclusion of this work is that multimodal electrophysiological investigation as a consciously extension of clinical examination can give important arguments that ischemic preconditioning protect spinal cord to infarction.

LEFT VENTRICULAR OUTFLOW TRACT ENDOCARDITIS: AN UNUSUAL CAUSE OF MULTIPLE BRAIN EMBOLISMS

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Objectives: Neurological complications arise among 15 and 30% of patients with infective endocarditis. We aim to describe an unusual cause of septic embolisms. **Methods:** We present a 50-year-old woman with previous arterial hypertension. She was admitted due to abrupt onset of fever, confusional state, and papular-erythematous spots located on the trunk, face and extremities. Cerebrospinal fluid analysis revealed 142 white blood cells per mm³ (96% neutrophils) with a negative Gram stain, 58.2 mg per dl of protein, and a normal glucose level. Empirical antimicrobial therapy was initiated. Brain magnetic resonance imaging showed multiple cortico-subcortical embolic lesions, located in both cerebral and cerebellar hemispheres and basal ganglia, as well as a mild leptomeningeal enhancement. In a transthoracic echocardiography, neither vegetations nor valve dysfunction were observed. **Results:** Two days after admission our patient presented an acute coronary syndrome with ST elevation. A transesophageal echocardiography identified a rounded 1 cm² echogenic mass anchored into left ventricular outflow tract (LVOT) endocardium, contacting with anterior mitral leaflet during diastole. Blood cultures were positive for Methicillin Sensitive Staphylococcus Aureus (MSSA). Due to clinical evolution and the inability to control septic emboli, the patient underwent emergency surgical removal of the intracardiac mass. The postoperative course was uneventful with no neurological deficits at discharge. **Conclusion:** LVOT is an infrequent location of abscesses and vegetations and their embolisms are commonly difficult to control. In case of brain embolisms without severe clinical impairment, surgery should not be delayed. Early surgical treatment significantly reduces mortality, without increased risk of new neurological events.

THE COMPARISON OF PROCEDURAL CHARACTERS AND CLINICAL OUTCOME BETWEEN SOLITAIRE STENT AND TREVO STENT IN ENDOVASCULAR TREATMENT FOR ACUTE ISCHEMIC STROKE

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Background: To compare the safety and effectiveness of two retrievable stent systems in EVT for AIS using Solitaire and Trevo. **Methods:** Patients were treated either with Trevo stent or Solitaire Stent according to the neurointerventionist preference. Recanalization was classified by TICI grade. Efficacy and safety during EVT were analyzed the rate of good recanalization after the first pass, clot retrieve rate, final recanalization grade, and use of rescue method, recanalization time, hemorrhagic complication and thromboembolic complication. **Results:** Seventy-nine patients were treated with Solitaire stent and 51 with the Trevo stent. Overall good recanalization (TICI 2b and 3) was achieved in 57 patients (72.2%) in the solitaire group and 46 (90.2%) of the Trevo group (P =0.01). The rate of good recanalization after the first pass, clot retrieve rate were not significant between two groups. However, use of rescue method was more frequent in Solitaire group. Good clinical outcome was higher in Trevo group, but not significant. The rate of symptomatic ICH and thromboembolism were not significantly different. **Conclusions:** Our study showed several superiorities of Trevo stent compared with the Solitaire stent in EVT. Trevo stent showed superiority to achieve more successful recanalization, less use of rescue method, less take a time for recanalization.

Even though the clinical outcome was not different between two stentriever, we think that Trevo stent would be better stentriever in EVT.

THE EFFECT OF INDUCED HYPERTENSIVE THERAPY IN ACUTE ISCHEMIC STROKE PATIENTS WITH STENO-OCCLUSIVE DISEASE AND HEMODYNAMIC INSTABILITY

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Objectives: Induced hypertensive therapy (IHT) has used to enhance cerebral perfusion pressure in subarachnoid hemorrhage and stroke, but there is no established indication for IHT in ischemic stroke. We report the usage of IHT in acute ischemic patients with hemodynamic instability caused by steno-occlusive disease of a main cerebral artery. **Method:** We reviewed acute ischemic stroke patients with cerebral perfusion deficit due to intracranial and extracranial steno-occlusive disease. IHT was applied for early neurological deterioration and maintained until hemodynamic instability was stabilized over 24 hours or neurointervention including angioplasty and extracranial intracranial arterial bypass surgery were performed. Result. 52 patients were analyzed. Territories of stroke were 31 of anterior circulation of intracranial vessels, 11 of posterior vessels, and 10 of extracranial vessels. Mean duration of IH therapy was 4176.04 minutes. Pre and post NIHSS score of IH therapy was 8.19 and 7.35, respectively. 30 patients (57.7%) were showed improvement and 13 patients (25%) were stabilized without further aggravation. 16 patients revealed bradycardia. There was no fatal complication of therapy. 15 patients were performed further treatment include bypass surgery, angioplasty, and stenting after IH therapy. At 3 months follow up, 34 patients showed good outcomes (modified Rankin scale 0, 1, and 2). **Conclusion:** IHT may be safe and effective for the neurologic deterioration or progression of acute ischemic stroke with hemodynamic instability due to severe steno-occlusive disease of major cerebral artery. Large randomized trials are needed to confirm this result.

DO GEOGRAPHICAL CONSIDERATIONS AND PATIENT VOLUME ARGUE TO CONVERT A PRIMARY INTO A COMPREHENSIVE STROKE CENTER

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Background: No comprehensive study exists about Mechanical Thrombectomy (MT) accessibility for patients admitted to a primary stroke center (PSC) without on-site interventional neuroradiology service. **Aims:** To evaluate MT accessibility within 6 hours after transfer from a PSC to a distant (1.5 hour by car) comprehensive stroke center (CSC). **Methods:** 3-year prospective registry of patients admitted to a PSC within 4.5 hours after symptom onset selected for transfer to a CSC for MT. Eligible patients had confirmed proximal arterial occlusion and no large cerebral infarction on MRI (DWI-ASPECTS ≥ 5). The rate of transfer, transfer without MT, MT, reperfusion (TICI score $\geq 2b-3$) and main relevant time measures were determined. **Results:** Among the 385 patients selected for intravenous thrombolysis (IVT) and/or potential MT, 211 were

considered as transferrable for MT. The rate of transfer was 56.4% (n=119/211), transfer without MT 56.3% (n=67/119), MT 24.6% (n=52/211) and overall reperfusion 18% (n=38/211). The relevant median times (interquartile range) were: 130 minutes (62) for IVT start to CSC door, 95 minutes (39) for PSC door-out to CSC door-in, 191 minutes (44) for IVT start to MT puncture, 354 minutes (107) for symptom onset to MT puncture and 417 minutes (124) for symptom onset to recanalization. **Conclusions:** Our study suggests that transfer to a distant CSC is associated with reduced access to early MT in patients with acute ischemic stroke and large artery occlusion. These results could be translated to other high volume distant PSC.

ACUTE ISCHEMIC STROKE IN MOYAMOYA DISEASE CAUSED BY THYROTOXICOSIS: A CASE REPORT

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Background and Significance: Moyamoya disease is a progressive cerebrovascular disorder of unknown cause, characterized by bilateral stenosis or occlusion of the arteries around the circle of Willis with prominent arterial collateral circulation. Moyamoya syndrome has rarely been reported in association with Graves' disease. Several studies suggest that an ischemic stroke might have occurred in patients with thyrotoxicosis. **Case:** A 41-year-old woman presented with dysarthria and aphagia. She also had episodic transient right arm weakness. Brain magnetic resonance (MR) imaging revealed an acute infarction in the territories of left anterior cerebral artery and middle cerebral artery. MR angiography showed total occlusion of both internal carotid arteries, anterior cerebral arteries and middle cerebral arteries. Thyroid function tests revealed thyrotoxicosis, with a TSH level of 0.01 uIU/mL, a T3 level of 523 ng/dL and a free T4 level of 9.08 ng/dL. After antithyroid medication, the patient's symptoms improved. **Conclusion:** Thyrotoxicosis due to Graves' disease is harmful to arterial walls because it may alter vascular reactivity and frequently provoked cerebral vasospasm. Therefore, thyrotoxicosis can be a cause of ischemic stroke and aggravate neurologic symptoms in the patient with Moyamoya disease.

ASSOCIATION BETWEEN MALIGNANT MIDDLE CEREBRAL ARTERY INFARCTION AND BRAIN NATRIURETIC PEPTIDE LEVELS IN STROKE PATIENTS WITH ATRIAL FIBRILLATION

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Background and objective: Ischemic stroke with atrial fibrillation (AF) leads to large infarction and severe neurological deficits. However, clinical characteristics associated with malignant middle cerebral artery infarction (MMI) in acute stroke patients with AF have not been previously reported. This study was aimed to elucidate the factors correlated with MMI in stroke with AF. **Methods:** Consecutive patients with acute ischemic stroke and AF who underwent magnetic resonance image within 24 hour from onset were retrospectively enrolled. Patients with posterior circulation stroke were excluded. All patients were divided into MMI and non-MMI groups using MMI definition of a National Institutes of Health Stroke Scale score 15 and infarct volume 82 cm³ on initial diffusion-weighted imaging or ischemic signs 50% of the MCA

territory on follow-up brain computed tomography. Multivariate regression analysis was used to identify factors associated with MMI. **Results:** A total of 142 patients were included and MMI was found in 31% of the patients. In univariate analysis, patients with MMI were older and had higher D-dimer and brain natriuretic peptide level. On multiple logistic regression analysis, earlier onset-to-image time (OR 0.85, 95% confidence interval [CI] 0.73-0.98, $P=0.025$ for 1 hour) and higher brain natriuretic peptide level (OR 1.22, 95% CI 1.07-1.39, $P=0.003$ for every 100 pg/mL) were independently associated with MMI after adjustment for potential confounders or mediators. **Conclusions:** Plasma brain natriuretic peptide level and onset-to-image time are independently associated with MMI among patients with stroke and AF.

NOVEL LOCUS-SPECIFIC GENETIC CHARACTERISTICS IN CADASIL

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Objective: We evaluated whether specific gene locus are related to clinical phenotypes. **Methods:** We screened patients with a suspected diagnosis of Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) between 2005 and 2015. Mutational hotspots of the Notch3 gene in exons 2-23 were screened by using Sanger sequencing. We analyzed magnetic resonance imaging (MRI) in those patients. **Results:** A total of thirty four patients (women, $n=21$ and mean age, 52 ± 10 years) were included in our study. The majority of the mutations were in exon 3 and exon 11. The most prevalent mutations were R75P mutations ($n=5$), followed by Y465C ($n=4$) and R544C ($n=4$). Patients with those mutations exhibited less frequent anterior temporal (AT) or external capsular (EC) hyperintensities compared to patients with other locus mutations. Hemorrhagic stroke was found to be associated with mutations in exon 3 (R75P), exon 9 (Y465C), exon 11 (R587C) and exon 22 (R1175W variants). **Conclusions:** In contrast to westernized countries, CADASIL patients in our study frequently had mutations in exon 3 (R75P) and exon 11, and they did not have typical AT or EC hyperintensities. Although the underlying genetic mechanisms remain unclear, we suggest that some CADASIL mutations appear to have locus-specific characteristics.

DIABETES DECREASES HIPPOCALCIN EXPRESSION IN FOCAL CEREBRAL ISCHEMIA

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Stroke is a major cause of disability and death in adults. Hyperglycemia causes intracellular calcium imbalance after ischemic insult, aggravates cytochrome c release into cytosol and activates caspase-3, and ultimately triggers apoptosis. Hippocalcin is a neuronal calcium-sensor protein that acts as a calcium buffer to regulate the intracellular concentration of Ca^{2+} . This study was investigated to elucidate hippocalcin protein expression of the cerebral cortex during ischemic brain injury between non-diabetic and diabetic animals. Adult male rats were injected with streptozotocin (40 mg/kg) via the intraperitoneal route to induce diabetes and underwent surgical middle cerebral artery occlusion (MCAO) 4 weeks after streptozotocin treatment. Cerebral cortex tissues were collected 24 h after MCAO. A proteomic approach and Western blot analysis revealed that hippocalcin protein was significantly decreased in diabetic animals with MCAO injury compared to diabetic-only and MCAO-only animals. The decrease of hippocalcin in hyperglycemic

condition suggest that hyperglycemia leads to intracellular calcium imbalance by regulating hippocampal expression levels in ischemic brain injury.

INFLAMMATORY PARAMETERS AND THEIR ASSOCIATION WITH STROKE VOLUME AND LOCALIZATION IN ACUTE ISCHEMIC STROKE PATIENTS: A THREE MONTH PILOT STUDY

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Background: The important pathophysiological role of inflammation in acute ischemic stroke (AIS) is indisputable, although the results of recent studies concerning the relation between several inflammatory markers and stroke volume (SV) as well as localization (SL) are controversial. This pilot study was designed to assess the association of specific inflammatory parameters with SV/SL in AIS patients, based on reliable and easy to perform methods.

Methods: Nineteen patients with AIS without signs of active infection or systematic disease were recruited from an inner-city hospital's neurology department in Athens, Greece, during a three-month period. Demographic and clinical data, mainly concerning vascular risk factors and metabolic profile, were collected. SL, supra- or infratentorial respectively, was determined by radiological findings whereas SV was estimated on Diffusion Weighted Imaging (DWI) by ABC/2 technique. Levels of C-reactive protein (CRP), White Blood Cells (WBC), body temperature (BT), ferritin and Erythrocyte Sedimentation Rate (ESR) were collected.

Results: According to SL, statistically significant association was observed between infratentorial strokes and higher levels of CRP ($p=0.001$) and ferritin ($p=0.022$), but performing multiple regression revealed only borderline significant association ($p=0.066$) between infra- SL and CRP levels. As SV concerns, statistically significant association was observed between higher SV and elevated levels of BT ($\rho=0.712$, $p=0.001$), ferritin ($\rho=0.450$, $p=0.022$) and ESR ($\rho=0.487$, $p=0.022$), but only the correlation between SV and BT was finally confirmed by multiple regression. **Conclusion:** Our study supports the assertion that higher SV and infratentorial SL are associated with elevated inflammatory parameters in AIS and are of clinical importance.

ASSOCIATION OF RED BLOOD CELL DISTRIBUTION WIDTH WITH STROKE AND 5-YEAR CEREBROVASCULAR AND CARDIOVASCULAR MORTALITY IN YOUNG PATIENTS WITH DIABETES

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Background: Red blood cell distribution width (RDW) is a measure of erythrocyte anisocytosis that has been recently associated with myocardial infarction, stroke and all-cause mortality. Nevertheless, no study has researched the association of RDW with stroke and cardiovascular mortality in young diabetic patients.

Methods: All diabetic patients aged 16-55 years, presenting with an ischemic stroke at the University

Hospital Centre "Mother Theresa", Tirana, during 2010-2011 were enrolled. Each patient was matched by age and gender with three stroke-free diabetic controls. Exclusion criteria were hematologic, infectious, inflammatory, autoimmune and malignant diseases. At baseline, the RDW cut-off value of 14% was used to discriminate between the two groups of stroke patients. After a 5-year long follow-up period, cerebrovascular mortality and cardiovascular mortality were assessed either physically or by phone interview in both groups.

Results: In the final analysis were included 42 diabetic patients (83.3% males), mean age 47.2 years (SD 6.18) and 126 stroke-free diabetic controls. RDW was significantly higher in stroke patients ($14.27\% \pm 1.1\%$ vs $13.82\% \pm 1.1\%$, $p=0.023$). During follow-up of stroke patients, higher cardiovascular and cerebrovascular mortality was registered in the higher RDW group ($\geq 14\%$) compared to the lower RDW group (14%), respectively 9 vs. 1 cerebrovascular deaths ($p=0.042$) and 6 vs. 2 cardiovascular deaths ($p=0.029$). **Conclusions:** RDW is associated with higher risk for ischemic stroke in young patients with diabetes. Moreover, higher RDW at baseline is associated with higher 5-year cerebrovascular and cardiovascular mortality.

DOSE SERUM D-DIMER IN NON-CARDIOEMBOLIC ISCHEMIC STROKE HAVE CLINICAL PROGNOSTIC VALUE?

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Background: Although D-dimer levels are significantly associated with cardioembolic infarction, the significance of D-dimer levels in relation to the severity and functional outcomes of other stroke subtypes, such as lacunar and large artery atherosclerosis (LAA) infarction, remains unclear. The purpose of this study was to evaluate whether elevated initial D-dimer levels are significantly and cross-sectionally associated with poor functional outcomes at each time point during a nine-month follow-up period. We also investigated the significance of D-dimer levels in longitudinal temporal changes of functional outcomes in these patients. **Methods:** We recruited 146 patients with lacunar infarction and 161 patients with LAA infarction who were consecutively admitted to our hospital after acute stroke. Serum D-dimer levels were evaluated initially and the modified Rankin scale (mRS) were measured initially and at 1-month, 3-month, 6-month, and 9-month follow-up visits. **Results:** Patients with higher D-dimer levels had significantly worse initial functional outcomes, and these worse outcomes were maintained throughout the 9-month follow-up period compared to the low D-dimer group. However, regardless of stroke subtype, D-dimer levels did not influence long-term changes in functional outcomes over the 9-month follow-up period. **Conclusion:** This study suggests that elevated D-dimer levels can be used as a surrogate marker for poor functional outcomes only during the acute stage. Further evaluation of serum D-dimer levels could provide a helpful predictive marker for stroke prognosis.

USING UPPER CASE LETTERS TO IMPROVE ALEXIA

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Our hypothesis is that individuals with aphasia will be more accurate word readers when the first letter is uppercase rather than letters are all small print. Unlike word reading, non-word reading is phototactically regular and may look like targets in that paraphasic errors or neologisms may be present when reading errors occur. Target items included reading real words and pseudo- words (2,3,4 words stimuli). 2 female and 7 male individuals with a medical diagnosis of ischemic left hemisphere stroke and presented with a clinical diagnosis of aphasia of different classifications (2 expressive, 3 mixed type, 2 anomic, 1 global). Eight

participants presented with alexia and one with alexia without agraphia and were between the ages of 46 and 80 (Mean=66.2). Participants trained daily and met with the experimenter 2x a week for a supervised 45-minute clinical session. The other homework sessions mirrored these and the experimenter monitored participants progress weekly. A multiple baseline design of 2,3,4 syllable word lists respectively. Pseudo-word reading therapy tasks was also used to prevent carryover effects at the end of each training session daily. Results of a t-test repeated sample showed reading performance were found to be significantly improved in real word reading vs non-word reading with first letter as uppercase across 2,3,4 syllable words ($p=0.044$, $.05$) as compared to all lower-case letters but not for pseudo word reading ($p=.062$ $.05$), respectively. Three of the nine subjects returned to normal levels of reading. Discussion also describes differences between non- word reading and word reading.

ANATOMICAL CAUSE OF GERSTMANN LIKE SYNDROME IDENTIFIED THROUGH MR DTI TRACTOGRAPHY

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Introduction: The symptom complex of finger agnosia, right-left disorientation, dysgraphia, and dyscalculia constitutes Gerstmann's syndrome. Gerstmann syndrome is usually caused by acquired lesions of the dominant parietal lobe including the angular and supramarginal gyri. We describe a patient who exhibited dysgraphia, acalculia, finger agnosia, left-right disorientation as well as anomia and was found to have cortical ischemic lesions in the dominant parietal lobe both through brain MRI and MR Diffusion Tensor Imaging(DTI) Tractography. **Case:** A 56 year old woman, smoker with a history of arterial hypertension and uterine fibroids was brought to the emergency department because of an episode of sudden loss of consciousness. Blood tests revealed low hematocrit and hemoglobin values and the patient was admitted to the Hematology clinic where the diagnosis of acute myelomonocytic leukemia was made. Neurological examination showed an intact level of consciousness, fluent paraphasic speech and the symptom complex of Gerstmann Syndrome. MR angiography identified a 80% stenosis of the left medial cerebral artery and head Diffusion Weighted(DW)-MRI showed multiple acute cortical and subcortical infarcts in the area of distribution of the left medial cerebral artery. The patient's symptoms were weighted with the Boston Diagnostic Aphasia Examination (BDAE) and the anatomic lesion was identified through an MR DTI Tractography. **Discussion:** MR DTI Tractography can visually represent complicated neural networks formed by short connections among different cortical and subcortical regions. In our case, we managed to interpret an unusual complex of symptoms and identify the anatomical cause of a rather rare clinical case.

ENDOVASCULAR THROMBOLYTIC THERAPY IN ACUTE ISCHEMIC STROKE PATIENTS WITH CURRENT MALIGNANCY

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Backgrounds and Purposes: Cancer causes a hypercoagulable state, increasing the risk of thromboembolic events including acute ischemic stroke. The safety of reperfusion treatment for acute ischemic stroke

in patients with cancer is not well established. Intravenous thrombolysis appears to be safe in patients with cancer. There are no previous detailed reports of endovascular thrombolytic therapy in this population. We investigated the outcomes of endovascular reperfusion treatment for acute ischemic stroke patients with current malignancy. **Methods:** We have recruited acute ischemic stroke patients with active cancer who were treated with endovascular therapy between 2011 to 2014 from stroke registry of Chonnam National University Hospital. Baseline characteristics, radiological findings and clinical outcomes were analyzed. **Results:** Total 10 patients were recruited. Three patients were administered endovascular therapy with intravenous thrombolysis, seven patient underwent only endovascular treatment. Symptomatic intracerebral hemorrhage was observed in 1/10 (10%) and petechial hemorrhage observed in 1/10 (10%). Five patients showed significant improvement in National Institute of Health Stroke Scale score at discharge and modified Rankin scale at 3 months (5/10, 50%). Two patients had no change in National Institute of Health Stroke Scale score and modified Rankin scale at 3 months and 3 patients dead after 3 months. Unfavorable prognosis was observed in patient who received intravenous thrombolysis concomitant with endovascular treatment. **Conclusion:** In carefully selected patients, endovascular treatment may be considered in the management of acute ischemic stroke patients with current malignancy.

BRAINSTEM CAVERNOUS MALFORMATIONS: CONSERVATIVE OR SURGICAL APPROACH?

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Cavernous malformations (CMs) are low-flow vascular lesions with an incidence of 0,4-0,8%. 20-35% are infratentorial with a predilection for the pons. Although frequently incidental, they can cause intracranial hemorrhage and focal neurological deficits. No clear consensus exists on whether CMs should be managed conservatively, surgically or with radiosurgery. We present the case of a 66-year old female who was referred for neurological evaluation due to recent onset double vision. She had a history of hypothyroidism and atrial fibrillation. Neurological examination revealed right abducens palsy. Brain MRI and MRA demonstrated a cavernous angioma of the right pons with intralesional bleeding. She received oral dexamethasone with a tapering regimen, showing full remission. There is a long-standing controversy on the optimal approach to brainstem cavernomas. A minimal consensus holds for incidental lesions where surgical-associated morbidity argues for conservative management. Radiosurgery, although presented as a treatment option, is not recommended. Regarding surgical treatment no clear consensus has been reached. Infratentorial CMs seem to have an increased risk of hemorrhage (3.8% per patient-year) This rate is further elevated in patients initially presenting with hemorrhage, those with deep CMs and female sex. Conversely there is a temporal decline in the hemorrhage risk within 2 years (up to 0.8%) This effect is influencing treatment options because the risk of hemorrhage and neurological deficit may decline based on natural history alone. Several studies propose surgical removal in cases of progressive neurological deficit, after the first clinically significant hemorrhage in noneloquent areas or after the second clinically significant hemorrhage in eloquent areas. No level A evidence exists and management still relies on clinical judgment. In our patient we chose a conservative approach under close future surveillance but more studies are warranted to form a reliable treatment algorithm.

VKA: OPTIMAL ANTICOAGULATION FOR SECONDARY STROKE PREVENTION OF NVAF PATIENTS WITH GOOD (66%) TTR

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Time in therapeutic range (TTR) is the major determinant of adequate anticoagulation for atrial fibrillation (AF) patients on vitamin K antagonists (VKA). Whereas in patients with TTR66% non-VKA anticoagulants (NOACs) are generally preferred for eligible patients, patients with efficient INR control (TTR66%) have a marginal benefit from switching to NOACs. Since there is no randomized controlled trial (RCT) of any NOAC comparing it to patients on VKA with TTR66%, we have to rely on pooled data from the existing NOAC RCTs. There seems to be an absolute risk reduction in stroke or systemic embolism with NOACs versus VKA that is inferior to 1%; this benefit is further mitigated in centers with TTR66%. In these same centers no significant difference in major hemorrhage is noted between NOACs and VKA. Advising in favor of switching of patients already on VKA with an efficient INR control to NOACs is a decision that would have minimal impact on efficacy and no impact on safety according to the limited and indirect, thus moderate-quality, data at our disposal. This choice concerns not only clinicians but also health-care policy makers as the financial burden of such a scenario seems unbearable for most, if not all, health care systems worldwide.

IS THERE THERAPEUTIC EFFECT OF ARGATROBAN IN CEREBRAL TERRITORY INFARCTION?

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Background: Therapeutic efficacy of argatroban is globally not known yet because few clinical studies in acute ischemic stroke are reported and the sample sizes of these studies is small. The aim of this study is to demonstrate an efficacy and safety in patients with cerebral territory infarction who received argatroban within 48 hours from symptom onset. **Methods:** This study included patients with acute cerebral territory infarction within 48 hours after stroke onset. All subjects were divided into 2 groups: those receiving argatroban on admission (argatroban group), and those receiving aspirin only (control group). We estimated the subjects' neurologic deficits and functional outcomes by using National Institute of Health Stroke Scale (NIHSS) and modified Rankin scale (MRS) prior to argatroban infusion and aspirin administration, on first day and 10th day after initiation of the therapy. **Results:** In comparison to the aspirin group, the argatroban group showed significant improvement of NIHSS and MRS among before treatment, first day and 10th day after treatment. There was a significant difference of NIHSS and MRS between the argatroban group and the control group at 10th day after initiation of the therapy, which proved superiority of the argatroban group with cerebral territory infarction within 48 hours after stroke onset. **Discussion:** The present study suggests that argatroban has added benefit in early neurological outcomes after acute cerebral territory infarction and provides safe anticoagulation in acute cerebral territory infarction.

THROMBUS IN SUPERIOR VENA CAVA AS A CAUSE OF VENOUS STROKE

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Thrombosis of superior vena cava is a common complication of malignancy, some cardiac and inflammatory diseases, and others. The most common symptoms are swelling of face, arms and chest-wall (87.6%) with associated venous congestion over these areas. We present a case of the patient with thrombosis of superior vena cava resulted in venous stroke. 71 years old man presented in ER with hemianopsia, somatosensory and visual hemineglect right side and confusion. In history the patient had paroxysmal atrial fibrillation, arterial hypertension and upper respiratory tract infection. Brain CT showed cerebral small vessel disease. On ultrasound small atheromatous plaques in both carotid arteries without hemodynamic abnormalities in extra and intracranial arteries were seen. On carotid examination however the abnormally enlarged right jugular vein and thrombosis with total occlusion of left jugular vein were found. Brain MR DWI/ADC showed ischemic focus in left occipital lobe accompanied by incomplete thrombosis of left sigmoid sinus and no flow in left jugular vein. Venous infarct was diagnosed. Hypokinetic right ventricle wall on transthoracic echo and thrombosis of superior vena cava with incomplete obstruction of venous lumen on transoesophageal echocardiography were found. Warfarin was administered. On one month follow-up there was echogenic blood with slow flow in left jugular vein and diameter of right jugular vein has been diminished. No neurological symptoms were present except of somatosensory hemineglect right side. On work-up no predisposing diseases were found. In a patient with common vascular risk factors a less common cause of stroke should be taken into account.

FOCAL LOW AND GLOBAL HIGH PERMEABILITY PREDICT THE POSSIBILITY, RISK, AND LOCATION OF HEMORRHAGIC TRANSFORMATION FOLLOWING INTRA-ARTERIAL THROMBOLYSIS THERAPY IN ACUTE STROKE

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Background and Purpose: K^{trans} , which reflects blood-brain-barrier permeability (BBBP), is influenced by circulation and measurement conditions. We hypothesized that focal low BBBP values can predict the spatial distributions of hemorrhagic transformation (HT), and global high BBBP values can predict the likelihood of HT. **Patients and Methods:** We retrospectively enrolled 106 patients with hemispheric stroke who received intra-arterial thrombolytic treatment. K^{trans} maps were obtained using first-pass perfusion CT data. The K^{trans} values at the region level, obtained using the Alberta Stroke Program Early CT Score (ASPECTS) system, were compared to determine the differences between the HT and non-HT regions. The K^{trans} values of the whole ischemic region based on baseline PCT were obtained as a variable to predict HT possibility at the patient level. **Results:** Of a total of 106 patients, 48 (45.28%) had HT and 21 (19.81%) had symptomatic intracranial hemorrhage (sICH). At the region level, there were 72 regions of interest (ROIs) with HT (mean K^{trans} : 0.49 ± 0.53 /min). The mean K^{trans} value of 615 non-HT ROIs was 0.69 ± 0.61 /min, which was significantly lower than that in the non-HT regions ($P=0.0066$). At the patient level, there was significant difference ($P=0.0113$) between the K^{trans} values of patients with sICH (1.31 ± 0.88) and without sICH (0.76 ± 0.37). Only a high K^{trans} value at patient level could predict the occurrence of sICH ($P=0.001$; OR:5.040, 95% CI:2.009-

12.651). **Conclusion:** Global high K^{trans} values can predict the likelihood of HT or sICH at the patient level, whereas focal low K^{trans} values can predict the spatial distributions of HT at the region level.

SYNUCLEIN MUTATIONS

THE DIFFERENT FACES OF THE P.A53T ALPHA-SYNUCLEIN MUTATION: A SCREENING OF GREEK PATIENTS WITH PARKINSONISM AND/OR DEMENTIA

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Introduction: The p.A53T mutation in the alpha-synuclein (*SNCA*) gene is a rare cause of autosomal dominant Parkinson's disease (PD). Although generally rare, it is particularly common in the Greek population due to a founder effect. A53T-positive PD patients often develop dementia during disease course and may very rarely present with dementia. **Methods:** We screened for the p. A53T *SNCA* mutation a total of 347 cases of Greek origin with parkinsonism and/or dementia, collected over 15 years at the Neurogenetics Unit, Eginition Hospital, University of Athens. Cases were classified into: "pure parkinsonism" (PD, atypical parkinsonism), "pure dementia" (frontotemporal dementia, Alzheimer disease, "other") and "parkinsonism plus dementia" (frontotemporal dementia with parkinsonism, PD dementia, Lewy Body disease, atypical parkinsonism). **Results:** In total, 4 p. A53T *SNCA* mutation carriers were identified. All had autosomal dominant family history and early onset. Screening of the "pure parkinsonism" category (137 cases) revealed 2 cases with typical PD. The other two mutation carriers were identified in the "parkinsonism plus dementia" category (89 cases). One had a diagnosis of PD dementia and the other of behavioral variant frontotemporal dementia. Screening of patients with "pure dementia" (121 cases) failed to identify any further A53T-positive cases. **Conclusion:** Our results confirm that the p.A53T *SNCA* mutation is relatively common in Greek patients with PD or PD plus dementia, particularly in cases with early onset and autosomal dominant family history. However, routine screening of patients with "pure dementia" is unlikely to be clinically useful even in the Greek population.

DATSCAN IMAGING IN P.A53T A-SYNUCLEIN-ASSOCIATED PARKINSON'S DISEASE: COMPARISON WITH SPORADIC PARKINSON'S DISEASE

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Objective: The objective of this study was to assess striatal dopaminergic denervation in a cohort of symptomatic carriers of the p.A53T α -synuclein (*SNCA*) mutation as compared to sporadic PD (sPD). **Methods:** DaTSCAN SPECT imaging was acquired at Parkinson's Progression Markers Initiative (PPMI) imaging centers as part of the PPMI imaging protocol and sent to imaging core for processing and calculation of striatal binding ratios. Data from the PPMI database of 10 symptomatic p.A53T *SNCA* mutation carriers

who underwent DaTSCAN at our site, were compared to those of 21 age-, gender- and disease duration- matched sPD patients. **Results:** The striatal dopaminergic denervation was so severe in 3/10 p.A53T mutation carriers, that corresponding binding ratios were unmeasurable. The remaining 7 p.A53T mutation carriers had significantly lower left caudate nucleus binding ratio ($p=0,01$), and a similar trend for the right caudate, compared to sPD patients. There was no difference in the putaminal binding ratios. The caudate / putamen signal ratio was significantly lower bilaterally in the p.A53T cohort (Right side $p=0,028$, Left side $p=0,018$). A similar degree of striatal asymmetry was observed in both the p.A53T and sPD subgroups. **Conclusions:** PD patients harboring the p.A53T SNCA mutation show evidence of a more severe, albeit variable, dopaminergic nigrostriatal denervation, mainly involving the caudate nucleus. This finding possibly reflects a more rapid disease progression, as well as a differential topography of nigrostriatal degeneration in the mutation carriers compared to sPD. This study was funded by the Michael J. Fox Foundation (PPMI study).

THE BRAIN AND MIND IN GREEK PHILOSOPHY AND MYTHOLOGY

MORBUS HERCULES. THE ROLE OF HERACLES IN EPILEPTOLOGY AND GREEK AND SCYTHIAN MYTHOLOGY

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The word "epilepsy" is derived from Ancient Greek "ἐπίληψις" (a seizure) which comes from "ἐπιλαμβάνειν" – "to seize, possess or afflict". In medical tractate "On the Sacred Disease" Hippocrates (c.460 – c.370 BC) gave the earliest available biological interpretation of the nature of epileptic process as brain disturbance. Epilepsy was also known by Greek and Latin physicians as "morbus Hercules" because Heracles (Hercules) was one of the most famous epileptic patients. Epilepsy caused a severe tragedy in life of Hercules - in the condition of complex partial seizure he killed his wife, two sons and also two children of his half maternal twin brother Iphicles. To expiate the crime, Heracles was required to carry out ten labors by the order of his cousin – Eurystheus, basileus of Argolid. During his life Heracles periodically had complex partial and secondary generalized seizures that were explained in Greek mythology as a penalization from the goddess Hera out of jealousy and revenge to the illegitimate son of her unfaithful husband - god Zeus. Episodes of rage, fury and crazy behavior of Hercules in the state of altered consciousness, accompanied by hyperemia, ophthalmic phenomena, hypersalivation with expired foam from mouth, chaotic automatisms, destroying everything and everyone, was noted in a number of legends and written sources, including the Euripides' drama "Madness of Heracles". Heracles is famous for his polygamy and fertility, and a lot of dynasties and tribes proclaimed Heracles as forefather. During his journey Heracles met in the cave the beautiful snake-woman Echidna, who bore him three sons, whose name was Agaphirs, Gaelon and Skyth - the ancestor of the Scythians. Famous Russian poets of "silver age" symbolists stiled at the beginning of XX century - Alexander Block suffered from epilepsy and Valery Bryusov suffered from nightmares used antic legends, Heraclius and epileptic motives in their creativity.

BRAIN AND MIND: WHO IS THE PUPPET AND WHO THE PUPPETEER?

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The question in the title has fundamental social and legal implications. If the mind controls the brain, then there is FREE WILL and its corollaries, responsibility and dignity. If the brain controls the mind then there can be no FREE WILL because we cannot influence the brain connections and neurotransmitters that make the decisions for us. Hippocrates expressed what is taught in neuroscience today. "Men ought to know that from the brain, and from the brain only, arise our pleasures, joys, laughter and jests, as well as our sorrows, pain, griefs and tears". Neuroscience, considers the mind to be the activity of the brain (Hebb, 1949) and believes there is no ghostly substance inside us. Consistent with this, psychology abandoned the concept "soul" in the 1930s. Behavior is the outcome of two influences: genetic endowment and environment – nature and nurture. As Praxiteles sculpted Hermes out of a block of marble, so experience sculpts our character from the genetic material we are granted. Importantly, we have no choice of parents or the society we are born in. If only we could abandon our undesirable desires, our depression, our obsessions, our compulsions, our unrequited love. If only we were the authors of our thoughts and not merely observers of what the brain presents us. If only we could get hold of one of the strings with which our brain makes us dance. It seems the puppet is free only in as much as it loves its strings (Harris, 2012).

EPILEPSY - THEN AND NOW

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Hippocrates (460-370 BC) is called the father of medicine, founding the Hippocratic school. They were convinced that the brain is the source of all emotions and knowledge, although the ancient greek view differs from the present.

One of the most studied was the epilepsy, due to the spectacular aspect of the crisis.

In his book - 'On the Sacred disease', Hippocrate rises some theories, revolutionary from his predecessors, but quite far from the present view. Ul. The origin: hereditary, in the uterus a lack of 'purification' appears, conducting to a 'phlegmatic' person, as his parents. But, this may be depurated in childhood by skin eruptions. If not, the person becomes epileptic. They present with curved spine or mental retard. The clinic is well documented. The determinant factors: changing in temperature – cold, emotions. It may affect the lung or heart- the choking and hypersalivation or the bowel – spontaneous diarrhea. It presents on several forms: left seizures / right / both. Physiopathology: it is a defluxion of cold phlegma into the cava veine, that makes a blockage in the blood and inspiration and determines the hypersalivation, abnormal breathing and movement, loss of conscious, intellect. Prognostic is reserved for children and the elderly, as the young may heat the phlegma/ulAlthough the psysiopathology is far from the truth, the Hippocratic theories closely analysed may be interpreted in ways that modern medicine confirmed, increasing the value of logic observation, taking in consideration that the Corpus didn't make dissections on humans.

TRAUMATIC BRAIN INJURY

SLEEP): A SINGLE-SENSOR AUTOMATIC SLEEP-STAGE CLASSIFICATION BASED ON CROSS-FREQUENCY COUPLING

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Clinical specialists of sleep often score manually the sleep stages by visually inspecting the characteristic waveforms of a patient's neurophysiological signals like electroencephalogram (EEG), electrooculogram (EOG), electrocardiogram (ECG) and electromyogram (EMG). The whole approach of sleep scoring the neurophysiological recordings of a patient last over eight hours is a very demanding, difficult and time consuming procedure. Complementary, the limitations of manual sleep stage scoring have forced the scientists to develop techniques based on signal processing and machine learning for a completely Automatic Sleep Stage Classification (ASSC). Our first aim was to propose a novel EEG single-sensor ASSC based on dynamic reconfiguration of cross-frequency coupling (CFC) estimates using three different algorithms for the estimation of phase-to-amplitude coupling (PAC). The dynamic PAC (dPAC) was estimated between predefined frequency pairs applied to 10 s epoch lengths. We attempted to predict sleep stages (non-REM:N1,N2,N3,N4,REM:R) and wake (W) condition simultaneously as a six-class classification problem applied to 10 s epoch lengths. The proposed analytic scheme was demonstrated using the PhysioNet Sleep European Data Format (EDF) Database using sleep recordings from 41 subjects. The presented methodology achieved an absolute classification sensitivity, specificity and accuracy of $90.3 \pm 4.1\%$, $94.2 \pm 4.1\%$, and $94.6 \pm 4.2\%$, respectively, when multi-class Bayes Naive classifier is applied. Finally, our novel method was compared with those in recently published studies, enhancing further the high classification accuracy performance presented here.

AN UPDATE ON NEURORADIOLOGY OF TRAUMATIC BRAIN INJURY: THE LSU APPROACH

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Patients with traumatic brain injury complain of symptoms like headaches, insomnia, depression, memory loss, bursts of anger, difficult in planning, bad social relationship, loss of some praxias. We present our magnetic resonance protocol, capable to explain those symptoms and provide a better diagnosis and prognosis for these patients as well as some examples from our daily routine. **Material and methods:** We have a standard protocol for patients suspected to have traumatic brain injury. The sequences are 3D T1-SPGR(BRAVO), 3D FLAIR, 3D susceptibility sequence (SWAN), Tensor, magnetic resonance spectroscopy with ROIs in frontal lobe and cingulate gyrus and resting state functional magnetic resonance. The subjects are 30 patients consulting for litigation, diagnosed with post-traumatic syndrome, no less than one year after trauma. 16 men and 14 women. Mean age: 38 yo (10yo-67 yo). **Results:** Susceptibility sequence was positive in 37% of patients. Cortical thinning was present in all patients in a following distribution: orbito-frontal cortex 90%, dorsal medial frontal cortex 83%, occipitaltemporal cortex 70%, central cortex 50%,

hippocampus 26.7%, temporal cortex 23%, parietal cortex 20%. Fractional anisotropy was decreased in cingulum 57%, genu of the corpus callosum 50%, uncinate fasciculus 43%, splenium and inferior longitudinal fasciculus 23% each, superior longitudinal fasciculus 13%. Increased fractional anisotropy was present in cingulum 20%, superior longitudinal fasciculus 17%, splenium of the corpus callosum 13%, uncinate fasciculus and inferior longitudinal fasciculus 7% each. Magnetic resonance spectroscopy was abnormal in the frontal lobes (decreased NAA) in 73% and in posterior cingulate cortex in 28%. Abnormal connectivity in resting state fMRI was found in anterior cingulum 75%, posterior cingulum 67%, hippocampus 42%, insula 37%, caudate 25%, thalamus and prefrontal cortex in 13% each. Midbrain abnormal connectivity (13%) was always present in patients with persistent headache. **Conclusion:** Abnormal findings in our protocol matched neuropsychological examination and explained the symptomatology in patients with normal computed tomography and standard magnetic resonance. The symptoms, started after traumatic brain injury, correlated well in these patients

UTILITY OF ANATOMIC MRI AND SPECIFIC NEUROLOGICAL ASSESSMENTS IN MILD TBI

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Objective: This study investigated the utility of specific assessments and findings on high resolution anatomic MRI to evaluate Mild Traumatic Brain Injury (mTBI). **Background:** 3-word recall is commonly employed in patients with mTBI to assess memory function (Folstein et al., 1975). This test is usually normal and is probably inadequate for assessing these patients. 5-word recall, BESS, and Digits Backward are incorporated into the SCAT 2 (McCrorry et al., 2009), but research has not demonstrated their effectiveness as longitudinal assessments (McCrea et al., 2013). The extent of incidental MRI findings in mTBI patients also remains unclear. **Methods:** 86 patients (15-50 years old), enrolled in the study either within 72 hours or 6-10 days of head injury, were followed over 3 months. Patients completed a maximum of 4 encounters which included a clinical exam, neurological assessments, and a multi-modal MRI at each visit. Chi-square and linear mixed models were used to longitudinally assess clinical symptoms found in the SCAT2. **Results:**

Three longitudinal neurological assessments provided statistically significant results. The success rate of three trials of 5-Word recall increased from 14.1 correct out of 15 at Encounter 1 (E1) to 14.9 at Encounter 4 (E4) ($p=0.001$). Only the Single-Leg test of the Modified BESS was significant, dropping from an average of 4.1 errors at E1 to 1.8 at E4 ($p=0.001$). Subjects demonstrated a significant increase in successful 5-Digit Backward Recall (57.5% at E1 to 71.7% at E4; $p=0.043$). Anatomic MRI also provided interesting data; 20 of the 81 subjects imaged had stable white matter changes across encounters (24.7%) and 23 had incidental findings (28.4%). **Conclusion:** Neurologists may consider 5-Digits Backward, Single-Leg Balance, and 5-Word Recall tests over traditional 3-Word Recall, Gait/Romberg, and full BESS testing when assessing progression of mTBI patients over multiple visits. Incidental findings and white matter changes may be more prevalent in patients with mTBI compared to the normal population (Katzman et al., 1999, Hopkins et al., 2006).

SLEEP DISORDERS AFTER TRAUMATIC BRAIN INJURIES IN AMATEUR SPORTS

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Introduction: Sleep disorders and other related problems are common situations after traumatic brain injuries **Aim:** Aim of this study was to evaluate such disorders **Material-We** evaluate 20 amateur sportsmen(range 18 to 38), after traumatic brain injuries, during amateur sports activity. The specific sports activity was -soccer in 5 cases-25%- -basket ball in 3 cases-15%- -volley ball in 3 cases-15%- -hand ball in one case-5%- -tennis in one case-5%- -running in one case-5%- -beach volley ball in one case-%_ - boxe in one case-5%- -karate in one case-5%- -taekwondo in one case-5%- -wrestling in 2 cases-10%, **Methods:** -A relation between sleep disorders and other related problems with 1)headache 2) dizziness 3) psychiatric symptoms was performed. **Results:** 19 sportsmen were retrospectively considered (95%). The most common types of injuries were falls, 10,52,6%. There is also a correlation between sleep disorders and other related problems (headache, dizziness, psychiatric symptoms). Neurologic and psychiatric evaluation was very usefull such as appropriate medication in all 19,100%,cases **Conclusions:** We need more cases but that cognitive-accurate therapy and medication could be helpful in these situations. Sleep disorders after traumatic brain injuries are conditions that needs accurate evaluation and approach.

SLEEP DISORDERS AFTER TRAUMATIC BRAIN INJURIES IN ELDERLY PEOPLE

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Introduction: Sleep disorders and other related problems are common situations after traumatic brain injuries in elderly people (65 years old) **Aim-Aim** of this study was to evaluate such disorders (65 years old) **Material-We** evaluate 20 elderly male people (range 65 to 75), after traumatic brain injuries. **Methods:** A relation between sleep disorders and other related problems with 1)headache 2) dizziness 3) psychiatric symptoms was performed. **Results:** 19 elderly men were retrospectively considered (95%). The most common types of injuries were falls, 10,52,6%. The second common type of injury was rood traffic accident, 5, 26,3%. The third common type of injury was domestic injuries, 4, 21,1%. There is also a correlation between sleep disorders and other related problems (headache, dizziness, psychiatric symptoms). Neurologic and psychiatric evaluation was very usefull such as appropriate medication in all 19,100%, cases. **Conclusions:** We need more cases but that cognitive-accurate therapy and medication could be helpful in these situations. Sleep disorders after traumatic brain injuries are conditions that needs accurate evaluation and approach.

MOLECULAR MECHANISMS OF POSTINJURY AXONAL REGENERATION IN PRIMATE RETINAL GANGLION CELLS

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Purpose: To examine molecular mechanisms which are involved in regeneration of primate retinal ganglion cell axons in the monkey-human paradigm. **Methods:** Retinas were obtained from newborn to adult monkeys (*Callithrix jacchus*) immediately after death, freed from surrounding tissue and used to prepare explants which were cultured *in vitro*. Growth of axons was monitored using phase contrast microscopy and time-lapse video cinematography. Immunohistochemistry, Western blotting, qRT-PCR, proteomics and genomics were performed to characterize molecules associated with axonal growth. Then, siRNA experiments were conducted to identify the causal involvement of selected molecules in triggering axonal growth. **Results:** Primate retinal ganglion cells (RGCs) are known to lose the ability to regenerate cut axons during postnatal maturation, but the underlying molecular mechanisms are unknown. We screened for regulated genes in monkey RGCs during axon growth in retinal explants obtained from eye cadavers on the day of birth from New World marmosets (*Callithrix jacchus*), and hybridized the regeneration-related mRNA with cross-reacting cDNA on human microarrays. Neuron-specific human ribonucleoprotein N (snRPN) was found to be a potential regulator of impaired axonal regeneration during neuronal maturation in these animals. In particular, up-regulation of snRPN was observed during retinal maturation, coinciding with a decline in regenerative ability. Axon regeneration was reactivated in snRPN-knockout adult monkey retinal explants. These results suggest that coordinated snRPN-driven activities within the neuron-specific ribonucleoprotein complex regulate the regenerative ability of RGCs in primates, thereby highlight a potential new role for snRPN within neurons and the possibility of novel postinjury therapies. **Conclusions:** The data show that even after postnatal maturation, the molecular mechanisms for postinjury axonal growth are still existing, and can be reactivated to result in growth cone formation and lengthy axon extension. Understanding of the molecular mechanisms of axonal regeneration will help to develop therapeutic concepts for brain injuries.
